KSMRM·KSMCB 2020

2020.10.8. THU. GRAND JOSUN BUSAN

OVERCOME

Ongoing Voyage of Exciting Research Communications On Mitochondrial Enigma

건강한 100세 시대의 준비

뉴로셀텍정

뉴로셀텍은 엽산, 비타민A, 비타민B_{12}, 비타민C, 비타민D, 비타민E 및 피로 회복에 필요한 피타민B군을 고함량으로 함유한 건강 100세 시대의 **맞춤형 스마트 종합비타민제** 입니다.

1. **뉴로셀텍**은 호모시스테인 농도를 낮추는 엽산과 비타민B_{12} 함유로 **심혈관[1] 및 신부전 환자의 동맥경화증 발생 위험[2]을 낮추어 줍니다.**

1) J Am Diet Assoc. 97(1997) 167-173
2) The Korean Journal of medicine 72(2007) 607-615

2. **뉴로셀텍**은 당뇨병 치료제(Metformin) 장기 복용 시 엽산과 비타민B_{12} 결핍으로 인한 **말초신경병증(Peripheral Neuropathy) 발생위험을 낮추어 줍니다[3].**

3) British medical journal 340(2010) 1177-1183

3. **뉴로셀텍**은 골다공증 골절 위험을 유발하는[4] 호모시스테인의 농도를 낮추고 비타민D는 필요한 혈중 칼슘 농도 유지로 **골대사에 도움을 줍니다[5].**

4) N Engl Med 2004 350 2033-41
5) Journal of American Medical Association 294(2005) 2336-2341

4. **뉴로셀텍** 함유 비타민류를 복용 시 비만 여성의 HDL-C와 휴식기 에너지 소비량은 증가하고 지방량과 LDL-C는 감소하여 **고지혈증 위험을 감소 시킵니다[6].**

6) International Journal of Obesity 34(2010) 1070–1077

5. **뉴로셀텍**은 혈중 비타민D 농도 부족으로 인한 **만성 피로증을 개선 시키는 비타민D를 함유하고 있습니다[7].**

7) Medicine (Baltimore) 95(52)(2017) 4985-5950

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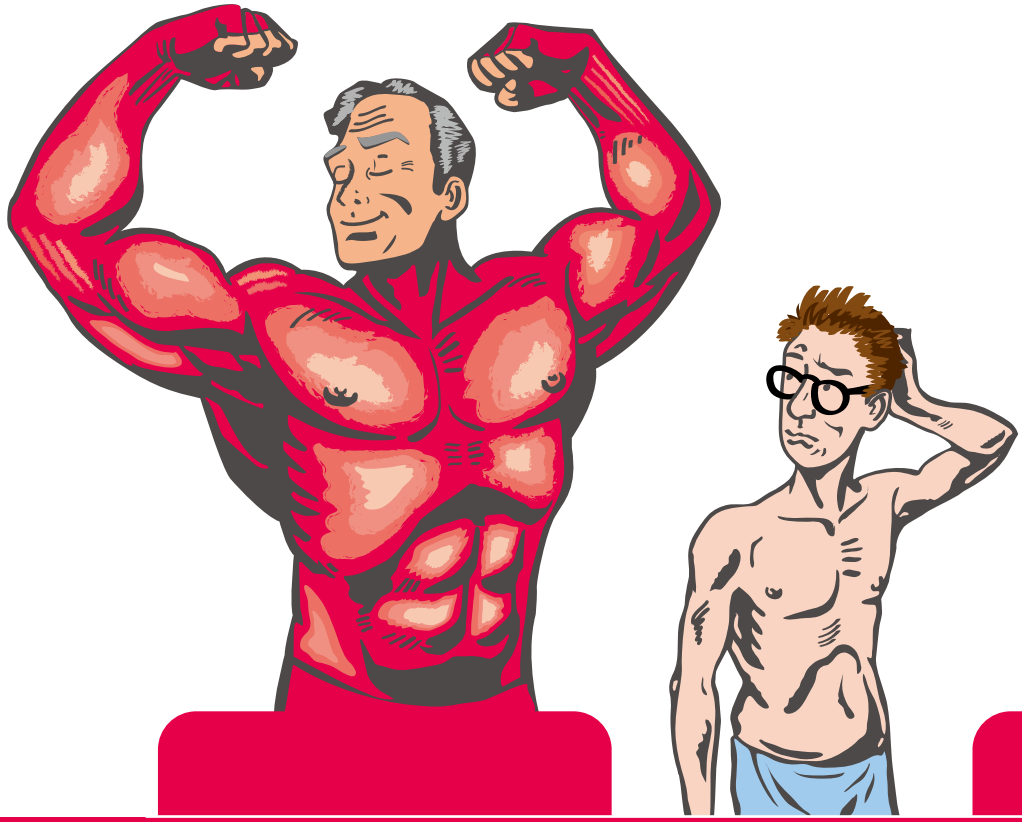

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**Ref) Kim H, Suzuki T, Saito K, Kojima N, Hosoi E, Yoshida H. Long-term effects of exercise and amino acid supplementation on muscle mass, physical function and falls in community-dwelling elderly Japanese sarcopenic women: A 4-year follow-up study. Geriatr Gerontol Int. 2016 Feb; 16(2):175-81.*

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References
1. Kim KJ, Kim SH, Yoon YW, *et al*. Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients with primary hypercholesterolemia: MRS-ROZE (Multicenter Randomized Study of ROsuvastatin and eZEtimibe). *Cardiovasc Ther*. 2016 Oct;34(5):371-82. **2**. UBIST 2020년 누적 매출 기준

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Ref.
1. Lee M S, et al. J Rheum Dis. 2003;10(4):413-21 2. Ilich J Z, et al. J Am Coll Nutr. 2002;21(6):536-44. 3. Paolisso G, at al. Am J Hypertens. 1997;10(3):346-55. 4. Kurt R, et al. Arch Med Res. 2010;41(5):369-72.
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"이상지질혈증 환자"의 영양소 관리

Ref.
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"고혈압 환자"의 영양소 관리

Ref.
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Ref.
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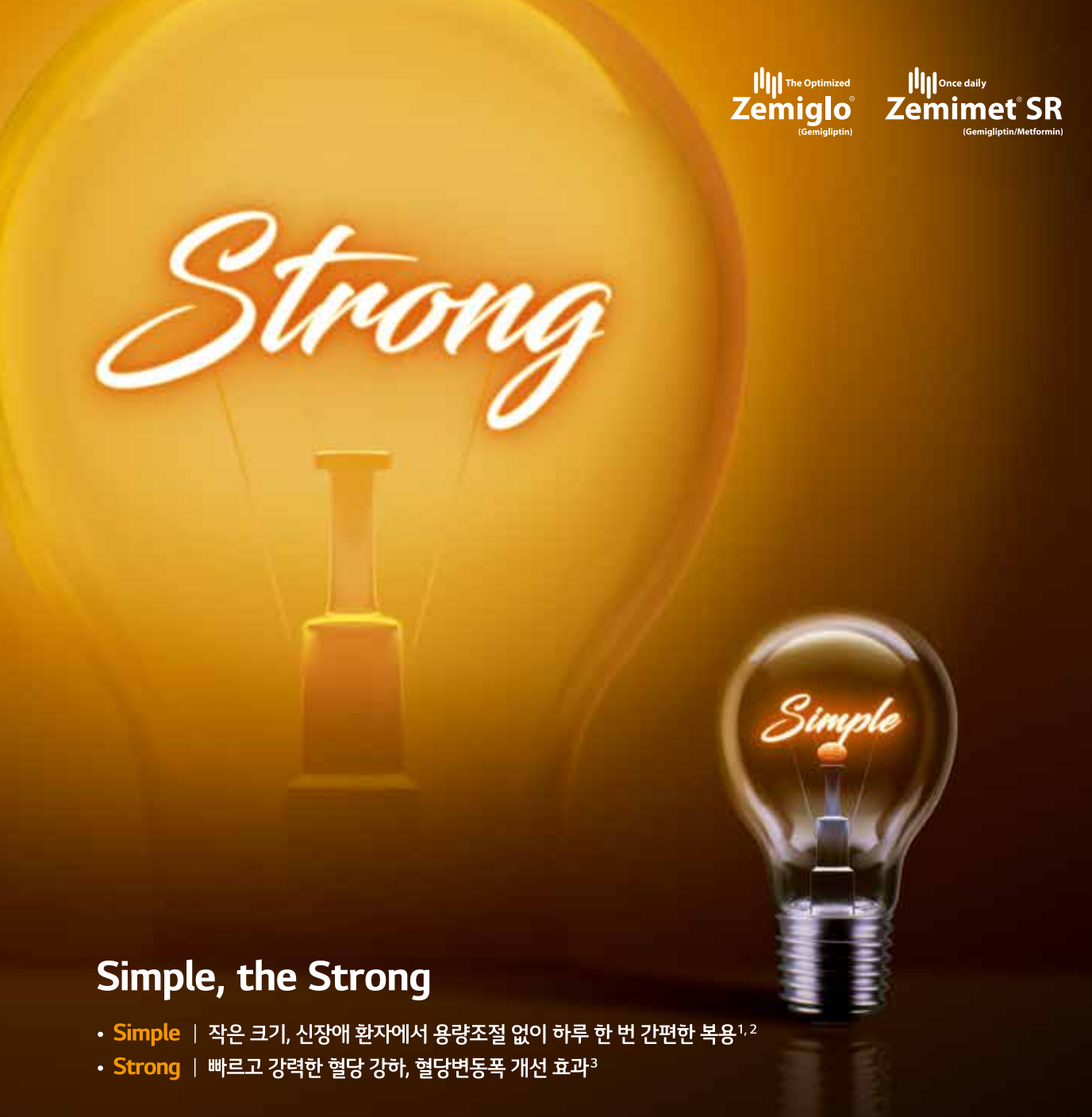

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• **효능·효과** 인슐린 비의존성(제2형) 당뇨병환자의 혈당조절을 향상시키기 위해 식사요법 및 운동요법의 보조제로 투여. 1. 단독요법으로 투여 2. 다음의 경우 병용요법으로 투여. – 메트포르민 단독요법으로 충분한 혈당조절을 할 수 없는 경우. – 이전 당뇨병 약물치료를 받은 경험이 없으며 단독요법으로 충분한 혈당조절이 어려운 경우 메트포르민과 병용투여. – 메트포르민과 설포닐우레아 병용요법으로 충분한 혈당조절을 할 수 없는 경우. - 인슐린 요법(인슐린 단독 또는 메트포르민 병용)으로 충분한 혈당조절을 할 수 없는 경우. • **용법·용량** 1일 1회 1정 투여하며, 1일 최대용량은 50 mg로 식사와 관계없이 투여 가능. 신장애 환자 및 경증 및 중등도의 간장애 환자에서 용법, 용량 조정이 필요하지 않음. • **사용상 주의사항** 금기-본제 또는 다른 dipeptidyl-peptidase 4(DPP4) 저해제에 중대한 과민반응을 보인 환자, 제1형 당뇨병 및 당뇨병성 케톤산증 환자. • **이상반응** 임상시험(단독요법)에서 3% 이상의 환자에서 보고된 이상반응은 관절통, 코인두염, 세균뇨이었음. 시판 후 추가로 확인된 이상사례로 구토, 두드러기, 말초부종, 발진, 스티븐스-존슨증후군, 얼굴부종, 입술부기, 저혈당 반응, 혀장염, 폐렴이 보고되었으나, 불특정 다수의 인구집단에서 자발적으로 보고된 것이기 때문에 신뢰성 있는 발생빈도의 예측 및 약물과의 인과관계 확립은 일반적으로 가능하지 않음. **[최신 제품정보 개정일 2019.09.04]**

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LUMEN X / BIO X
4D Bio Printing System

Tel : 042) 483-3001
Fax : 042) 483-3005
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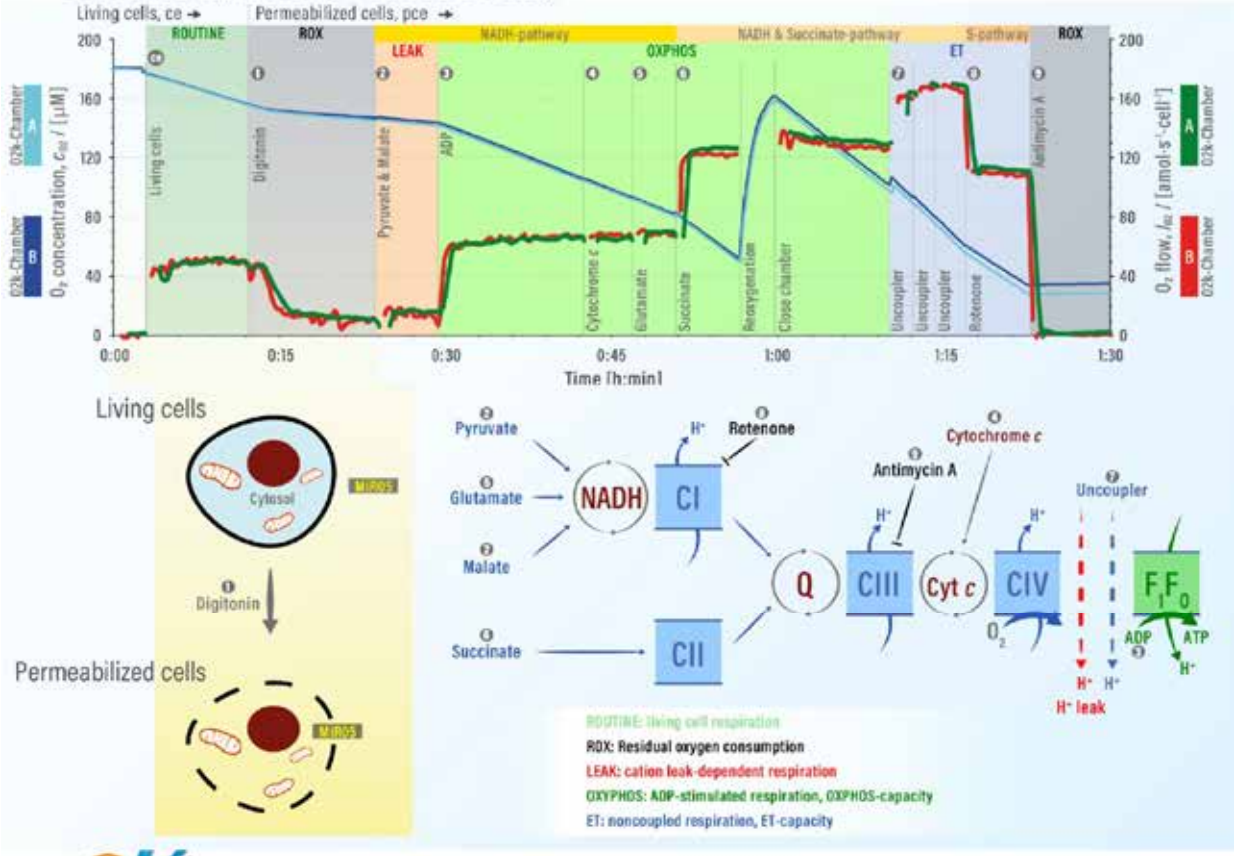
Homepage : doctorbio.or.kr

Oroboros O2k – Mitochondria and Cell Research

Oroboros O2k-SUIT protocol

2 chambers (A and B) - reproducibility



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Oxymax/CLAMS

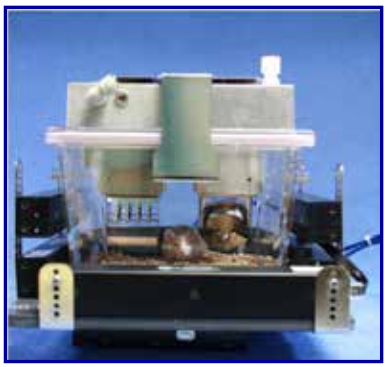
Comprehensive Lab Animal Monitoring system

24 Station CLAMS-CF
with two 12-station enclosures

Features

- **Activity**
  X,Y & Z axis monitoring
- **Feeding**
  Mass monitoring
- **Drinking**
  Volume & Lick detection
- **Running Wheel**
  Rotation Monitoring
- **Urine Collection**
  Mass monitoring and cooling
- **Food Access Control**
  Mass & Event monitoring
- **Environmental Control**
  of Temperature and Lighting
- **Calorimetric Assessment**
  by Oxymax
- **Environmental Monitoring**
  of Temperature and Humidity
- **Temperature & Heart Rate**
  By Telemetry

Home cage chamber



Urine chamber

Oxymax/CLAMS [Example data snippet form chamber]

Int	Ch	Date	VO2	O2 In	O2 Out	ΔO2	O2 Acc	VCO2	CO2 In	CO2 Out	ΔCO2	CO2 Acc	RER	Heat	V1
#	#	Time	ml/kg/h	%	%	%	ml	ml/kg/h	%	%	%	ml		Cal/h	L/m
19	01	7/19/06 16:00	4810	20.94	20.66	0.28	535.4	3239	0.043	0.281	0.237	422.3	0.816	0.5	0.597
20	01	7/19/06 16:18	4695	20.94	20.67	0.27	565.4	3804	0.043	0.273	0.230	446.7	0.810	0.5	0.597
21	01	7/19/06 16:35	4342	20.94	20.69	0.25	594.0	3483	0.043	0.253	0.210	469.7	0.802	0.5	0.597
22	01	7/19/06 16:53	4153	20.94	20.66	0.28	622.7	3918	0.043	0.280	0.237	493.1	0.824	0.5	0.597
23	01	7/19/06 17:10	4544	20.94	20.68	0.26	652.1	3592	0.043	0.260	0.217	516.0	0.787	0.5	0.597
24	01	7/19/06 17:28	3316	20.94	20.75	0.19	676.9	2852	0.043	0.215	0.172	537.1	0.860	0.3	0.597
25	01	7/19/06 17:45	3605	20.94	20.73	0.21	698.8	3130	0.044	0.233	0.189	556.0	0.868	0.4	0.597

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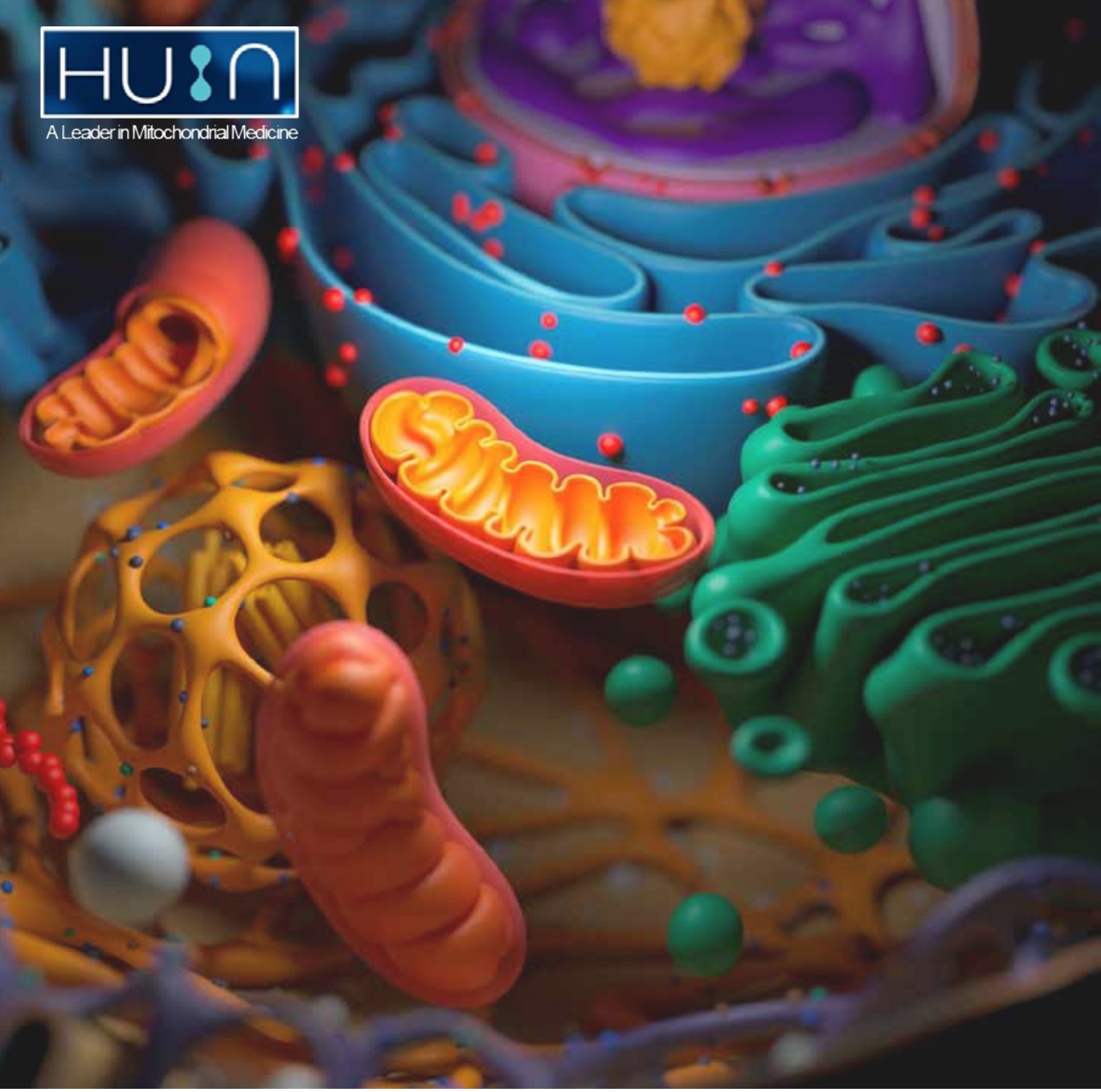
HUEN

A Leader in Mitochondrial Medicine



- Huen Co., Ltd. is a leader of mitochondrial medicine, and has differentiated R&D platform and pipelines.
- Huen is conducting research and development of therapeutic agents for diseases closely related to mitochondrial dysfunction such as metabolic diseases, degenerative diseases, cancer and rare diseases.

HUEN

VISIT
huenbio.com

SUWON, SOUTH KOREA
+82-31-8064-1611

EMAIL
ksseo@huenbio.com

CONTENTS

GREETING

Dear colleagues and friends,

Welcome to the KSMRM·KSMCB 2020! On behalf of the organizing committee, it is my great pleasure to share with you the most updated mitochondrial festival under the theme on “Ongoing Voyage of Exciting Research Communications On Mitochondrial Enigma (OVERCOME)” in the 14th Conference of the Korean Society for Mitochondrial Research and Medicine (KSMRM 2020) in conjunction with 11th Symposium of the Mitochondrial Section of Korean Society for Molecular and Cellular Biology (KSMCB 2020), which will be held on October 8th, 2020 at the Grand Josun Busan, Korea. The KSMRM·KSMCB 2020 is a joint venue between the KSMRM and the Mitochondrial section of KSMCB, and is held annually. It is our goal to expose participants to ground breaking mitochondrial research from renowned international scientists while providing a platform for young researchers to interact with the larger scientific community. This year’s program will focus on molecular aspects of mitochondria and diseases, mitochondria in inter- and intra-cellular communications, recent progress on mitochondria in biology and medicine and mitochondria as clinical focal points. The conference will consist of the main talk sessions combined with the presidential lecture by professor Minho Shong (Mitochondrial proteostasis), and poster sessions. All speakers are the top experts in the field of mitochondrial research and medicine. Your participation through exchanging ideas and in-depth discussions will be a great contribution to the success of the KSMRM·KSMCB 2020. I would like to strongly encourage young researchers to join our conference and enjoy this exciting ‘OVERCOME’.

Particularly, we are now on the global COVID-19 pandemic and fighting against it. Interestingly, the localization of viral RNA and proteins in mitochondria is important in SARS-CoV-2 pathogenesis and a hot issue of COVID-19 pathologies. An investigation into interaction between SARS-CoV-2 and host mitochondria will provide critical insights into to OVERCOME COVID-19.

I and the organizing committee will try to make it a memorable, scientific and social experience. I look forward to seeing you at the KSMRM·KSMCB 2020.

Yours sincerely,

한진

Jin Han, MD, PhD

President, Korean Society for Mitochondrial Research and Medicine

Chair, Mitochondrial Section of Korean Society for Molecular and Cellular Biolog

ORGANIZATION

Honorary President	Hong Kyu Lee (Honorary President of KSMRM, Advisor at PAEAN Biotechnology Inc.)
President	Jin Han (Inje University)
Vice President	Kyu-Sang Park (Yonsei University)
Secretary General	Byoung Heon Kang (UNIST)
Scientific Program	Seung-Jae V. Lee (KAIST)
Scientific Program Committee	Hail Kim (KAIST) Hyoung Kyu Kim (Inje University) Jun Namkung (Yonsei University)
Treasurer 1	Hyon-Seung Yi (Chungnam National University)
Treasurer 2	Jun Namkung (Yonsei University)
Treasurer 3	Hyeongseok Kim (Chungnam National University)
Clinical Research	Young-Mock Lee (Yonsei University)
Clinical Research Committee	Joon Won Kang (Chungnam National University) Koon Soon Kim (Chungnam National University) Sae Hoon Kim (Yonsei University) So Yong Um (Yonsei University) Ji hoon Lee (Sungkyunkwan Univerisity) Byung Chan Lim (Seoul National University)
Public Relation	Hyoung Kyu Kim (Inje University)
Planning	Chan Bae Park (Ajou University)
Auditor	In-Kyu Lee (Kyungpook National University) Jongkyeong Chung (Seoul National University) Minho Shong (Chungnam National University)
Directors	Hong Kyu Lee(Honorary President of KSMRM, Advisor at PAEAN Biotechnology Inc.), Myunghee Jung (Seoul National University), In-Kyu Lee (Kyungpook National University), Eun Bo Shim (Kangwon University), Ki-Up Lee(University of Ulsan), Hun Taeg Chung (University of Ulsan) , Minho Shong (Chungnam National University), Hongdeok Yun (Seoul National University), Kyong Soo Park (Seoul National University), Young Jun Seo(Seoul National University), Gyesoon Yoon (Ajou University), Young Kyu Ko(Korea Universtiy), Youngmi Kim Pak (Kyung Hee University), Young Hyun Yoo (Dong-A University), Soon Ha Kim (LG chem.), Myung-Shik Lee (Sungkyunkwan University), Jin Han (Inje University), Jung Jun Min (Jeonnam University), Sung Soo Kim (Kyung Hee University), Jongkyeong Chung (Seoul National University), YongKyung Choe (KRIBB), Young-Myeong Kim (Kangwon National University)

ORGANIZATION HISTORY

2006-2009

President	Hong Kyu Lee (Seoul National University)
Vice Presidents	Jin Han (Inje University)
	Ki-Up Lee (University of Ulsan)
Scientific Program	Youngmi Kim Pak (Kyung Hee University)
Secretary General/ Treasurer	Young Min Cho (Seoul National University)
Auditor	Cheol Min Kim (Pusan National University)
	Hyung-Ryong Kim (Wonkwang University)
President, ASMRM (2003-2005)	Hong Kyu Lee (Seoul National University)

2010-2014

President	Hong Kyu Lee (Seoul National University)
Vice President	Ki-Up Lee (University of Ulsan)
Secretary General	Jin Han (Inje University)
Scientific Program	Youngmi Kim Pak (Kyung Hee University)
Treasurer	Minho Shong (Chungnam National University)
Public Relation	Gyesoon Yoon (Ajou University)
Planning	Kyu-Sang Park (Yonsei University)
Auditor	Cheol Min Kim (Pusan National University)
	Hyung-Ryong Kim (Wonkwang University)

ASMRM 2013 ORGANIZING COMMITTEE

KSMRM President	Hong Kyu Lee (Eulji University, Korea)
Chairperson	Hong Kyu Lee (Eulji University, Korea)
	Bong Yun Cha (Catholic University, Korea)
General Chair	Minho Shong (Chungnam National University, Korea)
Secretary General	Kyu-Sang Park (Yonsei University, Korea)
Finance	Jin Han (Inje University, Korea)
Members	Eun Hee Koh (University of Ulsan, Korea)
	Gyesoon Yoon (Ajou University, Korea)
	Hyoung Kyu Kim (Inje University, Korea)
	Hyun Jin Kim (Chungnam National University, Korea)

	In Kyu Lee (Kyungpook National University, Korea)
	Inhee Mook-Jung (Seoul National University, Korea)
	Koon Soon Kim (Chungnam National University, Korea)
	Myung-Shik Lee (Sungkyunkwan University, Korea)
	Soo Lim (Seoul National University, Korea)
	Young Hyun Yoo (Dong-A University, Korea)
	Youngmi Kim Pak (Kyung Hee University, Korea)
Abstract Review Committee	Gyesoon Yoon (Ajou University, Korea)
	Jin Han (Inje University, Korea)
	Youngmi Kim Pak (Kyung Hee University, Korea)

2015-2017

President	Minho Shong (Chungnam National University)
Vice President	Jin Han (Inje University)
Secretary General	Kyu-Sang Park (Yonsei University)
Scientific Program	Chan Bae Park (Ajou University)
Treasurer	Eun Hee Koh (University of Ulsan)
Clinical Research	Young-Mock Lee (Yonsei University)
Clinical Research Committee	Joon Won Kang (Chungnam National University)
	Koon Soon Kim (Chungnam National University)
	Sae Hoon Kim (Yonsei University)
	So Yong Um (Yonsei University)
	Ji hoon Lee (Sungkyunkwan Univerisity)
	Byung Chan Lim (Seoul National University)
Public Relation	Hail Kim (KAIST)
Planning	Koon Soon Kim (Chungnam National University)
Auditor	In-Kyu Lee (Kyungpook National University)
	Jongkyeong Chung (Seoul National University)
President, ASMRM (2015-2016)	Myung-Shik Lee (Yonsei University)

2018

Honorary President	Hong Kyu Lee (Eulji University)
President	Minho Shong (Chungnam National University)
Vice President	Jin Han (Inje University)
Secretary General	Kyu-Sang Park (Yonsei University)
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	Byung Chan Lim (Seoul National University)
Public Relation	Hail Kim (KAIST)
Planning	Hyon-Seung Yi (Chungnam National University)
Auditor	In-Kyu Lee (Kyungpook National University)
	Jongkyeong Chung (Seoul National University)

ASMRM 2018 ORGANIZING COMMITTEE

KSMRM President	Minho Shong (Chungnam National University)
General Chair	Jin Han (Inje University)
Members	Chan Bae Park (Ajou University)
	Joong-Yeol Park (University of Ulsan)
	Eun-Kyeong Jo (Chungnam National University)
	Joon Won Kang (Chungnam National University)
	Gyesoon Yoon (Ajou University)
	Joo-Yeon Yoo (POSTECH)
	Hail Kim (KAIST)
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	Hyo-Bum Kwak (Inha University)
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	Hyoung Kyu Kim (Inje University)
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	Jeong Hyun Park (Inje University)
	Youngmi Kim Pak (Kyung Hee University)
	Jong Chul Won (Inje University)
	Young Min Cho (Seoul National University)
	Jongkyeong Chung (Seoul National University)
	Young-Mock Lee (Yonsei University)
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	Min-Xin Guan (Zhejiang University)

	Chii-Ruey Tzeng (Taipei Medical University Hosptial)
	Quan Chen (Chinese Academy of Sciences)
	Chin-San Liu (Changhua Christian Hospital)
	Soon Ha Kim (LG chem.)
	Hong Kyu Lee (Eulji University)
	Sung Soo Kim (Kyung Hee University)
	Hsin-Chen Lee (National Yang-Ming University)
	Yasutoshi Koga (Kurume University)
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	Ki-Up Lee (University of Ulsan)
	Yong Zhang (Tianjin University of Sport)
	Makoto Yoneda (Fukui Prefectural University)
	Young-Myeong Kim (Kangwon National University)
	Masashi Tanaka (Tokyo Metropolitan Institute of Gerontology)

2019

Honorary President	Hong Kyu Lee (Eulji University)
President	Minho Shong (Chungnam National University)
Vice President	Jin Han (Inje University)
Secretary General	Hail Kim (KAIST)
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	Hyoung Kyu Kim (Inje University)
Scientific Program	young Heon Kang (UNIST)
Treasurer	Hyon-Seung Yi (Chungnam National University)
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	Byung Chan Lim (Seoul National University)
Public Relation	Hail Kim (KAIST)
Planning	Hyon-Seung Yi (Chungnam National University)
Auditor	In-Kyu Lee (Kyungpook National University)
	Jongkyeong Chung (Seoul National University)

HISTORY

History

2006. 11. 18	Foundation of KSMRM (Korean Society for Mitochondrial Research and Medicine)
	First Conference of KSMRM, Seoul
2007. 02. 02-03	4th Conference of ASMRM (Asian Society for Mitochondrial Research and Medicine), Seoul
2007. 11. 16-17	2nd Conference of KSMRM, Busan
2009. 07. 24-25	3rd Conference of KSMRM in conjunction with Satellite symposia (Mitochondria as therapeutic targets in diseases) of International Union of Physiological Sciences (IUPS) 2009, Seoul
2010. 06. 19	4th Conference of KSMRM in conjunction with 1st Symposium of Mitochondrial Section of KSMCB (Korean Society for Molecular and Cellular Biology), Daejeon
2010. 09. 15	KSMRM Symposium, Seoul
2010. 10. 19	KSMRM Symposium, Busan
2011. 01. 10	KSMRM Symposium, Seoul
2011. 01. 15	Symposium of Mitochondrial Section of KSMCB, Suwon
2011. 03. 15	KSMRM Symposium, Seoul
2011. 05. 17	KSMRM Symposium, Busan
2011. 06. 07	KSMRM Symposium, Daegu
2011. 06. 18	5th Conference of KSMRM in conjunction with 2nd Symposium of Mitochondrial Section of KSMCB, Daegu
2012. 03. 10	KSMRM-Mitochondrial Section of KSMCB Joint Symposium, Seoul
2012. 05. 10	KSMRM-Mitochondrial Section of KSMCB- Korean Diabetes Association (KDA) Joint Symposium, Daegu
2012. 11. 23	6th Conference of KSMRM in conjunction with 3rd Symposium of Mitochondrial Section of KSMCB, Seoul
2013. 05. 09	KSMRM-Mitochondrial Section of KSMCB- Korean Diabetes Association (KDA) Joint Symposium, Jeju
2013. 05. 25	KSMRM-Mitochondrial Section of KSMCB Joint Symposium, Seoul
2013. 07. 11	Mitochondrial Section of KSMCB-Cardiovascular Metabolic Disease Center, Inje University Joint Symposium, Busan
2013. 11. 04-05	7th Conference of KSMRM in conjunction with 4th Symposium of Mitochondrial Section of KSMCB & 10th Conference of ASMRM, Seoul
2014. 05. 23	8th Conference of KSMRM in conjunction with 5th Symposium of Mitochondrial Section of KSMCB, Busan
2015. 06. 11	IMPACT (Integrative Medicine: Physical Activity is a Core Tip) 2015 Symposium of Mitochondrial Section of KSMCB, Suwon
2015. 11. 20	9th Conference of KSMRM in conjunction with 6th Symposium of Mitochondrial Section of KSMCB, Daejeon

2016. 12. 09-10	10th Conference of KSMRM in conjunction with 7th Symposium of Mitochondrial Section of KSMCB, Hoengseong
2017. 11. 09	11th Conference of KSMRM in conjunction with 8th Symposium of Mitochondrial Section of KSMCB, Daejeon
2018. 11. 07-08	12th Conference of KSMRM in conjunction with 9th Symposium of Mitochondrial Section of KSMCB & 15th Conference of ASMRM, Busan
2019. 06. 19	13th Conference of KSMRM in conjunction with 10th Symposium of Mitochondrial Section of KSMCB, Daejeon
2020. 10. 08	14th Conference of KSMRM in conjunction with 11th Symposium of Mitochondrial Section of KSMCB, Busan

PROGRAM

09:20 - 09:30	**Opening Address**
	Jin Han (President of KSMRM / Chair of Mitochondrial Section of KSMCB)

Session 1	**Molecular Aspects of Mitochondria and Diseases**
	Chairperson: Dongryeol Ryu (Sungkyunkwan University)
09:30 - 09:50	**Mapping the Mitochondrial Proteome in Aging and Disease**
	Jae Myoung Suh (KAIST)
09:50 - 10:10	**Mitochondrial Glutamine Transport and Cancer**
	Jung Min Han (Yonsei University)
10:10 - 10:30	**Mitochondria and Innate Host Defense**
	Eun-Kyeong Jo (Chungnam National University School of Medicine)
10:30 - 11:00	**Coffee Break (+Poster Viewing)**

Session 2	**Mitochondria in Inter-and Intra-Celluar Communications**
	Chairperson: Joo-Yeon Yoo (Pohang University of Science and Technology)
11:00 - 11:20	**Nuclear-encoded N-formylmethionyl Proteins in Cancer Cells**
	Cheol-Sang Hwang (Pohang University of Science and Technology)
11:20 - 11:40	**Caspase 9 is Essential for Autophagosome Maturation through Regulation of Mitochondrial Homeostasis**
	Seong-Woon Yu (DGIST)
11:40 - 12:00	**Evolutionary Relationship between Two Endosymbiotic Organelles, Mitochondria and Chloroplasts, Elucidated by the Protein Targeting Mechanisms**
	Inhwan Hwang (Pohang University of Science and Technology)
12:00 - 13:30	**Lunch**

Session 3	**Presidential Lecture**
	Chairperson: Myung-Shik Lee (Yonsei University College of Medicine)
13:30-14:10	**Cell Autonomous and Non-autonomous Regulation of Mitochondrial Proteostasis in Mammal**
	Minho Shong (Chungnam National University School of Medicine)

Session 4	Recent Progress on Mitochondria in Biology and Medicine
	In-Kyu Lee (Kyungpook National University)
14:10 - 14:30	**Stem Cells and Mitochondrial Diseases**
	Jae Ho Kim (Pusan National University)
14:30 - 14:50	**Lacation Improves Pancratic β Cell Mass and Function through Serotonin Production**
	Hail Kim (KAIST)
14:50 - 15:10	**Growth Differentiation Factor 15 Protects against Aging-mediated Systemic Inflammatory Response in Humans and Mice**
	Hyon-Seung Yi (Chungnam National University School of Medicine)
15:10 - 15:40	**Coffee Break (+Poster Viewing)**

Session 5	Mitochondria as Clinical Focal Points
	Chairperson: Young-Mock Lee (Yonsei University College of Medicine)
15:40 - 16:00	**Mitochondrial Diabetes and Mitochondrial DNA Mutant Load in MELAS**
	Hyun-Wook Chae (Yonsei University College of Medicine)
16:00 - 16:20	**Mitochondrial DNA Mutant Load of A3243G Mutation and Clinical Correlation in Neurology**
	Ha Neul Lee (Yonsei University College of Medicine)
16:20 - 16:40	**Effectivity and Safety of Corpus Callosotomy to Intractable Epilepsy of Mitochondrial Dysfunction**
	Ji-Hoon Na (Ewha Womans University College of Medicine)
16:40 - 17:00	**Closing Remarks**
	Chairperson: Hong Kyu Lee (Honorary President of KSMRM, Advisor at PAEAN Biotechnology Inc.)

VENUE

GRAND JOSUN BUSAN

292, Haeundae Haebyun-ro, Jung-dong, Haeundae-gu, Busan, Republic of Korea

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METRO Line 1	Line 1 Busan Station → Transit to Line 2 Seomyeon Station → Exit 3/5 on Haeundae Station → → Towards Haeundae Beach within a 10-minute walk Line 1 Nopo Station → Transit to Line 2 Seomyeon Station → Exit 3/5 on Haeundae Station → Towards Haeundae Beach within a 10-minute walk Line 1 Nopo Station → Transit to Line 3 Yeonsan Station → Transit to Suyeon Station → Exit 3/5 on Haeundae Station → Towards Haeundae Beach within a 10-minute walk
METRO Line 2	Line 2 Sasang Station → Exit 3/5 on Haeundae Station → Towards Haeundae Beach within a 10-minute walk
BUS	Express 1003(Busan Station) → Get off at Haeundae Hot Spring Intersection → Towards Haeundae Beach within a 6-minute walk → Hotel Express 1001(Busan Station) → Get off at Haeundae Station → Towards Haeundae Beach within a 14-minute walk → Hotel Express 1002(Nopo-dong Busan Central Bus Terminal) Get off at Centum Sensivill & transit to 100 / 115-1 / 200 / 39 / 141→ Get off at Haeundae Hot Spring Intersection → Towards Haeundae Beach within a 6-minute walk → Hotel 31(Seobu Intercity Bust Terminal) → Get off at Haeundae → Towards Haeundae Beach within a 6-minute walk → Hotel 307(Gimhae Airport) → Get off at Haeundae Beach → Hotel

SESSION 1

MOLECULAR ASPECTS OF MITOCHONDRIA AND DISEASES

Jae Myoung Suh, Ph.D.

Assistant Professor

Graduate School of Medical Science and Engineering, KAIST

291 Daehak-ro, Yuseong-gu, Daejon, Republic of Korea

Office 042-350-4247 Lab 042-350-4283 Mobile 010-4886-7146

jmsuh@kaist.ac.kr

EDUCATION

2006	Ph.D., Genetics and Development, University of Texas Southwestern Medical Center (2006) Advisor: Jonathan M. Graff, M.D., Ph.D.
1996	M.S., Biology, Yonsei University, Seoul, Korea (1996) Advisor: In Kwon Chung, Ph.D.
1994	B.S., Biology, Yonsei University, Seoul, Korea (1994)

EMPLOYMENT AND EXPERIENCES

2014-present	KAIST, Graduate School of Medical Science and Engineering, Assistant Professor
2009-2014	Salk Institute for Biological Studies, Research Associate Advisor: Ronald M. Evans, Ph.D.
2007-2008	University of Texas Southwestern Medical Center, Post-doctoral fellow Advisor: Jonathan M. Graff, M.D., Ph.D.
1999-2006	University of Texas Southwestern Medical Center, Graduate Research Assistant
1998-1999	Yonsei University, Research Assistant
1996-1998	Republic of Korea Army, Sergeant (compulsory service)
1996	Yonsei University, Research Assistant
1994-1996	Yonsei University, Graduate Teaching Assistant
1992	Rockefeller University, Summer Undergraduate Research Fellow

PUBLICATIONS

Kim, K.E., Park, I., Kim, J., Kang, M.G., Choi, W.G., Shin, H., Kim, J.S.*, Rhee, H.W.*, Suh, J.M.* (2020) Dynamic tracking and identification of tissue-specific secretory proteins in the circulation of live mice. In preparation (*co-corresponding author)

Son, M.J., Oh, K.J., Park, A., Kwon, M.G., Suh, J.M., Kim, I.C., Kim, S., Lee, S.C., Kim, W.K., Bae, K.H. (2020) GATA3 Induces the Upregulation of UCP-1 by Directly Binding to PGC-1α During Adipose Tissue Browning. Metabolism, 109, 154280

Kang, H.S., Lee, J.H., Oh, K.J., Lee, E.W., Han, B.S., Park, K.Y., Suh, J.M., Min, J.K., Chi, S.W., Lee, S.C., Bae, K.H., Kim, W.K. (2020) IDH1-dependent α-KG regulates brown fat differentiation and function by modulating histone methylation. Metabolism, 105, 154173.

Kim, H., Yoon, B.H., Oh, C.M., Lee, J., Lee, K., Song, H., Kim, E., Yi, K., Kim, M.Y., Kim, H., Kim, Y.K., Seo, E.H., Heo, H., Kim, H.J., Lee, J., Suh, J.M., Koo, S.H., Seong, J.K., Kim, S., Ju, Y.S., Shong, M., Kim, M., Kim, H. (2020) PRMT1 is Required for the Maintenance of Mature β Cell Identity. Diabetes, 69, 355-368.

Choi, S., Dong, B., Lin, C.J., Kim, K.H., Sun, Z., Wagner, M., Suh, J.M., Wang, M.C., Moore, D.D. (2020) Methyl-sensing nuclear receptor Liver Receptor Homolog-1 regulates mitochondrial function in mouse hepatocytes. Hepatology, 71, 1055-1069.

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Mapping the mitochondrial proteome in aging and disease

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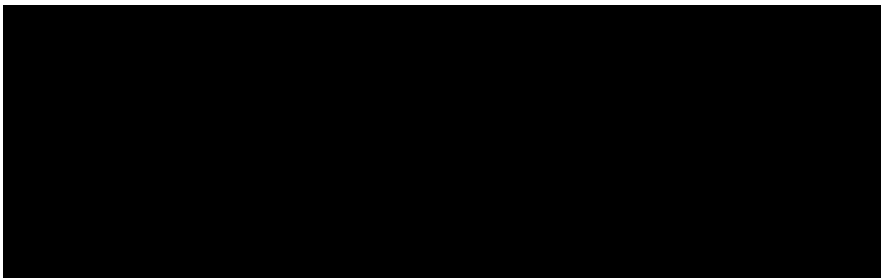
Aging entails a multifactorial sequence of changes across developmental time at the level of molecules, organelles, cells, tissues and systems. Within this complexity, metabolic alterations arise as a pervasive feature within the hierarchy of age-associated changes. Mitochondria stand at the center of metabolism and increasing evidence points to mitochondrial dysfunction as a driver of the aging process. As such, understanding the molecular changes that underlie mitochondrial dysfunction during aging is essential to clarify the link between aging and metabolism. However, robust methods to dissect molecular changes in mitochondria during organismal aging are lacking. Here we report the development of an in vivo tool to profile mitochondrial proteomes utilizing proximity labeling techniques. We generated transgenic mice which ubiquitously express mitoAPEX, an engineered peroxidase containing a mitochondrial matrix targeting sequence. Upon label activating conditions, mitoAPEX rapidly (<1 min) catalyzes production of biotin radicals which biotinylate proteins within a 20 nm radius. mitoAPEX transgenic mice expressed APEX in the mitochondrial matrix compartment of multiple tissues. Spot-ID analysis of biotinylated proteomes from proximity labeled mitoAPEX mouse tissues confirmed specific and efficient labeling of the mitochondrial proteome and tissue-specific patterns of the matrix proteome. We next characterized changes in the mitochondrial proteome during the aging process focusing on muscle tissues. Muscle mitochondrial proteome analysis from old and young mitoAPEX mice revealed significant changes in the quantity and composition of protein species. Of these, Reticulon 4 interacting Protein 1 (RTN4IP1), previously reported to be localized to the mitochondrial outer membrane, was found to be downregulated in muscle tissue of old mice. Furthermore, we have confirmed RTN4IP1 is present in the mitochondrial matrix and not in the outer membrane. We are currently characterizing the molecular function of RTN4IP1 in mitochondria along with its physiological role in muscle aging. Taken together, we have generated and validated the mitoAPEX mouse as a new tool to map dynamic changes of the mitochondrial proteome in vivo. The mitoAPEX mice will allow for detailed characterization of the aging mitochondrial proteome to gain new insight into the relationship between mitochondrial function, metabolism, and aging.

Keywords

mitochondria, proximity labeling, proteomics, muscle aging



Notes

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Education

1993 - 1997	B.S. in Life Science, POSTECH, Korea
1997 - 1999	M.S. in Life Science, POSTECH, Korea
1999 - 2002	Ph.D. in Division of Molecular and Life Sciences, POSTECH, Korea

Professional Experience

2002 - 2008	Principal Investigator, Imagene, Co. Ltd.
2008 - 2011	Research assistant professor, Research Institute of Pharmaceutical Sciences, Seoul National University
2011 - 2013	Research associate professor, Medicinal Bioconvergence Research Center, Seoul National University
2011 - 2013	Principal Investigator/Drug Screening group leader, Medicinal Bioconvergence Research Center, Seoul National University
2015 - 2017	Bioconvergence major chair, Integrated Science and Engineering Field, Underwood International College, Yonsei University
2013 - present	Associate professor, WCU Integrated OMICS for Biomedical Science, Yonsei University
2013 - present	Associate professor, College of Pharmacy, Yonsei University

Representative Publications

A Variant of SLC1A5 is a Mitochondrial Glutamine Transporter for Metabolic Reprogramming in Cancer Cells, Cell Metabolism, 31(2):267-283, 2020.

Glucose-dependent control of leucine metabolism by leucyl-tRNA synthetase 1, Science, 367(6474):205-210, 2020.

Non-translational function of Leucyl-tRNA synthetase regulates myogenic differentiation and skeletal muscle regeneration, Journal of Clinical Investigation,129(5): 2088-2093, 2019.

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Somatic mutations in TSC1 and TSC2 cause focal cortical dysplasia, American Journal of Human Genetics, 100, 454-472, 2017

Mitochondrial Glutamine Transport and Cancer

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Glutamine has a versatile role in cell metabolism, participating in ATP energy production, tricarboxylic acid (TCA) cycle supplementation and the biosynthesis of nucleotides, glutathione (GSH), and other nonessential amino acids. As knowledge of cancer metabolism has advanced, glutamine has been considered an important amino acid that supplies carbon and nitrogen to fuel biosynthesis. Thus, glutamine deprivation suppresses cancer growth and even induces cell death in many cancers. This metabolic dependency of transformed cells on glutamine constitutes the recently defined glutamine addiction. Despite the importance of mitochondrial glutamine metabolism, the mitochondrial glutamine transporter, encoded by a transcript variant of the SLC1A5 gene, which encodes a well-known plasma membrane glutamine transporter, was only recently discovered. A recent study provided a new perspective on mitochondrial glutamine metabolism, offering mechanistic insights into metabolic adaptation during tumor hypoxia, the emergence of drug resistance, and glutaminolysis-induced metabolic reprogramming, and presenting metabolic strategies to target glutamine metabolism in cancer cells. In this talk, we introduce the various biosynthetic and bioenergetic roles of glutamine based on mitochondrial compartmentalization of glutamine metabolism to explain why cells exhibit metabolic reliance on glutamine.

Keywords

mitochondria, glutamine, glutamine transport, metabolic reprogramming, Warburg effect

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Educational Background & Professional Experience

1991. 2.	M.D. from College of Medicine, Chungnam National University (CNU), Korea
1996. 2.	Ph.D. in Department of Microbiology, College of Medicine, CNU, Korea
1997 - 2003	Full-time instructor (1997-1999); Assistant Professor (1999-2003); Associate Professor (2003-2008), Dept. of Microbiology, College of Medicine, CNU
2003 - 2004	Research Associate, Imperial College London, U. K.
2008 - present	Professor, Dept. of Microbiology, College of Medicine, CNU
2007 - present	Director, Medical Research Center (ISNRC; i-MRC), CNU

Research Interest

- Autophagy and innate immune responses in mycobacterial infection
- Identification of new regulators and their molecular mechanisms in innate immune signaling
- Development of therapeutic modalities to control infection and inflammation

Selected Publications

Kim TS, Jo EK*, et al. SIRT3 promotes antimycobacterial defenses by coordinating mitochondrial and autophagic functions. Autophagy 2019; 17:1-20.

Kim JK, Jo EK*, et al. GABAergic signaling linked to autophagy enhances host protection against intracellular bacterial infections. Nat Commun. 2018 Oct 10;9(1):4184.

Kim SY, Jo EK*, et al. Estrogen-related receptor-alpha is a key coordinator of transcriptional and post-translational activation of autophagy to promote innate host defense. Autophagy 2018; 14(1):152-168.

Yuk JM, Jo EK*, et al. Orphan nuclear receptor ERRα controls macrophage metabolic signaling and A20 expression to negatively regulate TLR-induced inflammation. Immunity 2015 Jul;43(1):80-91.

Yang CS, Jo EK*, et al. Small heterodimer partner interacts with NLRP3 and negatively regulates activation of the NLRP3 inflammasome. Nat Commun. 2015 Feb 6;6:6115.

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Mitofusin-2 in Innate Host Defense against Bacterial Infection

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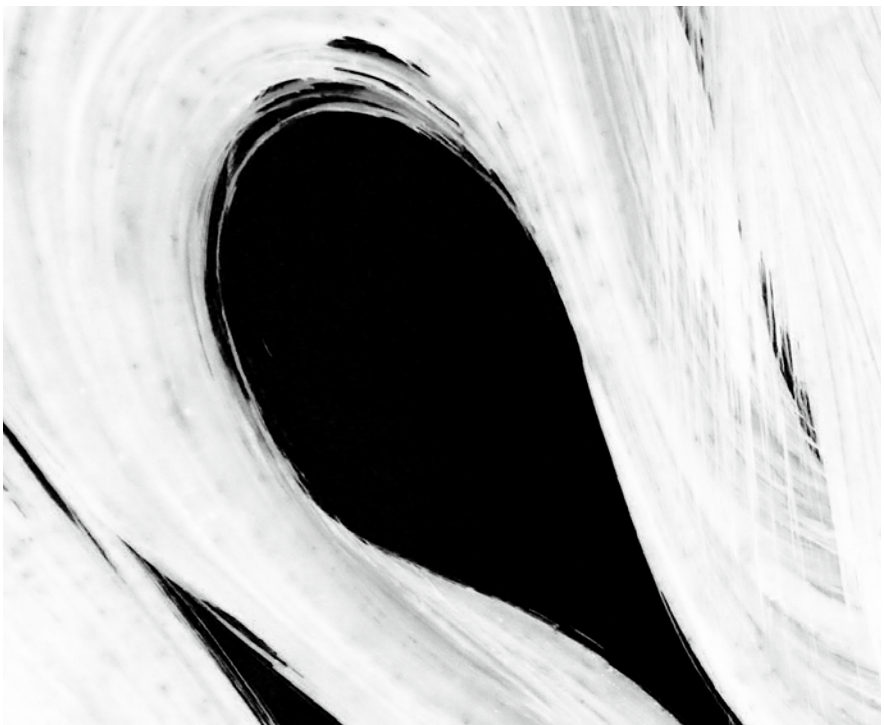
Mitochondria are the major energy powerhouses and orchestrate a variety of intracellular biological functions including metabolic homeostasis, inflammation, and innate immunity. Mitochondrial morphological changes by coordinated fission and fusion processes are critical for the removal of damaged mitochondria and keeping mitochondrial quality control. Mitochondrial dynamics is tightly controlled by the dynamin-related GTPases which constitute the core system of mitochondrial fusion and fission cycle. Imbalance of mitochondrial dynamics between fusion and fission is associated with various pathological responses and diseases including type 2 diabetes, Alzheimer disease, heart failure, and etc. Despite this, it remains largely unknown the functions/mechanisms of mitochondrial shaping proteins in modulating host antimicrobial innate defenses. Among the mitochondria-shaping proteins, we focused on the function of mitofusin 2 (Mfn2), because it was transcriptionally regulated by estrogen-related receptor-α, a crucial regulator of controlling inflammation and host defense. In this talk, I'll introduce our recent findings that Mfn2 plays a critical role in antimicrobial immune responses through regulation of immunometabolism and xenophagy during intracellular bacterial infection.

Keywords: mitochondria, mitofusin-2, innate host defense, immunometabolism, xenophagy



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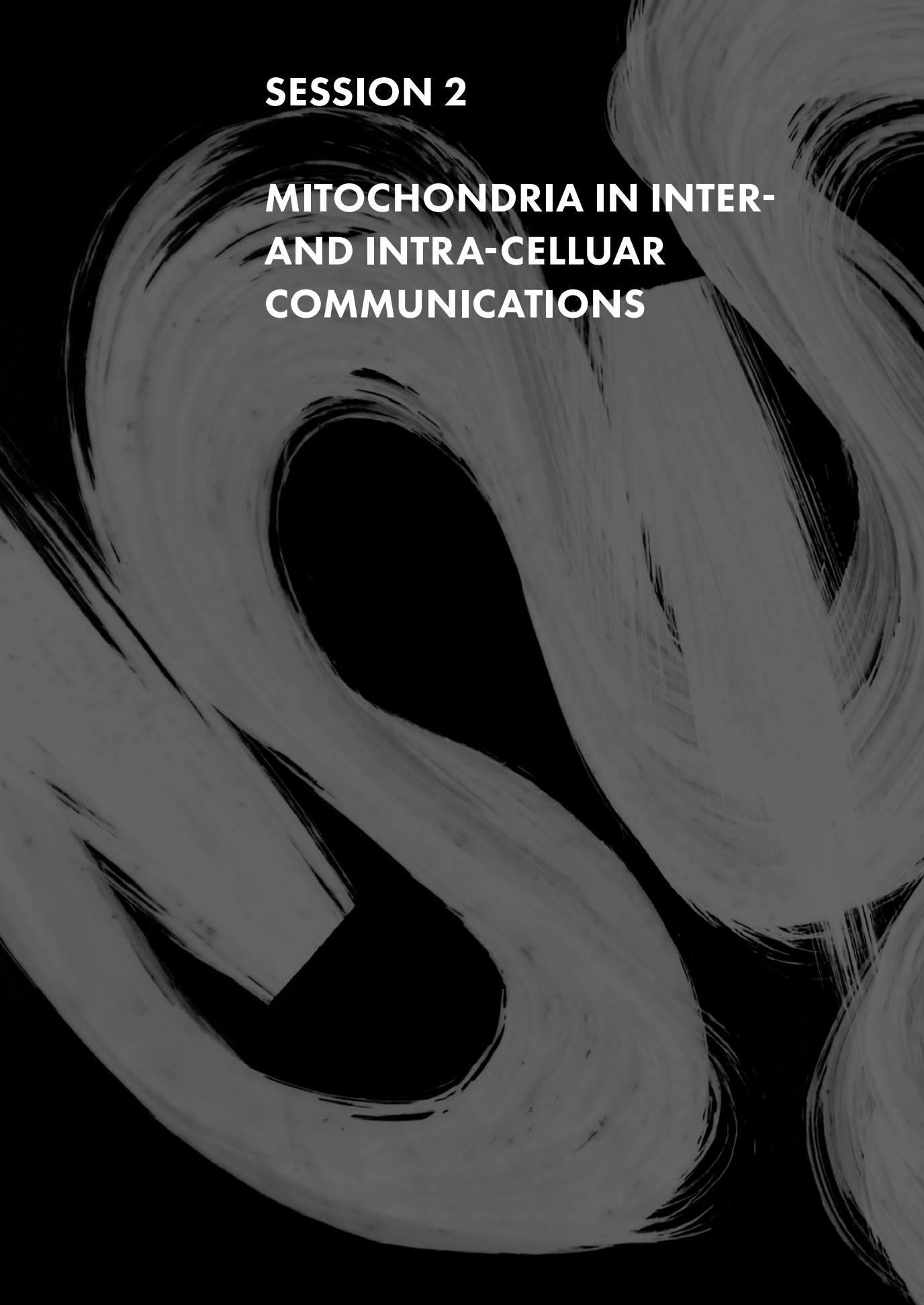

SESSION 2

MITOCHONDRIA IN INTER- AND INTRA-CELLUAR COMMUNICATIONS

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Education

1996-2000	Ph.D. Dept. of Biological Sciences, Seoul National University
1994-1996	M.Sc. Dept. of Microbiology, Seoul National University
1990-1994	B.Sc. Dept. of Microbiology, Seoul National University

Professional Experience

2020-present	Director, Leading Research Program, ProteoStasis Research Institute Muenjae Endowed-Chair Professor Professor, Dept. of Life Science, POSTECH
2015-2020	Associate Professor, Dept. of Life Sciences, POSTECH
2011-2015	Assistant Professor, Dept. of Life Sciences, POSTECH
2009-2011	Senior Staff Scientist, Div. of Biology, CALTECH
2003-2009	Post-doc, Div. of Biology, CALTECH
2000-2003	Post-doc, Dept. of Biological Sciences, SNU

Awards/Honors

2019	The 15th Kyung-Ahm Prize
2018	The 15th Macrogen Science Award
2016	The Top 30 Research Achievements in the POSTECH 30th Anniversary
2015	Postechian Award (Research Area)
2014	The Scientist of This Month Award, Korea Ministry of Science
2014	The Top 100 Achievements of National Research and Development
2013	The 4th POSCO TJ Park Science Fellowship for New Faculty

Research Interests	N-terminal acetylation and the N-degron pathways
	New ubiquitin code and signaling
	Formyl-methionine-mediated protein synthesis and degradation in eukaryotes
	Proteostasis in health and diseases

Representative Publications	Nguyen, K.T., Kim, J.-M., Park, S.-E., and Hwang. C.-S.* (2019) N-terminal methionine excision of proteins creates tertiary destabilizing N-degrons of the Arg/N-end rule pathway, J. Biol. Chem., 294(12):4464-4476.
	Nguyen, K.T., Lee, C.-S., Mun, S.-H, Truong, N.T., Park, S.K., and Hwang, C.-S.* (2019) N-terminal acetylation and N-end rule pathway control degradation of the lipid droplet protein PLIN2, J. Biol. Chem., 294(1):379-388.
	Kim, J.-M., Seok, O.-H., Ju, S., Heo, J.-E., Yeom, J., Yoo, J.-Y., Varshavsky, A., Lee, C*., and Hwang., C.-S.* (2018) Formyl-methionine as an N-degron of a eukaryotic N-end rule pathway, Science, 30; 362(6418).
	Park, S.-E.#, Kim, J.-M#., Seok, O.-H., Cho, H., Wadas, B., Kim, S.-Y., Varshavsky, A.* and Hwang C.-S.* (2015) Control of mammalian G protein signaling by N-terminal acetylation and the N-end rule pathway, Science, 347(6227):1249-1252. (*corresponding authors, #co-first authors).
	Kim, H.-K.#, Kim, R.-R.#, Oh., J.-H., Cho, H., Varshavsky, A.* and Hwang, C.-S.* (2014) The N-terminal methionine of cellular proteins as a degradation signal, Cell, 156:158-169. (*corresponding authors, #co-first authors).

Cytosolic Ribosomes of Eukaryotes Produce N-Terminally Formylated Proteins

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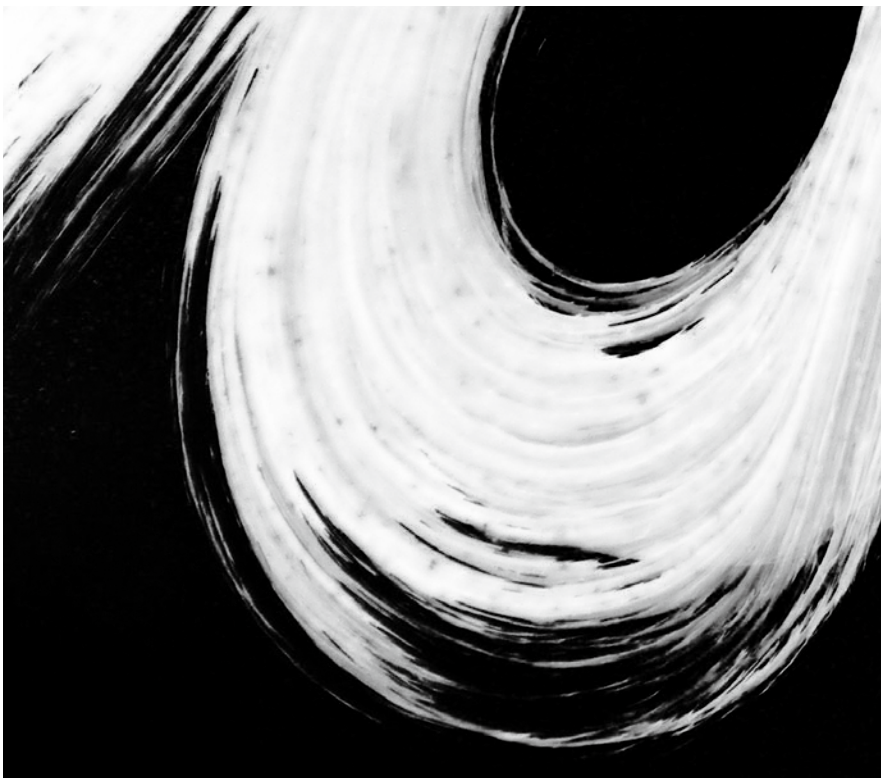
Formyl-methionine (fMet) of newly-made proteins is pre-created by methionyl-tRNA formyltransferases that attach a formyl group from 10formyltetrahydrofolate (10-fTHF) to the initiator MettRNAi. The fMet-driven protein synthesis was long-known to be confined to bacteria and eukaryotic mitochondria and plastids, whereas eukaryotic proteins are produced with unformylated Met by cytosolic ribosomes. Unlike this well-established assumption (without supporting unambiguous evidence), our previous study uncovered that the fMet-mediated protein synthesis also takes place even in the cytosol of the eukaryotic budding yeast Saccharomyces cerevisiae, due to a cytosolic location of mitochondrial Fmt1 formyltransferase upon stressful conditions including nutrient deprivation, and subsequent fMet-tRNAi production, which mediates the synthesis of Nt-formylated proteins in the cytosol. Despite the evident occurrence of fMet-mediated protein synthesis in the eukaryotic cytosol, its molecular details have not been explored thus far. Here we identify and characterize key components for the fMet-mediated translation by the cytosolic ribosomes in yeast and mammalian cells.

Keywords formyl-methionine, formyltransferase, mitochondria, ribosome, translation



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Educational Experience

1993.3 – 1999.2	Ph.D., Department of Microbiology, Seoul National University
1991.3 – 1993.2	M.S., Department of Microbiology, Seoul National University
1987.3 – 1991.2	B.S., Department of Microbiology, Seoul National University

Professional Experience

2016 – Present	Professor, Department of Brain and Cognitive Sciences, DGIST
2010 – 2016	Associated Professor, Department of Brain and Cognitive Sciences, DGIST
2016 – 2010	Assistant Professor, Department of Neurology and Ophthalmology, Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI
2000 – 2006	Post-doctoral fellow, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD

Academic Awards and Honors

2019	The Korean Society for Neuroglia Best Research Award
2008	Raymond B. Bauer Award by Michigan Parkinson Foundation
2004	Association of Korean Neuroscientists, President's Outstanding Research Award
2004	Cayman Chemicals Travel Award
1997	Research Promotion Grant for Young Researchers by Korea Research Foundation

Selected Publications

Younghwan Lee, Ji-Won Lee, Hyeri Nam, and Seong-Woon Yu. "Cx3cr1CreERT2-driven Atg7 deletion in adult mice induces intestinal adhesion." Molecular Brain 13:88 (2020)

Seonghee Jung, Hyeonjeong Jeong, and Seong-Woon Yu. "Autophagy as a decisive process for cell death." Experimental & Molecular Medicine 52:921-930 (2020)

Younghwan Lee, Youngjin Park, Hyeri Nam, Ji-Won Lee, and Seong-Woon Yu. "Translocator protein (TSPO): The new story of the old protein in neuroinflammation." BMB Reports 53:20-27 (2020)

Seonghee Jung, Seongwon Choe, Hangwoong Woo, Hyeonjeong Jeong, Hyun-Kyu An, Hye Young Ryu, Bo Kyoung Yeo, Ye Won Lee, Hyosun Choi, Ji Young Mun, Woong Sun, Han Kyoung Choe, Eun-Kyoung Kim, and Seong-Woon Yu. "Autophagic death of neural stem cells mediates chronic stress-induced decline of adult hippocampal neurogenesis and cognitive deficits." Autophagy 16:512-530 (2020)

Caroline Jeeyeon Hong, Jihye Yeon, Bo Kyoung Yeo, Hanwoong Woo, Hyun-Kyu An, Kyuhyung Kim, and Seong-Woon Yu. "Fas-apoptotic inhibitory molecule 2 localizes to the lysosome and facilitates autophagosome-lysosome fusion through the LC3 interaction region motif-dependent interaction with LC3." FASEB Journal 34:161-179 (2020)

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Seolsong Kim, Nayoun Kim, Seokjae Park, Yoonjeong Jeon, Jaemeun lee, Seung-Jun Yoo, Ji-Won Lee, Cheil Moon, Seong-Woon Yu, and Eun-Kyoung Kim. "Tanycytic TSPO inhibition induces lipophagy to regulate lipid metabolism and improve energy balance." Autophagy, Epub ahead of print (2020)

Sungwoong Jeon, Sangwon Kim, Shinwon Ha, Seungmin Lee, Eunhee Kim, So Yeun Kim, Sun Hwa Park, Jung Ho Jeon, Sung Won Kim, Cheil Moon, Bradley J. Nelson, Jin-Young Kim*, Seong-Woon Yu*, and Hongsoo Choi*. "Magnetically actuated microrobots as a platform for stem cell transplantation." Science Robotics 4:eaav4317 (2019) (*co-corresponding author)

Shinwon Ha, Seol-Hwa Jeong, Kyungrim Yi, Jamie Jeong-min Chu, and Seong-Woon Yu. "Autophagy mediates astrogenesis in adult hippocampal neural stem cells." Experimental Neurobiology 28:229-246 (2019)

Ji-Won Lee, Hyeri Nam, Leah Eunjung Kim, Yoonjeong Jeon, Hyunjung Min, Shinwon Ha, Younghwan Lee, Seon-Young Kim, Sung Joong Lee, Eun-Kyoung Kim, and Seong-Woon Yu. "TLR4 (toll-like receptor 4) activation suppresses autophagy through inhibition of FoxO3 and impairs phagocytic capacity of microglia." Autophagy 15:753-770 (2019)

Hyunhee Park, Kyung Min Chung, Hyun-Kyu An, Ji-Eun Gim, Jihyun Hong, Hanwoong Woo, Bongki Cho, Cheil Moon, and Seong-Woon Yu. "Parkin promotes mitophagic cell death in adult hippocampal neural stem cells following insulin withdrawal." Frontiers in Molecular Neuroscience 12:46 (2019)

Hyo Min Cho, Jae Ryun Ryu, Youhwa Jo, Tae Woong Seo, Ye Na Choi, Jee Min Chung, Bongki Cho, Ho Chul Kang, Seong-Woon Yu, Soon Ji Yoo, Hyun Kim, and Woong Sun. "Drp1-Zip1 interaction regulates mitochondrial quality surveillance system." Molecular Cell 73:1-13 (2019)

Hanwoong Woo, Caroline Jeeyeon Hong, Seonghee Jung, Seongwon Choe, and Seong-Woon Yu. “Chronic restraint stress induces hippocampal memory deficits by impairing insulin signaling.” Molecular Brain 11:37 (2018)

Jae Yeon Kim, Ameer Rasheed, Seung-Jun Yoo, So Yeun Kim, Bongki Cho, Gowoon Son, Seong-Woon Yu, Keun-A Chang, Yoo-Hun Suh, and Cheil Moon. “Distinct amyloid precursor protein processing machineries of the olfactory system.” BBRC 495:533-538 (2017)

Shinwon Ha, Seol-Hwa Jeong, Kyungrim Yi, Kyung Min Chung, Caroline Jeeyeon Hong, Seong Who Kim, Eun-Kyoung Kim, and Seong-Woon Yu. “Phosphorylation of p62 by AMP-activated protein kinase (AMPK) mediates autophagic cell death in adult hippocampal neural stem cells.” Journal of Biological Chemistry 292:13795-13808 (2017)

Seung-Jun Yoo, Ji-Hye Lee, So Yeun Kim, Gowoon Son, Jae Yeon Kim, Bongki Cho, Seong-Woon Yu, Keun-A Chang, Yoo-Hun Suh, and Cheil Moon. “Differential spatial expression of peripheral olfactory neuron-derived BACE1 induces olfactory impairment by region-specific accumulation of β-amyloid oligomer” Cell Death and Disease 8; e2977 (2017)

Min-Seok Kim, Geun-Hee Lee, Yong-Min Kim, Byoung-Wook Lee, Hae-Yun Nam, U-Cheol Sim, Suk-Jung Choo, Seong-Woon Yu, Jae-Joong Kim, Yunhee Kim Kwon, and Seong Who Kim. “Angiotensin II causes apoptosis of adult hippocampal neural stem cells and cognitive impairment through the activation of AMPK-PGC1α signaling in heart failure.” Stem Cells Translational Medicine 6:1491-1503 (2017)

Caspase 9 is essential for autophagosome maturation through regulation of mitochondrial homeostasis

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CASP9 (caspase 9) is a well-known initiator caspase which triggers intrinsic apoptosis. Recent studies also suggest various non-apoptotic roles of CASP9, including autophagy regulation. However, the involvement of CASP9 in autophagy and its molecular mechanisms are not well understood. Here we report the non-apoptotic function of CASP9 in positive regulation of autophagy through maintenance of mitochondrial homeostasis. Growth factor or amino acid deprivation-induced autophagy activated CASP9, but without apoptotic features. Pharmacological inhibition or genetic ablation of CASP9 decreased autophagy flux, while ectopic expression of CASP9 rescued autophagy defects. In CASP9 knockout (KO) cells, initiation and elongation of phagophore membranes were normal, but sealing of the membranes and autophagosome maturation were impaired, and the lifetime of autophagosomes was prolonged. Ablation of CASP9 caused an accumulation of inactive ATG3 and decreased lipidation of the Atg8-family members, most severely that of GABARAPL1. Moreover, it resulted in abnormal mitochondrial morphology with depolarization of the membrane potential, reduced reactive oxygen species production, and aberrant accumulation of mitochondrial fusion-fission proteins. CASP9 expression or exogenously added H2O2 in the CASP9 KO cells corrected the ATG3 level and lipidation status of Atg8-family members, and restored autophagy flux. Of note, only CASP9 expression but not H2O2 rescued mitochondrial defects, revealing regulation of mitochondrial homeostasis by CASP9. Our findings suggest a new regulatory link between mitochondria and autophagy through CASP9 activity, especially for the proper operation of the Atg8-family conjugation system and autophagosome closure and maturation.

Keywords

autophagosome maturation, caspase 9, mitochondria, reactive oxygen species

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Education

1977.3 - 1981.2	Seoul National University, Department of Chemistry, BS
1981.3 - 1983.2	Seoul National University, Department of Chemistry, M
1984.8 - 1988.12	University of North Carolina-Chapel Hill, Department of Biochemistry, PhD
1988.9 - 1993.8	Harvard Medical School, Genetics Department, Post-doctoral training

Work-related experiences

1993.10 - 1999.9	Geyongsang National University, Assistant and Associate professor
1999.10 - current	Pohang University of Science and Technology, Associate and Full professor
1998.9 - 2007.8	Director, Center of Protein trafficking in Plants, POSTECH
2008.9 - 2010.8	Chairman, Department of Life Science, POSTECH
2008.9 - 2013.8	Chairman, Division of Integrative Biosciences and Biotechnology, POSTECH
2008.9	Director, Genetic engineering Center
2019.8 - current	Chief Scientist, Beijing Forestry University, China

Awards and Honors

1998	The association of Korean Scientists: best paper award (Biochemistry)
2004	The association of Korean Scientists: best paper award (Plant Biology)
2005	Ilmac cultural foundation award (Science area)
2007	Postechian award (Science area)
2008	Inchon Foundation award (Science area)
2010	Postech contribution award
2011	Postech fellow
2015	Best scientist award in year 2015, Korean Society of Plant Biologists
2016	Presidential Award of Korea
2017	Presidential Award of Korean Society of Molecular and Cell Biologists
2018	Special Scientific Achievement Award, Rural Development Agency, Korea
2019	Award for Industrial contribution from Vice Prime minister and Minister of Education

Research Areas

- Intracellular trafficking in plant cells
- Organelle biogenesis and communication between organelles
- ABA metabolism and signaling
- Development of plant cells as a bioreactor system

List of publications

- Razzak MA, Lee JM, Lee DW, Kim JH, Yoon HS, and Hwang I (2019) Expression of seven carbonic anhydrases in red alga Gracilariopsis chorda and their subcellular localization in a heterologous system, Arabidopsis thaliana. Plant Cell Reports 38(2):147-159.
- Park Y, An DJ, Choe S, Lee Y, Park M, Park S1 Gu S, Min K, Kim NH, Lee S, Kim JK, Kim HY, Sohn EJ, Hwang I (2019) Development of recombinant protein-based vaccine against classical swine fever virus in pigs using transgenic Nicotiana benthamiana. Frontiers in Plant Science 10:624.
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Evolution of chloroplasts and mitochondria: a new look through a window of the cellular system, protein targeting mechanism

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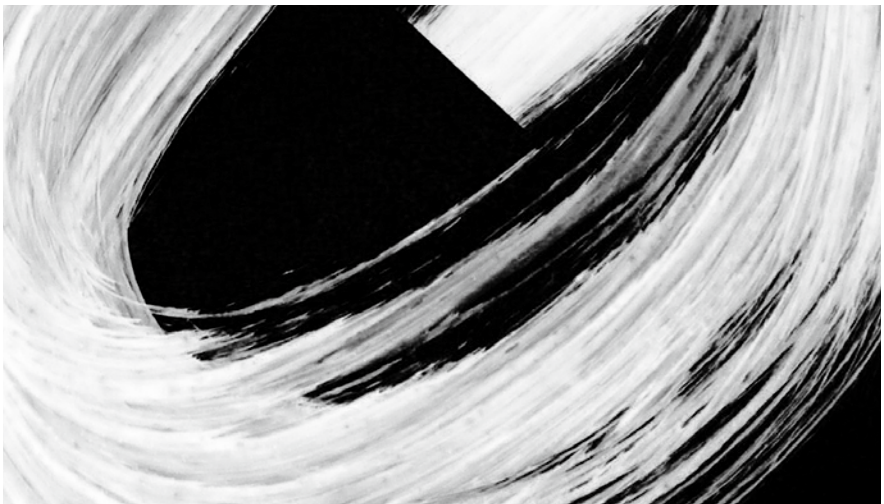
One of most fascinating questions in biology is how the current form of eukaryotic cells with many different types of organelles has arisen during evolution. Of these organelles, chloroplasts and mitochondria are thought to be derived from two bacteria, cyanobacterium and α-proteobacterium, respectively. For their conversion to organelles, the most critical event for successful endosymbiosis should have been the establishment of protein targeting mechanisms from the host cell to the endosymbionts. These mechanisms should have been established after reflecting cellular conditions of the host cell to ensure specific targeting of proteins to new organelles, implying that protein targeting mechanisms may contain a clue to reveal the evolutionary process of the target organelles. In this talk, I will present evidence that the targeting signals of outer membrane proteins have a hierarchical ranking of the ER, chloroplasts and mitochondria. The targeting signal, presequence, of mitochondrial proteins might have been generated by fusion of the targeting signal, transit peptide, of chloroplasts with a bacterial targeting signal. This kind of relationship in the targeting signals was conserved among three different types of organisms, animals, plants and yeasts.

Keywords

Evolution of eukaryotic cells, chloroplast and mitochondria, endosymbiotic conversion, targeting mechanism, organelles



SESSION 3

PRESIDENTIAL LECTURE

Minho Shong, M.D., Ph.D.

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Educational background & professional experience

1980.03 - 1986.02	College of Medicine, Chungnam National University	B.A. Degree
1987.03 - 1989.02	Postgraduate School, Chungnam National University	Master Degree
1992.03 - 1998.08	Postgraduate School, Chungnam National University	Ph. D
1994.10 - 1999.03	Chungnam National University School of Medicine	Assistant professor
1999.04 - 2004.03	Chungnam National University School of Medicine	Associate professor
2004.06 - present	Chungnam National University School of Medicine	Professor
2013.01 - 2015.11	Chungnam National University School of Medicine	Dean
2016.11 - 2019.12	Chungnam National University Hospital	President

Research interests

Endocrine Metabolism

Publications

Choi MJ, Jung SB, Lee SE, Kang SG, Lee JH, Ryu MJ, Chung HK, Chang JY, Kim YK, Hong HJ, Kim H, Kim HJ, Lee CH, Mardinoglu A, Yi HS, Shong M. An adipocyte-specific defect in oxidative phosphorylation increases systemic energy expenditure and protects against diet-induced obesity in mouse models. Diabetologia. 2020 Apr;63(4):837-852. IF;7.113

Jung SB, Choi MJ, Ryu D, Yi HS, Lee SE, Chang JY, Chung HK, Kim YK, Kang SG, Lee JH, Kim KS, Kim HJ, Kim CS, Lee CH, Williams RW, Kim H, Lee HK, Auwerx J, Shong M. Reduced oxidative capacity in macrophages results in systemic insulin resistance. Nature Communications. 2018 Apr;9(1):1551. IF:11.878

Lee SE, Kang SG, Choi MJ, Jung SB, Ryu MJ, Chung HK, Chang JY, Kim YK, Lee JH, Kim KS, Kim HJ, Lee HK,Yi HS, Shong M. Growth Differentiation Factor 15 Mediates Systemic Glucose Regulatory Action of T-Helper Type 2 Cytokines. Diabetes. 2017 Nov;66(11):2774-2788. IF;7.199

Chung HK, Ryu D, Kim KS, Chang JY, Kim YK, Yi HS, Kang SG, Choi MJ, Lee SE, Jung SB, Ryu MJ, Kim SJ, Kweon GR, Kim H, Hwang JH, Lee CH, Lee SJ, Wall CE, Downes M, Evans RM, Auwerx J, Shong M. Growth differentiation factor 15 is a myomitokine governing systemic energy homeostasis. Journal of Cell Biology. 2017 Jan;216(1):149-165. IF; IF;8.891

Kim SJ, Kwon MC, Ryu MJ, Chung HK, Tadi S, Kim YK, Kim JM, Lee SH, Park JH, Kweon GR, Ryu SW, Jo YS, Lee CH, Hatakeyama H, Goto Y, Yim YH, Chung J, Kong YY, Shong M. CRIF1 is essential for the synthesis and insertion of oxidative phosphorylation polypeptides in the mammalian mitochondrial membrane. Cell Metabolism. 2012 Aug;16(2):274-83. IF:22.415

Interorgan Coordination of Organ-specific Mitoribosomal Stress Response

Minho Shong

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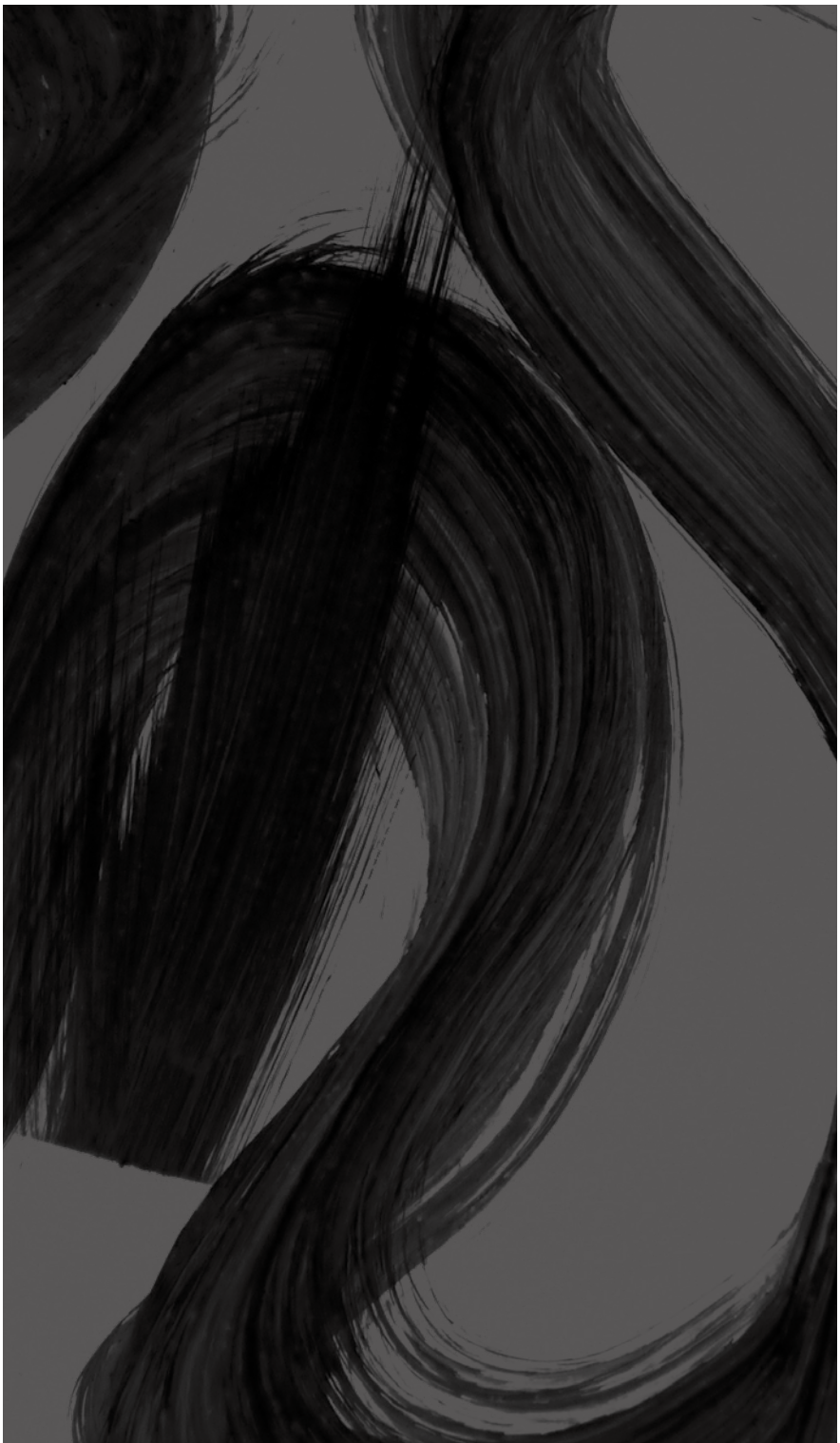
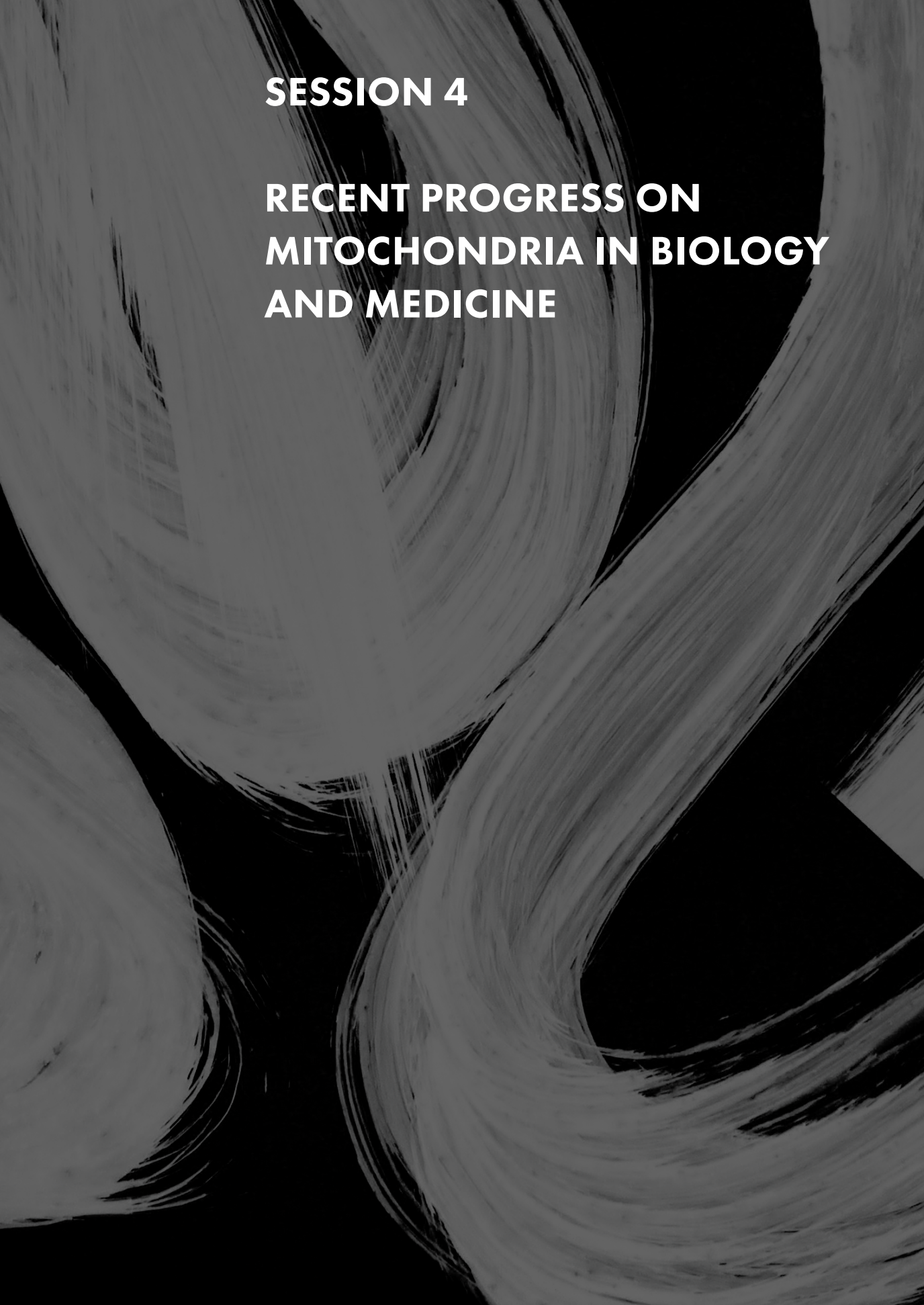
Mitoribosome is essential in cell viability, growth, differentiation and function.(Greber and Ban, 2016; Ott et al., 2016). Loss or mutations of any of the 78 proteins in mitoribosomal components might affect the mitoribosomal RNA processing and produce human mitochondrial disorders (Sylvester et al., 2004). In fact, the expression of genes encoding for mitoribosomal proteins (MRPs), mitoribosome assembly factors and mitochondrial translation factors is modified in numerous diseases (De Silva et al., 2015) (Kim et al., 2017a). Mutations of the single component of MRPs frequently do not fully inactivate mitoribosomal function resulting diminished oxidative phosphorylation capacity. Although all of the MRPs genes are candidate for primary mitochondrial disease, but only a small numbers of MRPs mutations (MRPL9, MRPL27, MRPL45) manifest diabetes (Sylvester et al., 2004). These findings indicate that the mutations of MRPs may also manifest in a tissue-specific manner that give rise to a spectrum of disorders including diabetes. Surprisingly, it has been demonstrated that linkage of MRPs with organismal lifespan (Houtkooper et al., 2013). These observations suggest that functional expression level of MRPs may affect tissue homeostasis and organismal health.

Reduced mitochondrial electron transport chain activity promotes longevity and improves energy homeostasis via cell-autonomous and –non-autonomous factors in multiple model systems. This mitohormetic effect is thought to involve the mitochondrial unfolded protein response (UPRmt), an adaptive stress-response pathway activated by mitochondrial proteotoxic stress. Using mice with skeletal muscle–specific deficiency of Crif1 (muscle-specific knockout [MKO]), an integral protein of the large mitoribosomal subunit (39S), we identified growth differentiation factor 15 (GDF15) as a UPRmt-associated cell–non-autonomous myomitokine that regulates systemic energy homeostasis. MKO mice were protected against obesity and sensitized to insulin, an effect associated with elevated GDF15 secretion after UPRmt activation.

To identify the differential effects of mitokines, GDF15 and FGF21 on the metabolic phenotype of adipocyte-specific Crif1 (also known as Gadd45gip1) knockout (AdKO) AdKO mice, we generated AdKO mice with global Gdf15 knockout (AdGKO) or global Fgf21 knockout (AdFKO). Under high-fat diet conditions, AdKO mice were resistant to weight gain and exhibited higher EE and improved glucose tolerance. In vivo genetic inhibition of OxPhos in adipocytes significantly upregulated mitochondrial unfolded protein response-related genes and secretion of mitokines such as GDF15 and FGF21. We evaluated the metabolic phenotypes of AdGKO and AdFKO mice, revealing that GDF15 and FGF21 differentially regulated energy homeostasis in AdKO mice. Both mitokines had beneficial effects on obesity and insulin resistance in the context of decreased adipocyte OxPhos, but only GDF15 regulated EE in AdKO mice.

Our data from AdGKO mice fed an HFD for 8 weeks revealed that long-term induction of GDF15 in AdKO mice attenuated progression of obesity in this context through increased EE. Our findings in AdFKO mice suggested that prolonged induction of FGF21 in AdKO mice did not affect EE, but remarkably ameliorated HFD-induced obesity and insulin resistance. The present study demonstrated that the muscle and adipose tissue adaptive mitochondrial stress response affected systemic energy homeostasis via cell-autonomous and non-cell-autonomous pathways.





SESSION 4

RECENT PROGRESS ON MITOCHONDRIA IN BIOLOGY AND MEDICINE

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Current Positions

2013 - present	PNU BK21 Plus Biomedical Science Education Center, Director
2015 - present	Department of Physiology, School of Medicine, Pusan National University, Chair

Professional Experience

1997 - 1999	POSTECH, Dept of Life Science	Post-doctoral fellow
1999 - 2002	Johns Hopkins University, School of Medicine	Post-doctoral fellow
2002 - 2006	Pusan National University, School of Medicine	Assistant professor
2006 - 2011	Pusan National University, School of Medicine	Associate professor
2011 - present	Pusan National University, School of Medicine	Full professor
2009 - 2010	University of Virginia, School of Medicine	Visiting professor
2013 - 2015	Pusan National University, School of Medicine	Director for research affairs
2014 - 2016	National Research Foundation	Review board member

Honors & Awards

March 2016	The 15th Busan Science and Technology Award (Society for Busan Science and Technology)
Dec 2015	Academic Research Award (Biomedical Research Center, PNUH)
Oct 2011	Yudang Academic Science Award (Korean Physiological Society)
May 2011	Dongchun the Best Investigator Award (Korean Society for Biochemistry and Molecular Biology)
May 2011	Research Award for Basic Biomedical Science (Basic Biomedical Science Society)
Feb 2009	Blue Ribbon Lecture Award (Korean Society for Molecular & Cellular Biology)
Dec 2008	The Best Research Award (Pusan National University Hospital)

Patents and Publications or Major research achievements

Jeon, E. S. et al. (2008) A Rho Kinase/MRTF-A-Dependent Mechanism Underlies the Sphingosylphosphorylcholine-Induced Differentiation of Mesenchymal Stem Cells into Contractile Smooth Muscle Cells. Circ. Res. 103(6):635-42.

Choi, Y. H. et al. (2015) Injectable PLGA microspheres encapsulating WKYMVm peptide for neovascularization. Acta Biomater. 25:76-85.

Seo, E. J. et al. (2016) Autotaxin regulates maintenance of ovarian cancer stem cells through lysophosphatidic acid-mediated autocrine mechanism. Stem Cells, 34(3):551-64.

Woo, S. J. et al. (2016) Synthesis and Characterization of Water-Soluble Conjugated Oligoelectrolytes for Near-Infrared Fluorescence Biological Imaging. ACS Appl Mater Interfaces. 8(25):15937-47.

Heo, S. C. et al. (2017) Formyl Peptide Receptor 2 is Involved in Cardiac Repair after Myocardial Infarction Through Mobilization of Circulating Angiogenic Cells. Stem Cells. 35(3):654-665.

Kwon, Y. W. et al. (2017) N-acetylated proline-glycine-proline accelerates cutaneous wound healing and neovascularization by human endothelial progenitor cells. Sci Rep. 7:43057

Kim, B. S. et al. (2018) 3D cell printing of in vitro stabilized skin model and in vivo pre-vascularized skin patch using tissue-specific extracellular matrix bioink: A step towards advanced skin tissue engineering. Biomaterials, 168:38-53

Stem cells and mitochondrial diseases

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Mitochondrial dysfunction is known to be responsible for a number of human diseases. Recent studies have shown that direct transfer of healthy mitochondria can restore the function of cells with mitochondrial dysfunction. Therefore, preparation of healthy mitochondria is great significance for therapy of mitochondrial diseases. In order to isolate a large number of mitochondria, in this study, human mesenchymal stem cells (MSC) and human embryonic stem cells-derived cardiomyocytes (hESC-CM) were used as donor cells for mitochondria transfer. MSC was isolated from human tonsil tissues, and hESC-CM was produced by inducing differentiation of H9 human embryonic stem cells. The mitochondria in hESC-CM exhibited highly organized tubular structures containing elongated cristae compared with that in MSC. The mitochondria isolated from hESC-CM and MSC could be transferred to recipient MSC in vitro. The mitochondria-transferred recipient MSC exhibited increased mitochondrial number and membrane potential. These results suggest that MSC and hESC-CM could be good donor cells for mitochondrial transfer and therapy of mitochondrial diseases.

Keywords

mitochondria, stem cells, differentiation, mitochondrial diseases, mitochondria tranfer

Notes

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EDUCATION

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Feb. 2002	Ph. D., Yonsei University

JOB EXPERIENCE

1998 – 2001	Teaching and Research Assistant, Yonsei University College of Medicine, Korea
2001 – 2002	Research Fellow, Yonsei University College of Medicine, Korea
2002 – 2005	Investigator, Armed Forces Medical Institute of Korea (mandatory military service)
2005 – 2009	Instructor / Assistant Professor, Yonsei University College of Medicine, Korea
2006 – 2011	Postdoctoral Fellow, Diabetes Center, University of California San Francisco, USA
2011 –	Assistant / Associate Professor, GSMSE, KAIST, Daejeon, Korea

AWARDS AND HONORS

Richard Wunsch Medical Prize for Young Investigator, Korean Academy of Medical Sciences, 2004

Postdoctoral Fellowship, Juvenile Diabetes Research Foundation, USA, 2007~2009

Young Investigator Travel Grant Awards, 69th ADA Scientific Session, New Orleans, USA, 2009

Advanced Postdoctoral Fellowship, Juvenile Diabetes Research Foundation, USA, 2010~2013

Yonkang Medical Paper Academic Award, Yonkang Foundation, Korea, 2011

PUBLICATIONS

Park HS, Kim HZ, Park JS, Lee J, Lee SP, Kim H, Ahn CW, Nakaoka Y, Koh GY, Kang S. β-Cell-Derived Angiopoietin-1 Regulates Insulin Secretion and Glucose Homeostasis by Stabilizing the Islet Microenvironment. Diabetes. 2019 Apr;68(4):774-786.

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Kim J, Kim H, Noh SH, Jang DG, Park SY, Min D, Kim H, Kweon HS, Kim H, Aum S, Seo S, Choi CS, Hail Kim, Kim JW, Moon SJ, Gee HY, Lee MG. Grasp55-/- mice display impaired fat absorption and resistance to high-fat diet-induced obesity. Nat Commun. 2020 Mar 17;11(1):1418.

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Lactation improves pancreatic β cell mass and function through serotonin production

Joon Ho Moon[1,2], Hyeongseok Kim[1,3], Hyunki Kim[1], Jungsun Park[1], Wonsuk Choi[1], Wongun Choi[1], Hyun Jung Hong[4], Hyun-Joo Ro[5], Sangmi Jun[5], Sung Hee Choi[2], Minho Shong[4], Nam Han Cho[6], Hak Chul Jang[2], and Hail Kim[1]

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Pregnancy imposes a substantial metabolic burden on women through weight gain and insulin resistance. Lactation reduces the risk of maternal postpartum diabetes, but the mechanisms underlying this benefit are unknown. Here, we identified long-term beneficial effects of lactation on β cell function, which last for years after the cessation of lactation. We analyzed metabolic phenotypes including β cell characteristics in lactating and non-lactating humans and mice. Lactating and non-lactating women showed comparable glucose tolerance at 2 months after delivery, but after a mean 3.6 years, glucose tolerance in lactated women had improved compared to non-lactated women. In humans, the disposition index, a composite insulin secretory function of β cells considering the degree of insulin sensitivity, was higher in lactated women at 3.6 years after delivery. In mice, lactating mice had improved glucose tolerance and increased β cell mass compared to non-lactating mice at 3 weeks after delivery. During lactation, increased plasma prolactin induces serotonin production in β cells. Secreted serotonin stimulated β cell proliferation through serotonin receptor 2B in an autocrine/paracrine manner. Amelioration of glucose tolerance and insulin secretion was maintained up to 4 months after delivery in lactated mice. Glucose tolerance and insulin secretion was impaired in β cell-specific Tph1 or Htr2b knockout (KO) mice during lactation. In addition, intracellular serotonin acted as an antioxidant to mitigate oxidative stress and improved β cell survival. Taken together, our results suggest that serotonin mediates the long-term beneficial effects of lactation on female metabolic health by increasing β cell proliferation and reducing oxidative stress in β cells.

Notes

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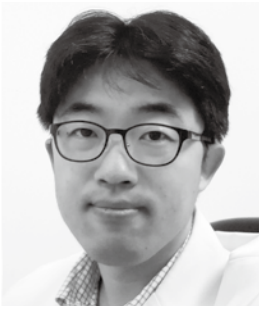

학력 / 경력

2006	가천의과대학교 의학과 학사
2011	가천의과대학교 내과학 석사
2015	카이스트 의과학대학원 의과학 이학박사
2017	충남대학교병원 내분비/전임의, 진료교수, 임상교수
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연구관심분야

근감소증/골다공증, 지방간 및 간섬유화, 면역학

주요연구실적

1. Growth differentiation factor 15 protects against the aging-mediated systemic inflammatory response in humans and mice Aging Cell. 2020 Jul 21;e13195. (Corresponding author)
2. An adipocyte-specific defect in oxidative phosphorylation increases systemic energy expenditure and protects against diet-induced obesity. Diabetologia. 2020 Apr;63(4):837-852. (Corresponding author)
3. Implications of Mitochondrial Unfolded Protein Response and Mitokines: A Perspective on Fatty Liver Diseases. Endocrinol Metab (Seoul). 2019 Mar;34(1):39-46. (First author and Corresponding author)
4. T cell senescence contributes to abnormal glucose homeostasis in humans and mice. Cell Death Dis. 2019 Mar 13;10(3):249. (First author and Corresponding author)
5. The mitochondrial unfolded protein response and mitohormesis: a perspective on metabolic diseases. J Mol Endocrinol. 2018 Oct;61(3):R91-95 (First author)
6. GDF15 deficiency exacerbates chronic alcohol- and carbon tetrachloride-induced liver injury. Sci Rep. 2017 Dec 8;7(1):17238 (Corresponding author)
7. Growth Differentiation Factor 15 Mediates Systemic Glucose Regulatory Action of T Helper Type 2 Cytokines. Diabetes. 2017 Nov;66(11):2774-2788. (Corresponding author)

Growth differentiation factor 15 protects against the aging-mediated systemic inflammatory response in humans and mice

Ji Sun Moon[1,2,†], Ludger J. E. Goeminne[3,†], Jung Tae Kim[1,2,†], Dongryeol Ryu[4,*], Hyon-Seung Yi[1,2,*]

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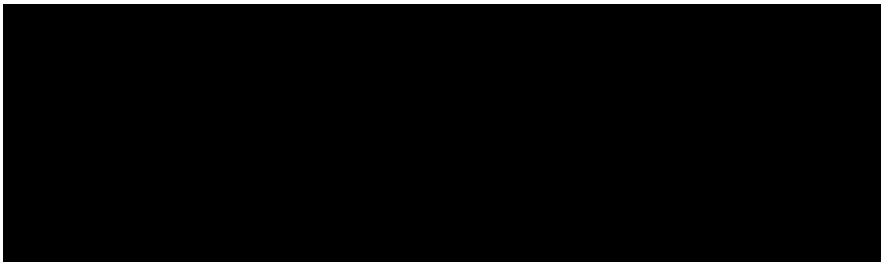
Mitochondrial dysfunction is associated with aging-mediated inflammation. Growth differentiation factor 15 (GDF15) is a major mitokine generated in response to mitochondrial stress and dysfunction; however, the implications of GDF15 to the aging process are poorly understood in mammals. In this study, we identified a link between mitochondrial stress-induced GDF15 production and protection from tissue inflammation on aging in humans and mice. We observed an increase in serum levels and hepatic expression of GDF15 in elderly subjects. In the BXD mouse reference population, mice with metabolic impairments and shorter survival were found to exhibit higher hepatic Gdf15 expression. Mendelian randomization links reduced GDF15 expression in human blood to increased body weight and inflammation. GDF15 deficiency promotes tissue inflammation by increasing the activation of resident immune cells in metabolic organs, such as in the liver and adipose tissues of 20-month-old mice. Aging also results in more severe liver injury and hepatic fat deposition in Gdf15-deficient mice. Although GDF15 is not required for Th17 cell differentiation, GDF15 contributes to regulatory T-cell-mediated suppression of conventional T-cell activation and inflammatory cytokines. Taken together, these data reveal that GDF15 is indispensable for attenuating aging-mediated local and systemic inflammation, thereby maintaining glucose homeostasis and insulin sensitivity in humans and mice.

Keywords

mitochondria, GDF15, aging, senescence, inflammation



OVERCOME

Ongoing Voyage of Exciting Research Communications On Mitochondrial Enigma

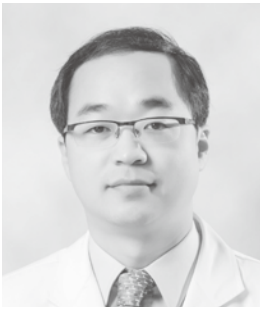
KSMCB 2020

11th Symposium of the Mitochondrial Section of KSMCB

2020.10.8.
THURSDAY
GRAND JOSUN BUSAN

SESSION 5

MITOCHONDRIA AS CLINICAL FOCAL POINTS



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학력

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2019	연세대학교 의학과 박사

경력

2010-2014	강남세브란스병원 임상조교수
2014- 현재	강남세브란스병원 조교수

연구실적

2019 SCI 공동 Incidence and Prevalence of Central Precocious Puberty in Korea: An Epidemiologic Study Based on a National Database. J Pediatr.3.890

2018 SCI 공동 Effect of the Orally Active Growth Hormone Secretagogue MK-677 on Somatic Growth in Rats. Yonsei Med J 1.564

2018 국내 교신 Visceral fat thickness and its associations with pubertal and metabolic parameters among girls with precocious puberty. Ann Pediatr Endocrinol Metab

2018 SCI 공동 A New Integrated Newborn Screening Workflow Can Provide a Shortcut to Differential Diagnosis and Confirmation of Inherited Metabolic Diseases Yonsei Med J 1.564

2017 국내 교신 Insulin resistance and bone age advancement in girls with central precocious puberty Ann Pediatr Endocrinol Metab.

2017 SCI 공동 Risk of Gonadoblastoma Development in Patients with Turner Syndrome with Cryptic Y Chromosome Material. Kwon A, Hyun SE, Jung MK, Chae HW, Lee WJ, Kim TH, Kim DH, Kim HS. 2017 Mar 27. [Epub ahead of print] Horm Cancer. 3.167

2016 SCI 공동 Assessment of myocardial function in elite athlete's heart at rest - 2D speckle tracking echocardiography in Korean elite soccer players. Eun LY, Chae HW. 2016 Dec 22;6:39772. Sci Rep. 5.228

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Mitochondrial diabetes and mitochondrial DNA mutation load in MELAS syndrome

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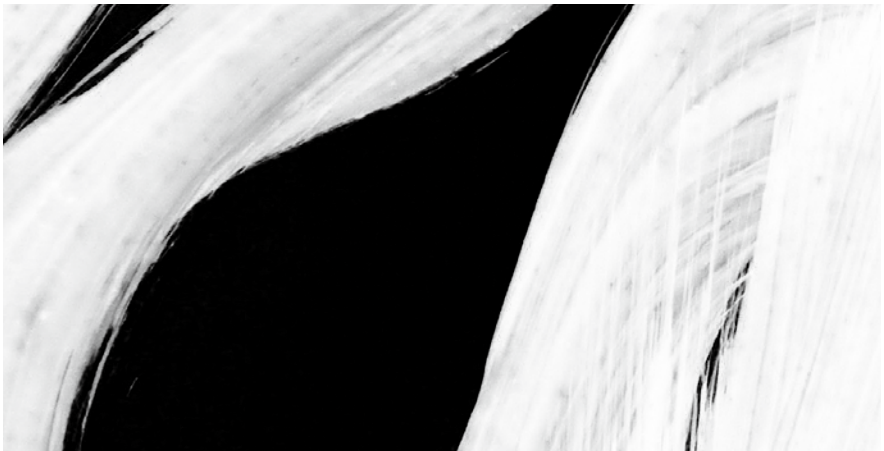
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a very rare condition; it encompasses a diverse group of disorders including diabetes. Phenotypic variability can be attributed to heteroplasmy along with varying proportions of mutant and wild type mitochondrial DNA (mtDNA). To examine the clinical relationship between mitochondrial diabetes and mutational load, we analyzed the mtDNA of children and young adolescents with MELAS syndrome using next generation sequencing (NGS).

Of 57 subjects with suspected MELAS syndrome, 32 children and young adolescents were diagnosed as MELAS syndrome with mtDNA A-to-G transition at nucleotide 3243. Mutation load studies and NGS were performed for 25 subjects. The mean mutation load was 60.4 $\pm$ 18.4 % (range 22.5–100). Of the 25 subjects with NGS results, 15 (60%) were diagnosed with DM and 2 (8%) were diagnosed with impaired glucose tolerance (IGT). The mutational load of subjects inversely correlated with first symptom onset, age at diagnosis of MELAS syndrome, and DM ($P<0.001$). However, mutational load did not correlate with the clinical severity or progression of DM/IGT. There was no significant difference in insulin resistance or sensitivity indices between the low- and high-mutation load groups. During the 3.7 years of follow-up, insulin resistance indices were not significantly different between baseline and follow-up.

We can infer that the mutation load in the MELAS syndrome is significantly associated with the onset of symptoms and associated diseases, including mitochondrial diabetes. However, it may not influence disease progression.

Keywords

mitochondrial diabetes, mitochondria, mutation load, mitochondrial DNA, MELAS syndrome



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Clinical fellowship in Pediatric Neuromuscular disorders program, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

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Research

Clinical research in pediatric neuromuscular and mitochondrial disorders

Mitochondrial DNA mutant load of A3243G mutation and its clinical correlation

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Background: Mitochondrial disorders are a group of genetically and clinically heterogenous disorders resulting from mutations in the nuclear or mitochondrial DNA (mtDNA), causing dysfunction, and resultant defective energy production. Among them, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is one of the most commonly inherited types of encephalopathy of maternal origin; that occurs through mutation in mtDNA. MELAS is characterized by ongoing and degenerative disease course because of recurrent stroke-like episodes and associated neurologic sequelae, involvement of other non-neurologic organs including the heart, kidney, gastrointestinal system, endocrine system, and even psychological issues. Around ~80% of MELAS patients harbor one specific mutation in mtDNA, A to G transition of tRNA gene for leucine (UUR) at nucleotide position 3243. Disease-causing mtDNA mutations are heteroplasmic, which implies that normal and mutant mitochondria are mixed within the same cells. The level of heteroplasmy, or in other words, mutant load, can vary in affected individuals, which contributes to extreme clinical variability. Several previous studies have investigated the natural history and disease progression of the MELAS syndrome, yet correlation between mtDNA mutant load and disease progression in MELAS is not completely understood. Therefore, I aimed to investigate the levels of blood mtDNA A3243G mutant load at the time of genetic diagnosis via next generation sequencing (NGS) technology of patients confirmed to have pathogenic A3243G mutation, and then to investigate the correlation of blood mtDNA mutant load and functional scale changes over time to reflect disease progression in MELAS. I also investigated the correlation, especially with respect to the neurological and muscular aspects in consideration of recurrent stroke-like episodes.

Methods: I performed whole mitochondrial DNA sequencing by NGS on samples from 57 patients with clinical suspicions of MELAS syndrome. Among them, 32 patients were confirmed to have mtDNA A3243G mutation. Finally, 25 patients who met the clinical critieria for MELAS, had mtDNA A3243G mutation and blood samples available for mtDNA mutant load analysis at the same time, were recruited for final inclusion. I collected the demographics and clinical data by retrospective electronic medical chart review. I applied functional scales that were previously published and validated in several other studies, including modified Rankin Scale (mRS), The Newcastle Paediatric Mitochondrial Disease Ratings Scale (NPMDS), and The Newcastle Mitochondrial Disease Adult Scale (NMDAS). As these scales contain large number of questions and with wide score range, especially NPMDS and NMDAS,

I modified and simplified the questions from these questionnaires and designed functional scales for the current study. Function_total, Neuromuscular_total, and Non-neuromuscular_total are 3 simplified and modified versions. I applied these 6 functional scales for 25 MELAS patients at 4 different time points during the disease progression – symptom onset, first year, second stroke-like episode and the last visit. Then I analyzed the correlation between the mtDNA mutant load at genetic diagnosis and obtained changes in functional scale over time. P-value <.05 was considered statistically significant.

Results: Quantitative analysis of mtDNA mutant load at genetic diagnosis via NGS method revealed the mean mutant load of 60.2±18.8% (22.5-100). I investigated the association between the mtDNA mutant load at genetic diagnosis and clinical variables, and functional scale changes at 4 different time points to reflect the degenerative disease course of MELAS. This study revealed that the mutant load at genetic diagnosis inversely correlated with age of symptom onset, age at seizure onset, and age at first clinical and MRI-confirmed stroke-like episode (all P<.0001, respectively). The mtDNA mutant load also negatively correlated with worse abnormality in MRS study and maximal serum lactic acidosis level (P=0.0032 and P=0.0007, respectively). When I analyzed the correlation between mtDNA mutant load and functional scales, the mtDNA mutant load did not significantly correlate with any of the 6 functional scales. When I looked further into each time point, Function_total correlated positively at symptom onset (r=0.5476, P=0.0046) but this trend did not persist through disease progression. Neuromuscular_total did not correlate significantly at symptom onset but it correlated positively with significance at the last visit (r=0.4418, P=0.027). Therefore, I further investigated the changes in functional scales in between each time point and their correlation with the mutant load, and I found that the changes in Neuromuscular_total (Δ) during disease progression (symptom onset – year 1- 2nd stroke-like episode – last visit or symptom onset – year 1 – last visit or symptom onset – 2nd stroke-like episode – last visit) all correlated positively with significance (r=0.5075, P=0.0096; r=0.532, P=0.0062; and r=0.4698, P=0.0178, respectively). When I investigated further to examine if this trend continued with increase in disease duration by 1 month, the trend was consistent with statistical significance (r=0.4284, P=0.0326, r=0.428, P=0.0328, r=0.4012, P=0.0468, respectively).

Conclusion: In conclusion, the blood mtDNA mutant load obtained at the time of genetic diagnosis (earlier in the disease course and close to first clinical stroke-like episode) in clinically symptomatic patients who were confirmed to have a mtDNA A3243G pathogenic mutation with a genetic diagnosis, the higher mutant load the earlier symptom onset, seizure onset, and stroke-like episode age, reflected worse clinical severity from the beginning. In addition, even though previously validated functional scales of mRS, NPMDS, and NMDAS reflect changes with time in these population with significance, yet they do not correlate with blood mutant load at genetic diagnosis. However, modified and simplified versions of Neuromuscular_total reflected disease progression with significant correlation with blood mutant load, which may enable better clinical decision making and provisions for expected counseling in these patients. The current study data was limited by the lack of validity of the modified and simplified versions of our functional scales which need further validation with a larger number of mitochondrial disease patients, and not only those with MELAS.

Keywords

MELAS; mitochondrial disease; A3243G mutation; mutant load; heteroplasmy; neuromuscular function

Notes

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2015 - 2018	B.A., Department of Statistics, Korea National Open University, Seoul, Korea
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Membership and Certification

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2016 -	Membership in Korea Society of Pediatric Critical Care Medicine
2017 -	Membership in Korea Society of Medical Genetics and Genomics
2017 -	Membership in Korea Society of Health informatics and Statistics
2018 -	Membership in Korean Child Neurology Association
2018 -	Membership in Korean Epilepsy Society

Major Publications

The Clinical Significance of Serum Ferritin in Pediatric Non-Alcoholic Fatty Liver Disease. Pediatric Gastroenterology, Hepatology & Nutrition 17/4 :248-256,2014

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Effective application of corpus callosotomy in intractable epilepsy patients with mitochondrial dysfunction

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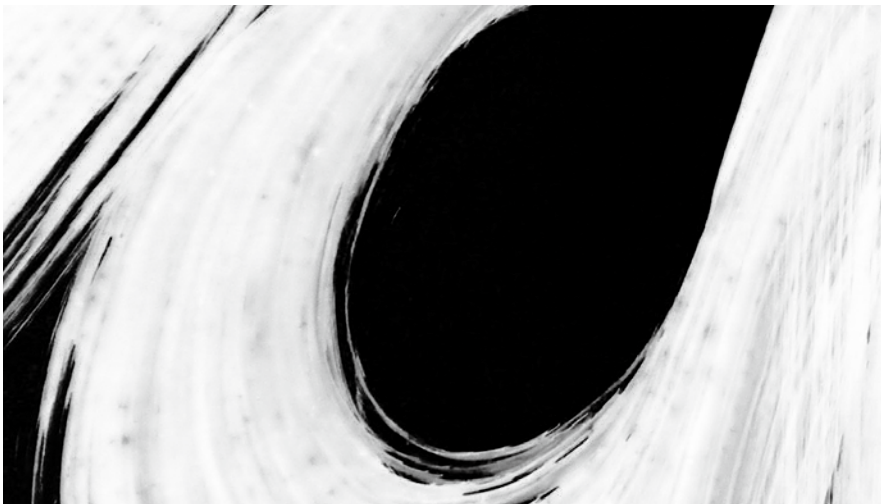
Whether epilepsy surgery such as corpus callosotomy is effective in patients with intractable epilepsy with mitochondrial dysfunction is controversial and there is rare literature about this issue. This study aimed to assess and describe the effective application of corpus callosotomy for treating patients with intractable epilepsy with mitochondrial dysfunction in a single institution in Korea. This was a retrospective study of patients with intractable epilepsy with mitochondrial dysfunction who underwent corpus callosotomy in a single tertiary care center. Ten patients with intractable epilepsy with mitochondrial dysfunction were included and ten patients with intractable epilepsy with non-mitochondrial dysfunctions were included as a control group. Outcomes of corpus callosotomy of the two groups were evaluated and compared. Corpus callosotomy was safely performed and was efficacious in reducing seizure frequency in both groups. The group with non-mitochondrial dysfunction showed slightly better treatment outcomes, with greater reductions in overall seizures, traumatic falling seizures, and EEG improvements, but the differences in treatment effects were not statistically significant. Our study is meaningful as it identified the use of corpus callosotomy as a means to save lives and improve quality of life by reducing the frequency of seizures and those associated with traumatic falling in patients with intractable epilepsy with mitochondrial dysfunction. Larger and multicenter studies are necessary to confirm the efficacy of the procedure.

Keywords

corpus callosotomy, mitochondrial dysfunction, epilepsy, epilepsy surgery, seizure



POSTER PRESENTATION

P01

Tetrahydrobiopterin regulated cardiac energy metabolism in diabetic hearts

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Diabetic cardiomyopathy (DCM) is a major cause of mortality/morbidity in diabetes mellitus patients. Although tetrahydrobiopterin (BH4) shows therapeutic potential as an endogenous cardiovascular target, its effect on myocardial cells and mitochondria in DCM and the underlying mechanisms remain unknown. Here, we determined the involvement of BH4 deficiency in DCM and the therapeutic potential of BH4 supplementation in a rodent DCM model. We observed a decreased BH4:total biopterin ratio in heart and mitochondria accompanied by cardiac remodeling, lower cardiac contractility, and mitochondrial dysfunction. Prolonged BH4 supplementation improved cardiac function, corrected morphological abnormalities in cardiac muscle, and increased mitochondrial activity. Proteomics analysis revealed oxidative phosphorylation (OXPHOS) as the BH4-targeted biological pathway in diabetic hearts as well as BH4-mediated rescue of downregulated peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α) signaling as a key modulator of OXPHOS and mitochondrial biogenesis. Mechanistically, BH4 bound to calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2) and activated downstream AMP-activated protein kinase/cAMP response element binding protein/PGC-1α signaling to rescue mitochondrial and cardiac dysfunction in DCM. These results suggest BH4 as a novel endogenous activator of CaMKK2.

Keywords

CaMKK2 / diabetic cardiomyopathy / mitochondria / PGC-1α / tetrahydrobiopterin

P02

Dual modulation of the mPTP and redox signaling synergistically promotes cardiomyocyte differentiation from pluripotent stem cells

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Concomitant increase of myofibrils and mitochondria is a key process of cardiomyocyte differentiation from pluripotent stem cells (PSCs). Specifically, development of mitochondrial oxidative metabolic capacity in cardiomyocytes is essential to providing the energy necessary to sustain the beating function. Therefore, the connection between transcriptional and metabolic regulation is important for cardiomyocyte specification and differentiation, and a nucleus-mitochondria interaction is required to translate signals that regulate cardiomyogenesis.
Although previous studies reported that mitochondrial function and oxidative metabolism have some correlation with the differentiation of cardiomyocytes, the mechanism by which mitochondrial oxidative metabolism is regulated and the link between cardiomyogenesis and mitochondrial function are still poorly understood. Additionally, reactive oxygen species modulate the differentiation of cardiomyocytes from embryonic stem cells (ESCs), but the exact role of redox signaling in PSC-derived cardiomyocyte differentiation remains controversial.
In this study, we demonstrate that Cyclosporin A (CsA) promotes differentiation of functional cardiomyocytes from mouse ESC-derived Flk1+ mesodermal precursor cells (MPCs) by inhibition of mitochondrial permeability transition pore (mPTP). This increase in differentiation appears to result from activation of mitochondrial oxidative metabolism. In addition, we found that antioxidant treatment augmented the cardiomyogenic effect of CsA. These data thus constitute novel evidence that activation of mitochondrial oxidative metabolism via inhibition of mPTP and subsequent changes in redox signaling pathways are contributing factors in PSC fate determination toward the cardiac lineage.

Keywords

mitochondria, oxidative, cardiomyocyte, differentiation, mPTP, CsA

P03

Oligosaccharyl transferase in C. elegans that maintains ER homeostasis and p38-dependent immunity against pathogenic bacteria

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The oligosaccharyl transferase (OST) protein complex regulates stability, activity, and localization of substrate proteins in the endoplasmic reticulum (ER) by modulating the N-linked glycosylation of its substrates. Although many OST substrate proteins have been identified, the physiological role of the OST complex is relatively unexplored. Here we show that the OST complex in C. elegans maintains ER protein homeostasis and immunity against pathogenic bacteria Pseudomonas aeruginosa (PA14), via immune-regulatory p38 MAP kinase. We found that genetic inhibition of components in the OST complex compromised protein processing in the ER, which subsequently boosted ER unfolded protein response (UPRER). We discovered vitellogenin VIT-6 as an OST-dependently glycosylated immune protein. In addition, we showed that the OST complex was required for upregulation of p38 MAP kinase signaling after PA14 infection. Our study demonstrates that a conserved OST complex is crucial for ER homeostasis and regulates host immune responses against pathogenic bacteria.

Keywords

oligosaccharyl transferase, endoplasmic reticulum, p38 MAP kinase, C. elegans, aging

P04

Loops of HIF1a and Cyclophilin D promote cancer metastasis through long-term ROS signaling.

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The majority of cancer cells have elevated basal reactive oxygen species (ROS), which is a cellular signal transduction that leads to tumor development and progression. Because mass ROS production can lead to cell death, a delicate ROS balance is required for survival and proliferation in cancer cells. Mitochondria are major organelles in ROS production, ATP production, cellular calcium homeostasis, and release of apoptosis factors, which ultimately determine metabolic changes and cell death. Cyclophilin D (CypD) is one of the well-known mitochondrial permeability transition pore components and is upregulated in human tumors, but a potential role in cancer cell is not understood. We have found for the first time that hypoxic conditions reduce the expression of CypD in various cancer cell lines. Loss or depletion of CypD in cancer cells increase basal ROS level and HIF1a stability, thereby promoting cancer cell metastasis through HIF-1α signaling. These results demonstrate that a novel function of CypD against mitochondrial retrograde signaling in cancer metastasis.

Keywords

mitochondria, Cyclophilin D, HIF1a, ROS, cancer metastasis

P05

A Golgi protein MON-2/MON2 promotes longevity via upregulating autophagy in mitochondrial respiration mutants

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Golgi apparatus is a crucial organelle for post-translational modification and trafficking of macromolecules, including proteins and lipids. Inhibition of Golgi proteins is associated with various diseases. However, the role of Golgi proteins in organismal longevity remains unclear. Here, we showed that a Golgi protein MON2, an Arf-GEF known to regulate endosome-to-Golgi trafficking, promoted longevity conferred by mitochondrial respiration mutations. By performing quantitative proteomics, we identified 65 proteins whose levels were altered over 2-fold in the mitochondrial respiration mutants. In a subsequent RNAi-based lifespan screen, we found that MON2 was required for the longevity of mitochondrial respiration mutants. We further demonstrated that MON2 upregulated autophagy and thereby promoted longevity of the mitochondrial respiration mutants. We found that MON2 was required for long lifespan conferred by other interventions, including dietary restriction and reduced insulin/IGF-1 signaling, both of which display enhanced autophagy. Altogether our study provides insights into the roles of organelle communications among mitochondria, Golgi and autophagosome in the regulation of longevity.

Keywords

Aging, mitochondria, MON2, autophagy, Golgi protein

P06

A Protein Kinase VRK-1 Functions as an Anti-aging factor that Activates AMPK

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Vaccinia virus-related kinase 1(VRK-1) a nuclear serine-threonine protein kinase that is highly conserved across species. Caenorhabditis elegans VRK-1 functions to regulate cell division and germline proliferation. However, the post-mitotic functions of VRK-1 has not been investigated. Here we demonstrated that somatic VRK-1 extends lifespan through activating AMP-activated protein kinase (AMPK), a longevity-promoting cellular energy sensor, via phosphorylation. We first found that VRK-1 was expressed in the post-mitotic somatic cells in multiple tissues throughout lifetime and was localized in the nucleus. Importantly, somatic overexpression of vrk-1 increased lifespan, whereas disruption of vrk-1 by null mutation reduced lifespan. By conducting RNA seq analysis, we found that the transcriptomic changes regulated by VRK-1 overlapped with those regulated by AMPK. Furthermore, AMPK was required for the increased lifespan by vrk-1 overexpression. These data suggest that VRK-1 and AMPK functions in same genetic pathway. We demonstrated that both C. elegans VRK-1 and human VRK1 directly phosphorylated AMPK, showing that VRK-1 acts upstream of AMPK. Together, our data suggest that VRK-1 is an evolutionarily conserved AMPK-activating upstream kinase and activated VRK-1-to-AMPK signaling promotes longevity.

Keywords

mitochondria, VRK-1, AMPK, C. elegans, aging, lifespan

P07

A PTEN Variant Uncouples Longevity from Impaired Fitness in C. elegans via Calibrating the Activity of FOXO and NRF

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Insulin/IGF-1 signaling modulates multiple physiological aspects in various organisms. In Caenorhabditis elegans, mutations in InsR/insulin/IGF-1 receptor dramatically increase lifespan and pathogen resistance, but generally cause defects in various fitness parameters. Whether these pleiotropic effects can be dissociated at specific steps in the insulin/IGF-1 signaling pathway remains largely unknown. Here we show that a specific amino acid change in PTEN phosphatase retains longevity and enhanced pathogen resistance in InsR(-) mutants compared to wild-type animals without defects in development and motility. Through a mutagenesis screen, we identified a missense mutation in PTEN [PTEN(yh1)], which suppressed developmental defects in InsR(-) mutants with small impacts on pathogen resistance. PTEN(yh1) caused a reduction in PTEN function, but maintained longevity, motility span, and resistance against various stresses in InsR(-) mutants. We further found that PTEN(yh1) retained the activity of FOXO transcription factor but suppressed the harmful activation of NRF transcription factor, for exerting beneficial physiological outputs. Our study will provide insights into how a single component in an evolutionarily conserved insulin/IGF-1 signaling pathway, PTEN, coordinates healthy longevity and fitness.

Keywords

C. elegans, insulin/IGF-1 pathway, PTEN, aging, fitness

P08

Reliably Lifespan-Extending S6 kinase/rsks-1 Mutant C. elegans

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S6 kinase (S6K) acting downstream of mechanistic target of rapamycin (mTOR) regulates cellular processes such as energy metabolism and translation, which lead to changes in growth and aging in organisms. Reduction-of-function mutations in S6K lengthen lifespan in various organisms, including the nematode Caenorhabditis elegans. However, the lifespan extension phenotypes of previously characterized C. elegans S6K mutants are variable and greatly affected by environmental factors, such as temperatures. Here, we functionally examined several previously uncharacterized S6K mutant C. elegans strains. We found that the sterility phenotype caused by RNAi knock down of mTOR was partially restored by mutations altering two amino acids, T379E and S439D, in S6K, while not affecting that of control animals. We then showed that a point mutation causing E255K change in C. elegans S6K, reproducibly and substantially extended lifespan with little or no gross phenotypes. Thus, these newly characterized S6K mutant C. elegans can serve as a new reliable model for animals displaying longevity conferred by reduced mTOR signaling.

Keywords

S6 kinase, C. elegans, aging, lifespan

P09

mRNA Quality Control Systems Are Crucial for Longevity in C. elegans

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Maintenance of protein and DNA homeostasis is crucial for promoting longevity. However, the role of RNA homeostasis in longevity remains relatively unknown. We recently reported that nonsense-mediated mRNA decay (NMD), a key mRNA quality control system, contributes to longevity in C. elegans. However, the roles of other mRNA quality control systems, no-go decay (NGD) and nonstop decay (NSD), in longevity remain elusive. Here, we aimed at determining the functions of NGD and NSD in aging. By utilizing NSD and NGD reporters, we found that NSD and NGD functions decrease with age. We showed that Ski2/SKIV2L and Dom34/Pelota, which encode key factors for NGD and NSD, were required for long lifespan caused by various interventions, including reduced insulin/IGF-1 signaling (IIS) and defective mitochondrial respiration. In addition, mutations in Ski2/SKIV2L and Dom34/Pelota increased protein aggregation. Together these results suggest that NSD and NGD are crucial for longevity and healthy aging in C. elegans. Our study will help uncovering mechanisms by which mRNA quality control contributes to extending healthspan and lifespan.

Keywords

Caenorhabditis elegans, aging, RNA quality control, lifespan

P10

Crosstalk between ER Unfolded Protein Response and Insulin/ IGF-1 Signaling for Modulating C. elegans Physiology

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Inositol-requiring enzyme 1 (IRE1) is an endoplasmic reticulum (ER) transmembrane receptor that is required for ER unfolded protein response(UPRER). In Caenorhabditis elegans, IRE1 plays a crucial role in various physiological processes, including longevity, immunity, development, metabolism, and starvation responses. However, the regulators of IRE1 remain largely unknown. Here, we performed a well-established genetic screen in C. elegans. We identified mutations that suppressed the starvation-induced arrest phenotype in ire1(ok799) mutant worms. Through an EMS mutagenesis screen, we obtained six mutants that suppressed starvation-induced arrest phentoype, named as sira (suppressor of ire-1(-) arrest) which potentially provides insights into novel mechanisms of the effects of IRE1 on physiology. Among these six mutations, we found that sira-1 mutation induced a constitutive dauer (a hibernation-like developmental stage) phenotype, at high temperatures. Based on the phenotypic similarity, it raise the possibility that sira-1 is a reduction-of-function mutation in a gene encoding a factor of insulin/IGF-1 signaling Our data suggest that ER homeostasis coordinates distinct physiological processes such as longevity mediated by evolutionarily conserved insulin/IGF-1 signaling.

Keywords

UPR^{ER}, IRE1, C. elegans, aging, insulin/IGF-1 pathway

P11

Regulation of systemic energy metabolism in mice with hepatic mitochondrial stress response

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Perturbation of mitochondrial proteostasis provokes the cell autonomous and the cell non-autonomous responses which contribute to achievement of the homeostatic adaptation. Here, we explore the influence of hepatomitokines induced by mitochondrial stress response (MSR) on systemic energy metabolism through the mice with genetic ablation of CR6-interacting factor-1 (Crif1) in liver. Liver-specific Crif1 deficient mice (LKO) caused hepatic mitochondrial OXPHOS dysfunction and typical mitochondrial unfolded protein response. Moreover, LKO mice resulted in improved insulin sensitivity and energy expenditure. We revealed that the representative hepatokines, growth differentiation factor 15 (GDF15) and fibroblast growth factor (FGF21), were highly produced in LKO mice. We evaluated the metabolic effects of hepatokines through the LKO mice with global deficiency of Gdf15 or Fgf21 respectively, suggesting that GDF15 plays a protective role in weight gain and high-fat diet-induced hepatic steatosis, whereas FGF21 regulates acute glucose disposal, energy expenditure, and UCP1-dependent thermogenesis in white adipose tissue.

Keywords

Mitochondria, Hepatokine, Mitochondrial stress response, CRIF1

P12 miR-351-5p/Miro2 axis induces hippocampal neural progenitor cell death through mitochondrial fission: pathophysiological implications of neurogenesis decline in Alzheimer's disease

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Adult hippocampal neurogenesis supports the structural and functional plasticity of the brain, while declines in newly forming neurons are associated with cognitive deficits and neurodegeneration common in Alzheimer's disease (AD). Although the dysregulation of certain microRNAs (miRNAs) in AD have been observed, the effects of miRNAs on hippocampal neurogenesis are unknown.

RNA sequencing data of Allen Brain Institute was utilized to investigate the association between miRNA-351-5p/Miro2 axis with AD. MiRNA-351-5p mimic, siRNA of Miro2, and recombinant adenovirus expressing Miro2, were applied to hippocampal neural progenitor cells to investigate cell viability, mitochondrial morphology and functions, as well as autophagy induction.

Here, we demonstrated miRNA-351-5p as a causative factor in hippocampal neural progenitor cell death through modulation of the mitochondrial GTPase, Miro2. Expression of miRNA-351-5p increased whereas the level of Miro2 decreased in the hippocampus of AD model mice, emulating expression in AD patients. In addition, downregulation of Miro2 by siMiro2 induced cell death, similar to miRNA-351-5p, whereas ectopic Miro2 expression using an adenovirus abolished these effects. Excessively fragmented mitochondria and dysfunctional mitochondria indexed by decreased mitochondrial potential and ATP production and increased reactive oxygen species were identified in miRNA-351-5p induced cell death. Moreover, subsequent induction of mitophagy via Pink1 and Parkin was observed by expression of miRNA-351-5p and siMiro2 in hippocampal neural progenitor cells. The suppression of mitochondrial fission by Mdivi-1 completely inhibited cell death induced by miRNA-351-5p, indicating that mitochondrial fission and the accompanying mitophagy was critical in hippocampal neural progenitor cell death. Collectively, the data indicates that the reduction of Miro2 by miRNA-351-5p provoked aberrant mitochondrial fission and excessive mitophagic stress, which subsequently lead to hippocampal neural progenitor cell death. It may thus be involved in the decline of hippocampal neurogenesis which characterizes Alzheimer's disease.

Keywords : Hippocampal neural progenitor cells, cell death, autophagy, mitophagy, miRNA-351-5p, Miro GTPase, Alzheimer's disease

P13

Isothiazolinone biocides induced the BBB dysfunction via disturbing the bioenergetic function of mitochondria

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Isothiazolinone (IT) biocide is the potent anti-bacterial substance commonly used as a preservatives or disinfectants. These chemicals can be absorbed by oral/dermal routes during the personal and industrial use, and internalized biocides can circulate in the blood, posing a human health risk. However, the effects of these compounds in the vascular system are poorly understood. To investigate the effects of IT biocides (OIT, BIT, and DCOIT) on the vascular system, we treated IT biocides to in vitro blood-brain barrier (BBB) model of b.End3 cells. BBB tightly limits the transport of molecules to the brain region and plays a crucial role in maintaining cardiovascular and neurological homeostasis. The effects of three IT biocides (OIT, BIT, and DCOIT) on the cell metabolic activity and bioenergetic parameters were examined in b.End3 cells. Mitochondrial damage and the disturbance of redox status were found to mediate IT-induced BBB damage. Moreover, functional integrity measured by transendothelial electrical resistance (TEER) was significantly impaired by IT biocides. In this study, we demonstrated that IT biocides might induce oxidative stress and mitochondrial damage leading to BBB dysfunction, and we hope that this finding gives an insight into the understanding of the hazardous effects of biocides.

Keywords: isothiazolinone biocide, BBB, bioenergetic disturbance, oxidative stress

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P14

Caenorhabditis elegans Lipin 1 Moderates the Lifespan-shortening Effects of Dietary Glucose by Maintaining ω-6 polyunsaturated Fatty Acids

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Excessive glucose causes diseases and shortens lifespan by altering metabolic processes, but how high glucose diets shorten lifespan remains incompletely understood. Here we found that Lipin1, a phosphatidic acid phosphatase and a putative transcriptional coregulator, prevents life-shortening effects of glucose-rich diets. Thus, we showed that depletion of Lipin1 decreased overall fat levels, despite increasing the expression of genes that promote fat synthesis and desaturation, and downregulation of lipolysis. We then showed that knockdown of Lipin1 altered the composition of various fatty acids in the opposite direction of that altered by dietary glucose. In particular, the levels of two ω-6 polyunsaturated fatty acids (PUFAs), linoleic acid and arachidonic acid, were increased by knockdown of Lipin1 but decreased by glucose-rich diets. Importantly, these ω-6 PUFAs protect Lipin1-deficient worms against the effects of glucose-rich diets. Our study indicates that the metabolic processes that produce ω-6 PUFAs are crucial for protecting animals from living very short on glucose-rich diets.

Keywords

glucose, aging, LPIN-1, ω-6 polyunsaturated fatty acids, C. elegans

P15

Beta-guanidinopropionic acid (b-GPA), a creatine analogue, as a mitokines inducer

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Creatine is known to regulate energy metabolism in high-energy demands by storing energy in the form of phosphorylcreatine (PCr) in vivo. Recently, it is known that creatine metabolism is involved in metabolic homeostasis by not only regulating the immune system but also involved in the thermogenesis of brown adipose tissue. B-GPA is an analogue of creatine that inhibit overall creatine metabolism through inhibition of creatine synthesis, transport, and creatine phosphorylation. Previous studies have shown that b-GPA reduces body weight, but how bGPA controls body weight is not poorly understood. We found that b-GPA regulates mitochondria-related signaling pathways by regulating cellular energy. Treatment of bGPA significantly reduced the oxygen consumption rate in primary hepatocytes of mice. To elucidate the role of b-GPA in vivo, we inject the b-GPA to mice. In these results, B-GPA-treated mice showed increased gene expression of oxphos complex, mitochondria unfolded protein response(UPRmt), and mitokines(GDF15 and FGF21) in the liver and skeletal muscle compared to control mice. In addition, an increase in the concentration of mitokines was observed in serum. To observe whether the function of GDF15 known in previous studies is exhibited by bGPA treatment, bGPA was treated in high-fat diet mice. In this experiment, it was observed that the mice treated with bGPA showed a decrease in body weight change and food intake compared to the control mice, similar to the previously known function of GDF15. Therefore, our results show the possibility that bGPA induces mitokines by regulating cellular energy homeostasis.

Keywords

mitochondria, creatine metabolism, mitokine, mitohormesis

P16

Exogenous putrescine induces adipocyte differentiation

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Polyamines are crucial for fundamental cellular processes including cellular proliferation and differentiation. It has been shown that intracellular polyamine metabolism is involved in adipocyte differentiation. However, the effects of exogenous polyamines on adipocyte differentiation. Have not been studied. In this study, we demonstrated that the treatment of exogenous putrescine significantly stimulates the adipocyte differentiation of 3T3-L1 preadipocytes. Exogenous putrescine increased intracellular lipid accumulation in a concentration-dependent manner without cell toxicity. We also investigated that putrescine induces the expression of both adipogenic and lipogenic genes. Moreover, putrescine regulates adipocyte differentiation tin the early and intermediated stages. These data suggest that the putrescine might be involved in adipogenesis.

Keywords

polyamine, putrescine, adipocyte, differentiation

P17

Mitochondrial Adenine Nucleotide Translocase 2 Regulates Adipocyte Differentiation

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Adenine nucleotide translocase (ANT) are mitochondrial proteins that facilitates the exchange of ADP and ATP across the mitochondrial inner membrane for cellular energy metabolism. However, the function of ANT2 on adipocyte differentiation is not fully studied. Here we observed that the reduction of ANT2 significantly reduces adipocyte differentiation with ANT2 siRNA knockdown. In addition, the similar results also observed in the stromal vascular cells isolated from the sWAT of ANT2 flox mice. The expression of the master adipogenic transcription factors, peroxisome proliferator-activated receptor gamma, CCAAT/enhancer-binding protein alpha, and CCAAT/enhancer-binding protein beta, was markedly decreased. The reduction of adipocyte marker genes, fatty acid binding protein 4 and adiponectin, was also observed. In addition, the mRNA expression of lipogenic genes including fatty acid synthase, stearoyl-CoA desaturase 1, and sterol regulatory element-binding transcription factor 1c, was also decreased in the cells reduced ANT2 expression. These results suggest that mitochondrial ANT2 may be involved in adipocyte differentiation.

Keywords

Adenine nucleotide translocase, adipocyte, differentiation

P18

HNL Methanol Extract Regulates 3T3-L1 Aidpocyte Differentiation

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HNL originated Eurasia and is cultivated for pharmaceutical purposes. HNL is used in traditional herbal medicine for diseases including rheumatism, asthma, nervous diseases, and stomach pain. However, the effect of HNL have not been studied on adipocyte differentiation. Here, we observed that methanol extract of HNL activates adipocyte differentiation and intracellular lipid accumulation during adipogenesis in a concentration-dependent manner. We also observed that methanol extract of HNL promotes not only the expression of adipogenic genes such as peroxisome proliferator-activated receptor γ, fatty acid-binding protein and adiponectin but the expression of lipogenic genes such as fatty acid synthase and acetyl CoA carboxylase. These results indicated that methanol extract of HNL positively regulates adipocyte differentiation.

Keywords

adipocyte, differentiation, 3T3-L1, natural extract

P19

Mitochondrial E3 Ubiquitin ligase MARCH5 is essential for NLRP3 inflammasome activation.

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The inflammasome is a macromolecular signaling complex in the immune response against pathogen infections and damage. Among these pattern recognition receptors (PRRs), NLRP3 (pyrin domain-containing protein 3) inflammasome can be activated by a variety of pathogen-associated molecular patterns(PAMPs) and promote caspase-1 dependent production of IL-1β. Recent studies report that PTMs (Post Translational Modification), such as ubiquitination and phosphorylation, are essential to the regulation of NLRP3 inflammasome activation. It is reported that NLRP3 mitochondrial localization is important for inflammasome activation. Previous studies, MARCH5 (a mitochondria-resident E3 ubiquitin ligase), are important to mitochondria quality control and play a role in the immune response. However, the mechanism of the NLRP3 inflammasome activation at mitochondria still remains unknown. Here, we found that MARCH5 KO mice reduced the IL-1β secretion in response to NLR. Together, our data demonstrate that ubiquitination mediated by MARCH5 associate with the NLRP3 inflammasome activation. These results indicate the MARCH5 plays the role of an innate immune regulator to NLRP3 inflammasome activation.

Keywords mitochondria, E3 ubiquitin ligase, Inflammasome

P20

Methanol Extract of Iris Bungei Maxim. Stimulates 3T3-L1 Adipocyte Differentiation

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Iris bungei Maxim., which is native to China and Mongolia, is used as a traditional medicine for conditions such as inflammation, cancer, and bacterial infections. However, the effects of Iris bungei Maxim. on adipocyte differentiation have not been studied. In the present study, we first demonstrated the molecular mechanisms underlying the adipogenic activity of the methanol extract of Mongolian I. bungei Maxim. (IB). IB significantly enhanced intracellular lipid accumulation and adipocyte differentiation in 3T3-L1 preadipocytes in a concentration-dependent manner. Moreover, IB markedly stimulated the expression of genes related to adipogenesis such as peroxisome proliferator-activated receptor, adiponectin, and aP2. We also observed that IB induces lipogenic genes such as fatty aid synthase, sterol regulatory element binding protein 1c, stearoyl-CoA desaturase, and acetyl-CoA carboxylase. In addition, IB regulated adipocyte differentiation in both the early and middle stages. Taken together, these adipogenic and lipogenic effects of IB suggest its efficacy for the prevention and/or treatment of type 2 diabetes.

Keywords

Iris bungei Maxim., adipocyte, differentiation, 3T3-L1

P21

The Expanding World of SUMO: from Epigenetics to Adaptive Mechanisms and Cellular Aging

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Environmental changes induce many acute and long-term adaptive cellular responses. Mammals have diverse adaptive mechanisms for stress resistance, such as immune responses to pathogens or hormone-mediated homeostatic processes. At the cellular level, acute changes in the local microenvironment, such as changes of pH or temperature, oxidative stress, or nutrient limitation, may induce programmed cell death or trigger adaptive changes that include gene mutation, aneuploidy, changes in gene expression or epigenetic alterations. The small ubiquitin-like modifier (SUMO) protein is a conserved post-translational modifier that regulates a host of proteins in eukaryotic cells and maintains cell homeostasis when the cell encounters endogenous or environmental stress, such as osmotic stress, hypoxia, heat shock, genotoxic stress, and nutrient stress. In response to acute loss of the Ulp2 SUMO-specific protease, yeast become disomic for chromosome I (ChrI) and ChrXII. Here we report that ChrI disomy, which creates an adaptive advantage in part by increasing the dosage of the Ccr4 deadenylase, was eliminated by extended passaging. Loss of aneuploidy is often accompanied by mutations in essential SUMO-ligating enzymes, which reduced polySUMO-conjugate accumulation. The mRNA levels for almost all ribosomal proteins increase transiently upon initial loss of Ulp2, but elevated Ccr4 levels limit excess ribosome formation. Notably, extended passaging leads to increased levels of many small nucleolar RNAs (snoRNAs) involved in ribosome biogenesis, and higher dosage of three linked ChrXII snoRNA genes suppressed ChrXII disomy in ulp2Δ cells. Our data reveal that aneuploidy allows rapid adaptation to Ulp2 loss, but long-term adaptation restores euploidy. Cellular evolution restores homeostasis through countervailing mutations in SUMO-modification pathways and regulatory shifts in ribosome biogenesis.

Keywords SUMO, aneuploidy, adaptive mechanisms, ribosome biogenesis

P22

Function of mitochondrial HSP90 in tumor angiogenesis

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Mitochondrial Heat shock protein 75 (HSP75), TRAP1 was initially identified as binding with tumor necrosis factor receptor-1. TRAP1 is one of the HSP90 family including GRP94, heat shock protein 90kDa beta which located in endothelial reticulum (ER), and molecular chaperone. In many tumor cells demonstrate that TRAP1 is over expressed compared with normal tissue. High level of TRAP1 expression has correlation with tumor progression stages.24 Therefore, TRAP1 is attractive biomarker for malignant tumor. Thus, inhibition of TRAP is potential for reduce hypoxic adaptation which is critical for resistant of cancer treatment.

Glioblasotma (GBM) is known as glioblastoma multifome or grade IV astrocytoma. GBM is usually found in the cerebral hemispheres of brain, but can be found anywhere in brain. GBM is the most malignant primary tumor because these cells reproduce quickly and they are supported by a huge network of blood vessels. Brain tumor loss their blood-brain barrier (BBB) integrity also shows severe hypoxia and tumor necrosis. These tumors rapidly generate the new blood vessel through diverse angiogenetic factors such as vascular endothelial growth factor (VEGF), angiopoietinlike4 (ANGPTL4) and platelet-derived growth factor(PDGF) etc.56-60 In the process of glioblastoma growth, cancer cells migrate to around the blood vessels and squeeze them to burst. As a result, vessels are reduced perfusion and cause hypoxic environment. So far, study about angiogenesis in brain tumors especially in low oxygen condition shows highly malignant phenotype and increased mortality.

We observed that TRAP1 regulates hypoxia inducible factor-1 α (HIF-1α) under acute hypoxic condition. We also found targeting TRAP1 in GBM suppress angiogenesis through vascular endothelial growth factor (VEGF), a major factor of new blood vessel formation and HIF-1α target gene, in mouse xenograft model.

Keywords

mitochondria, TRAP1,GBM, angiogenesis

P23

Inhibition of fine particulate matter-induced senescence of skin keratinocytes by Korean red ginseng

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In this study, we investigated whether Korean red ginseng may attenuate fine particulate matter -induced senescence of skin keratinocytes. The human keratinocyte cell lines and normal human epidermal keratinocytes were treated with fine particulate matter. Fine particulate matter-treated cells showed characteristics of cellular senescence, including an enlarged and flattened cell shape and irregular size, and decreased colony-forming ability, however, Korean red ginseng suppressed these characteristics of cellular senescence in both cell types. And fine particulate matter-treated cells exhibited β-galactosidase activity in the cytosol, a characteristic of cellular senescence, as evidenced by higher levels of green signal in fine particulate matter-treated cells than in untreated cells, however, Korean red ginseng suppressed the β-galactosidase activity in both cell types. Chromatin in senescent cells undergoes large-scale rearrangements, forming dense nuclear domains called senescence-associated heterochromatin foci. Fine particulate matter-treated cells displayed significantly more senescence-associated heterochromatin foci in the nuclei than the controls, however, Korean red ginseng decreased the number of senescence-associated heterochromatin foci. Moreover, the expression of cyclin dependent kinase inhibitor and senescence inducer, was strongly increased in fine particulate matter-treated cells compared to the corresponding untreated cells, however, Korean red ginseng decreased the expression of cyclin dependent kinase inhibitor. These results suggest that Korean red ginseng has the protective effects against fine particulate matter-induced senescence of skin keratinocytes.

Keywords

Fine particulate matter, senescence, red ginseng

P24

SC compound and ascorbic acid enhance mitochondrial respiration and improve cognition of mice

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Cognitive decline is observed in aging and neurodegenerative diseases, including Alzheimer's disease (AD) and dementia. Intracellular energy produced via mitochondrial respiration is used in the regulation of synaptic plasticity and structure, including dendritic spine length and density, as well as for the release of neurotrophic factors involved in learning and memory. Importantly, mitochondrial activity declines with aging, which is known to be involved with cognitive dysfunction. Mitochondrial dysfunction is also prominent in Alzheimer's disease (AD) model mice. To date, few synthetic agents have been developed for improving mitochondrial function and cognitive function. However, natural compounds that modulate synaptic plasticity by directly targeting mitochondria have not yet been developed. Here, we demonstrate that a mixture of SC compound and ascorbic acid (AA) increased the mitochondrial oxygen consumption rate in embryonic mouse hippocampal mHippoE-14 cells. Injection of the SC-AA mixture in mice significantly increased expression of postsynaptic density protein 95 (PSD95), an increase that was correlated with enhanced brain-derived neurotrophic factor (BDNF) expression. We also found that mice injected with the SC-AA mixture showed enhancing learning and memory. Our results demonstrate that a mixture of SC and AA improves mitochondrial function and memory, suggesting that this natural compound mixture could be used to alleviate Alzheimer's disease and aging-associated memory decline. (2017R1A5A2015385, 2019R1F1A1059586, 2019M3E5D1A02068575, HR20C0025, 2020R1I1A1A01061771)\

Keywords

SC compound, Ascorbic acid, Mitochondria, hippocampus

P25

Palmitoyl protein thioesterase 1 is essential for myogenic autophagy of C2C12 skeletal myoblast

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Skeletal muscle differentiation is an essential process for maintenance of muscle development and homeostasis. Reactive oxygen species (ROS) are critical signaling molecules involved in muscle differentiation. Palmitoyl protein thioesterase 1 (PPT1), a lysosomal enzyme, is involved in removing thioester-linked fatty acid groups from modified cysteine residues in proteins. However, the role of PPT1 in muscle differentiation remains to be elucidated. Here, we found that PPT1 plays a critical role in the differentiation of C2C12 skeletal myoblasts. The expression of PPT1 gradually increased in response to mitochondrial ROS during muscle differentiation, which was attenuated by treatment with antioxidants. Moreover, we revealed that PPT1 transactivation occurs through nuclear factor erythroid 2-regulated factor 2 (Nrf2) binding the antioxidant response element (ARE) in its promoter region. Knockdown of PPT1 with specific siRNA disrupted lysosomal function by increasing its pH. Subsequently, it caused excessive accumulation of autophagy flux, thereby impairing muscle fiber formation. In conclusion, we suggest that PPT1 is factor a responsible for myogenic autophagy in differentiating C2C12 myoblasts.

Keywords

palmitoyl protein thioesterase 1, mitochondrial reactive oxygen species, autophagy, muscle differentiation, mammalian target of rapamycin complex

P26

Novel Metabolic Stress Indices including Mitochondrial Biomarkers for Non-invasive Diagnosis of Hepatic Steatosis and Fibrosis

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Mitochondrial dysfunction with oxidative stress participates in non-alcoholic fatty liver disease (NAFLD) progression. Here, we investigated the steatosis and fibrosis predictive efficacy of a novel non-invasive diagnostic panel including mitochondrial stress biomarkers. A total of 343 participants randomly selected from a population-based general cohort underwent clinical and laboratory assessments and abdominal ultrasound. Liver fat content and stiffness were measured by magnetic resonance (MR) imaging-proton density fat fraction and MR elastography, respectively. Serologic stress biomarkers were quantitated by ELISA. By univariate logistic regression, fibroblast growth factor 21 (FGF21) correlated with liver steatosis with a high significance coefficient. Multivariate regression showed that waist-to-hip ratio, FGF21, FGF19, adiponectin-to-leptin ratio, insulin, albumin, triglyceride, total-cholesterol and alanine-aminotransferase were independent predictors for steatosis (rank-ordered by Wald). The area under receiver-operator characteristics curve (AUROC) of the metabolic stress index for steatosis (MSI-S) was 0.886. MSI-S had higher diagnostic accuracy (81.1%) than other steatosis indices. For hepatic fibrosis, growth differentiation factor 15 (GDF15) correlated to stiffness with a high coefficient. Waist-to-height ratio, GDF15, γ-glutamyltransferase, decorin and alkaline-phosphatase were independent predictors for fibrosis (rank-ordered). The MSI for fibrosis (MSI-F) had higher AUROC (0.912) and diagnostic accuracy (85.4%) than other fibrosis indices. MSI-S and MSI-F differentiated the severities of steatosis and fibrosis, respectively, while other indices showed less discrimination. Finally, both MSI-S and MSI-F are more effective to reduce unnecessary invasive examinations than other currently-available indices. Taken together, novel non-invasive indices based on mitochondrial stress biomarkers FGF21 and GDF15 showed strong predictive power to evaluate steatosis and fibrosis, suggesting that MSI-S and MSI-F may be efficient tools for prediction of NAFLD progression in a clinical setting inaccessible to MR equipment or invasive approach.

Keywords

mitochondrial stress, FGF21, GDF15, liver steatosis, liver fibrosis, non-invasive diagnosis

P27

Ca^{2+} inhibition on proteasomal degradation of mitochondrial proteins in mouse brown adipocytes

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Brown fat mass declines with ageing, while thermogenic induction in brown adipose tissue (BAT) improves insulin sensitivity and adiposity. We investigated the mechanism of acute sympathetic regulation on BAT thermogenesis. norepinephrine (NE) activated mitochondrial respiration with upregulations of uncoupling protein 1 (UCP1) and mitochondrial calcium uniporter (MCU) within 1 hour, whilst the transcriptional level of mitochondrial proteins remained unchanged. BAT has an active mitochondrial protein turnover rate. In the presence of MG132 and lactacystin, proteasome inhibitors, UCP1 and MCU maintained high protein levels without further increases by NE. Forskolin, an activator of adenylate cyclase, or dibutyryl-cyclic AMP (db-cAMP), a membrane permeable cAMP derivative, mimicked the NE-induced upregulations of mitochondrial proteins and respiration, all of which were blocked by inhibition of protein kinase A. However, neither NE- nor db-cAMP-induced activation was affected by the inhibition of mitochondrial fatty acid uptake. NE acutely increased cytosolic Ca2+ and inhibited proteasome activities. Intriguingly, Ca2+ chelator (BAPTA-AM) abolished NE-induced mitochondrial activities and protein abundance as well as NE-reduced proteasomal activities. Taken together, we suggest a novel molecular mechanism of sympathetic stimulation on acute thermogenesis of brown and beige adipocytes, which may provide significant implications for therapeutic application in obesity and various metabolic diseases.

Keywords

Brown adipose tissue (BAT), browning, thermogenesis, mitochondria, uncoupling protein 1 (UCP1), sympathetic stimulation, norepinephrine (NE), mitochondrial calcium uniporter (MCU).

P28

Ca^{2+}-activated mitochondrial biogenesis and functions improve stem cell fate in Rg3-treated human mesenchymal stem cells

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Although mitochondrial functions are essential for cell survival, their critical roles in stem cell fate, including proliferation, differentiation, and senescence, remain elusive. Ginsenoside Rg3 exhibits various biological activities and reportedly increases mitochondrial biogenesis and respiration. Herein, we observed that Rg3 increased proliferation and suppressed senescence of human bone marrow-derived mesenchymal stem cells. Osteogenic, but not adipogenic, differentiation was facilitated by Rg3 treatment. Rg3 suppressed reactive oxygen species production and upregulated mitochondrial biogenesis and antioxidant enzymes, including superoxide dismutase. Consistently, Rg3 strongly augmented basal and ATP synthesis-linked respiration with high spare respiratory capacity. Rg3 treatment elevated cytosolic Ca2+ concentration contributing to mitochondrial activation. Reduction of intracellular or extracellular Ca2+ levels strongly inhibited Rg3-induced activation of mitochondrial respiration and biogenesis. Taken together, Rg3 enhances capabilities of mitochondrial and antioxidant functions mainly through a Ca2+-dependent pathway, which improves the proliferation and differentiation potentials and prevents the senescence of human mesenchymal stem cells.

Keywords

mesenchymal stem cells, ginsenoside Rg3, cellular senescence, oxidative stress, mitochondria

P29

Evogliptin prevents cardiomyopathy via improvement of mitochondrial function and reduction of cardiac fibrosis in type 2 diabetic mice

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Dipeptidyl peptidase-4 (DPP-4) inhibitors are popularly used antihyperglycemic drugs for the treatment of type 2 diabetes mellitus (T2D). Currently, the pleiotropic effects of DPP-4 inhibitors have drawn much attention. Our investigation aimed to examine whether evogliptin, a recently developed DPP-4 inhibitor, could protect against T2D-induced cardiomyopathy. Eight-week-old diabetic and obese db/db mice received evogliptin treatment (100mg and 300mg/kg/day), db/db control mice and db/m control mice received with equal amounts of vehicle daily for 12 weeks. Body weight and feeding weight was measured every week. Cardiac function was assessed using echocardiography at before and after feeding 12 weeks. Histological and molecular markers of cardiac fibrosis were assessed in the left ventricle (LV) at 20 weeks old. The results showed that evogliptin improved T2D-induced cardiac dysfunction, as shown by analysis of 2D and doppler echocardiography (LV ejection fraction, fractional shortening was higher, E/A and e'/a' ratios increased, E/e' ratio and deceleration time decreased in evogliptin - treated groups compared to db/db control group). Evogliptin also attenuated interstitial fibrosis and reduced mitochondrial damage. Our data suggest that evogliptin might be of benefit in cardio-dysfuntion patients with type 2 diabetes.

Keywords

Dipeptidyl peptidase-4, evogliptin, type 2 diabetes mellitus, cardiac fibrosis, diabetic cardiomyopathy

P30

NecroX-5 preserves PGC1α expression levels during hypoxia/reoxygenation injury and protects phosphorylation capacity during mitochondrial oxidation

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The actioin of NecroX-5 on the mitochondrial oxidative phosphorylation system remains unclear even with the demonstration of antioxidant and cardioprotective effects of NecroX-5 on various in vitro and in vivo models. Here, the role of NecroX-5 in protecting mitochondrial oxidative phosphorylation capacity during hypoxia-reoxygenation (HR) is verified. Isolated rat hearts were subjected to 10 μM Necrox-5 treatment during hypoxia/reoxygenation treatment using an ex vivo Langendorff system. Proteomic analysis was performed using liquid chromatography-mass spectrometry (LC-MS) and non-labeling peptide count protein quantification. Real-time PCR, western blot, citrate synthases and mitochondrial complex activity assays were then performed to assess heart function. Treatment with NecroX-5 during hypoxia significantly preserved electron transport chain proteins involved in oxidative phosphorylation and metabolic functions. NecroX-5 also improved mitochondrial complex I, II, and V function. Additionally, markedly higher peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC1α) expression levels were observed in NecroX-5-treated rat hearts. These novel results provide convincing evidence for the role of NecroX-5 in protecting mitochondrial oxidative phosphorylation capacity and in preserving PGC1α during cardiac HR injuries.

Keywords

Hypoxia; Mitochondria; NecroX; Oxidative phosphorylation; PCG1α

P31

Pharmacological inhibition of AKT by novel inhibitor HS1793 in relapsed multiple myeloma

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Multiple myeloma (MM) is a neoplastic plasma cell disorder with high disease recurrence rates. Novel therapeutic approaches capable of improving outcomes in patients with MM are urgently required. The AKT signaling plays a critical regulatory role in MM pathophysiology, including survival, proliferation, metabolism, and has emerged as a key therapeutic target. Here, we identified a novel AKT inhibitor, HS1793, and defined its mechanism of action and clinical significance in MM. HS1793 disrupted the interaction between AKT and heat shock protein 90, resulting in protein phosphatase 2A-modulated phosphorylated-AKT (p-AKT) reduction. Moreover, we observed reductions in the kinase activity of the AKT downstream target, IκB kinase alpha, and the transcriptional activity of nuclear factor kappa B, which induced mitochondria-mediated cell death in MM cells exclusively. We confirmed the cytotoxicity and specificity of HS1793 via PET-CT imaging of a metastatic mouse model generated using human MM cells. We also evaluated the cytotoxic effects of HS1793 in primary and relapsed MM cells isolated from patients. Thus, HS1793 offers great promise in eliminating MM cells and improving therapeutic responses in primary and relapsed/refractory MM patients.

Keywords

AKT, anti-cancer drug, HS1793, HSP90, multiple myeloma

P32

GSK-3β inhibition renders cardioprotection in ischemic/reperfusion heart injury

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Sponges belonging to the genus Neopetrosia contain diverse bioactive metabolites. In a previous study we observed that Neopetroside A (NPS A), a natural pyridine nucleoside that contains α-glycoside bond, could upregulate mitochondrial functions without cytotoxicity. In this study, we examined the physiological effects of NPS A on mitochondrial metabolism and heart function and its role in cardioprotection against ischemia/reperfusion (I/R) injury. NPS A reduced ex vivo I/R-induced damage in hearts of 8-week-old male Sprague Dawley rats by preserving hemodynamics and mitochondrial respiration capacity. In an in vivo model, NPS A also exhibited significantly smaller infarct size of 8-week-old C57BL6 mice subjected to left coronary artery ligation myocardial infarction surgery. The effects in in vivo and ex vivo could be attributed to the increased cellular and mitochondrial functions such as increased glycolysis, oxidative phosphorylation, and metabolic processes which were observed using rat H9c2 cells. Interestingly, NPS A increased mitochondrial function and NAD+/NADH ratio. Using in vitro kinase activity assays, we showed that NPS A inhibits the GSK-3β. A docking simulation study demonstrated that NPS A could interact with GSK-3β. Furthermore, NPS A increased the NAD+/NADH ratio via the NRF2-NQO1 pathway, which is how NPS A can exert its effect on metabolic and cellular processes. NPS A, a natural marine compound, can enhance mitochondrial metabolism and protect the heart against I/R-damage via inhibition of GSK-3β without toxicity. The combined effects regulated by NPS a treatment can protect the heart against acute I/R damage and chronic myocardial infarction.

Keywords

Neopetroside A, marine pyridine a-nucleoside, mitochondria, ischemia/reperfusion injury, GSK-3 inhibition

P33

CRBN-induced mitochondrial dysfunction reverses multiple myeloma drug resistance

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Cereblon (CRBN) is a thalidomide-binding protein that induces anti-myeloma effects through the action of immunomodulatory drugs (IMiDs) and serves as a potential biomarker in predicting patient response to IMiDs. In cancer cells, mitochondrial biogenesis is essential to control mitochondrial metabolism. However, the correlation between CRBN and mitochondria is yet to be reported. Here we established the inverse relationship between CRBN and mitochondrial function in multiple myeloma. Survivability of multiple myeloma patients is correlated with high expression of PGC-1α and ERRα. In in vitro, thalidomide resistance or susceptibility depends on the CRBN level. Mitochondrial function and protein expressions were unchanged in thalidomide-resistant KMS20 cells, which exhibited lower CRBN expression levels, than thalidomide-sensitive KMS26 cells which had higher CRBN expression. CRBN overexpression in drug-resistant KMS20 cells during thalidomide treatment effectively killed the cells. Conversely, CRBN knockdown rendered KMS26 cells thalidomide resistant. CRBN overexpression in a KMS20 xenograft model increased thalidomide susceptibility and decreased tumor growth and significantly prolonged survival. These findings suggest the novelty of CRBN in overcoming thalidomide resistance in multiple myeloma by regulating mitochondrial function.

Keywords

mitochondria, CRBN, IMiDs, multiple myeloma, drug resistance

P34

Mitochondrial biogenesis is increased by cyclic stretch in a mouse cardiac cell line

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In this study, we assessed the effect of mimetic cyclic stretch on mitochondria in a cardiac cell line, as mitochondria play an essential role in maintaining heart function by producing biological energy molecules. To mimic the geometric and biomechanical conditions surrounding cells in vivo, cyclic stretching was performed on HL-1 murine cardiomyocytes seeded onto an elastic micropatterned substrate (10% elongation, 0.5 Hz, 4 h/day). The expression of mitochondria biogenesis-related genes and mitochondria oxidative phosphorylation-related genes and respective protein levels were increased in the cyclic stretch stimulated cell lines as opposed to the non-stimulated controls. Consequently, cyclic stretch increased mitochondrial mass and ATP production in treated cells. Our results suggest that cyclic stretch transcriptionally enhanced mitochondria biogenesis and oxidative phosphorylation without detrimental effects in the cultured cardiac cell line.

Keywords

Cyclic stretch, Mouse cardiac cell line, Mitochondria biogenesis

P35

Exercise Training Protects against Atorvastatin-Induced Skeletal Muscle Dysfunction and Mitochondrial Dysfunction in the Skeletal Muscle of Rats

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Statins are used to prevent and treat atherosclerotic cardiovascular disease, but they also induce myopathy and mitochondrial dysfunction. Here, we investigated whether exercise training prevents glucose intolerance, muscle impairment, and mitochondrial dysfunction in the skeletal muscles of Wistar rats treated with atorvastatin (5 mg kg-1 day-1) for 12 weeks. The rats were assigned to the following three groups: the control (CON), atorvastatin-treated (ATO), and ATO plus aerobic exercise training groups (ATO+EXE). The ATO+EXE group exhibited higher glucose tolerance and forelimb strength and lower creatine kinase levels than the other groups. Mitochondrial respiratory and Ca2+ retention capacity was significantly lower in the ATO group than in the other groups, but exercise training protected against atorvastatin-induced impairment in both the soleus and white gastrocnemius muscles. The mitochondrial H2O2 emission rate was relatively higher in the ATO group and lower in the ATO+EXE group, in both the soleus and white gastrocnemius muscles, than in the CON group. In the soleus muscle, the Bcl-2, SOD1, SOD2, Akt, and AMPK phosphorylation levels were significantly higher in the ATO+EXE group than in the ATO group. In the white gastrocnemius muscle, the SOD2, Akt, and AMPK phosphorylation levels were significantly higher in the ATO+EXE group than in the ATO group. Therefore, exercise training might regulate atorvastatin-induced muscle damage, muscle fatigue, and mitochondrial dysfunction in the skeletal muscles.

Keywords

exercise, mitochondria, myopathy, skeletal muscle, statin

P36

Deciphering the mechanism of the loss of cell identity in mouse model for early diabetes

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Loss of cell identity is thought to be an early event of functional β cell mass decrement during the development of type 2 diabetes. However, the mechanism how cells lose their identity has been poorly understood. Here, we propose a novel mouse model generated by knocking out Prmt1 in adult β cells (Prmt1 iKO) as an early diabetes model. This model recapitulates early and progressive diabetic phenotype. Importantly, cells in Prmt1 iKO mouse were functionally immature and the protein level of mature cell markers were decreased. Single cell transcriptomic analysis of Prmt1 βiKO β cells revealed groups of β cell subpopulations that serially ranged from transcriptomic normal β cells to the stressed β cells and immature β cells. Stressed β cells were increased in mRNA expression of both Insulin and ER stress-related genes whereas immature β cell population were decreased in mRNA expression of insulin, insulin biosynthesis gene and β cell transcription factors. Metabolic challenge in βiKO mice resulted in robust 'loss of identity' in β cells with profound proteomic and transcriptomic change. Pseudotemporal analysis revealed a biological meaningful wave of transcriptomic changes. Single cell transcriptomic analysis of Prmt1 iKO cells revealed groups of cell subpopulations that serially ranged from transcriptomic normal cells to the stressed cells-immature cells-bihormonal endocrine cells. Stressed cells were increased in mRNA expression of both Insulin and ER stress-related genes whereas immature cell population were decreased in mRNA expression of insulin and cell transcription factors. These results can provide a new insight into how cells lose their identity in type 2 diabetes.

P37

Inhibiting serotonin signaling through HTR2B in visceral adipose tissue improves obesity related insulin resistance

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Serotonin (5-hydroxytryptamine, 5-HT) is a bioamine and has diverse functions. 5-HT plays a distinct role depending on whether it is synthesized in the brain or in the periphery. Recent studies demonstrated that peripheral 5-HT has a significant role in regulation of systemic energy homeostasis. It induces lipid accumulation in liver and inhibits the UCP1 dependent thermogenesis in brown adipose tissue. However, it has not been completely elucidated how 5-HT influences visceral white adipose tissue dysfunction although visceral white adipose tissue is a major player in the development of obesity-related insulin resistance.

In this study, we found that the expression of serotonin receptor 2b (Htr2b) was increased in visceral adipose tissue upon high fat diet (HFD) feeding. Additionally, adipocyte specific Htr2b knockout mice showed improved insulin sensitivity, attenuated hepatic steatosis, inflammation and adipocytes hypertrophy. Most of all, HTR2B promotes adipocyte lipolysis via phosphorylation of HSL in obesity. We also reveal that pharmacological inhibition of HTR2B improves HFD-induced metabolic dysfunction. Furthermore, in human study, HTR2B expression in omental visceral adipose tissue correlates with BMI, AST level and ALT level in obese patients. These data suggested that 5-HT signaling through HTR2B can play an important role in visceral adipose tissue dysfunction and systemic insulin resistance. Therefore, unveiling the mechanism of 5-HT signaling through HTR2B in adipose tissue can broaden our understanding of the pathophysiological insight in obesity.

P38

Gut-derived serotonin regulates hepatic steatosis and ER stress in alcoholic liver disease

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Serotonin (5-hydroxytryptamine (5-HT)) is a monoamine neurotransmitter that has various functions in central and peripheral tissues. Upon high-fat diet (HFD), gut-derived serotonin (GDS) synthesized by enterochromaffin cells has been reported to travel to the liver through portal vein and regulate hepatic steatosis via serotonin receptor 2A (HTR2A) signaling. However, the role of GDS in alcoholic liver disease remains to be elucidated. Here, we demonstrate that inhibition of GDS synthesis ameliorates alcoholic liver disease through the reduction in HTR2A signaling. Plasma serotonin concentrations were increased in both ethanol-fed mice and human with alcoholic liver disease. Gut-specific Tph1 knockout (Tph1 GKO) mice fed a Lieber-DeCarli diet containing 5% ethanol for 4 weeks exhibited improved steatosis and decreased expression of genes involved in lipogenic pathway. Also, liver-specific Htr2a knockout (Htr2a LKO) mice phenocopied Tph1 GKO mice. Moreover, endoplasmic reticulum (ER) stress markers were decreased in both Tph1 GKO and Htr2a LKO mice. Thus, these data suggest that GDS plays a crucial role in alcoholic liver disease and that inhibition of serotonin to HTR2A signaling can afford attractive approach to treat alcoholic liver disease.

P39

Skeletal muscle mitochondrial dysfunction in mice is linked to bone loss via the bone marrow immune microenvironment

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Mitochondrial oxidative phosphorylation (OxPhos) is a critical regulator of skeletal muscle mass and function. Although muscle atrophy due to mitochondrial dysfunction is closely associated with bone loss caused by reduction of mechanical loading, questions remain about the biological characteristics in the relationship between muscle and bone. Here, we have shown that muscle atrophy caused by skeletal muscle-specific Crif1 knockout (MKO) modulates the bone marrow inflammatory response, leading to bone loss. Transcriptome analysis of the extensor digitorum longus revealed that local mitochondrial stress increased serum levels of fibroblast growth factor 21 (FGF21) in mice. However, we have shown by Fgf21 knockout in MKO mice that FGF21 is dispensable for muscle atrophy-mediated bone loss. RNA sequencing in MKO mice indicated that mitochondrial stress response in skeletal muscles induces an inflammatory response and adipogenesis in the bone marrow. We also found, using transcriptomic analysis of bone marrow, that the CXCL12–CXCR4 axis is important for T-cell homing to the bone marrow, which is an immunological mediator of muscle-bone communication. CXCR4 antagonism attenuated bone marrow inflammation and bone loss in MKO mice. Together, these data highlight the role that muscle mitochondrial dysfunction plays in triggering bone marrow inflammation via the CXCL12–CXCR4 signaling axis, which is critical for inducing bone loss.

Keywords

mitochondria, inflammation, bone marrow, bone loss

P40

Aerobic exercise decrease the levels of CRBN in the skeletal muscle of type 1 diabetes rats

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Cereblon (CRBN) has been reported as a negative regulator of adenosine monophosphate-activated protein kinase (AMPK). Aerobic exercise training has been shown to increase AMPK, which resulted in glucose regulation in skeletal muscle. However, the expression level of CRBN and its association with the physiological modulation of glucose are still unclear. Male Sprague-Dawley rats (5-week-old, n 1/4 18) were assigned to control, streptozotocin (STZ, 65 mg/kg)-induced diabetic group, and STZ þ exercise (STZ þ EXE) group with six rats in each group. Rats in the STZ þ EXE group exercised by treadmill running (20 m/min, 60 min, 4 times/week) for 8 weeks. Compared with the STZ group, blood glucose was significantly decreased in the STZ þ EXE group. The skeletal muscle of rats in the STZ þ EXE group showed a significant decrease in CRBN levels and an increase in AMPK, protein kinase B, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, fibronectin type III domain-containing protein 5, glucose transporter type 4, superoxide dismutase 1, and uncoupling protein 3 levels. These results suggest that CRBN is a potential regulator of glucose homeostasis in the skeletal muscle. Moreover, our results suggest that aerobic exercise training may provide an important physiological treatment for type 1 diabetes by decreasing CRBN and increasing AMPK signaling in skeletal muscle.

Keywords

Aerobic exercise, CRBN, AMPK, Type 1 diabetes, Skeletal muscle, FNDC5

P41

Functional Nanosome for Enhanced Mitochondria-targeted Gene Delivery and Expression

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Mitochondria dysfunction plays a role in many human diseases. Therapeutic techniques for these disorders require novel delivery systems that can specifically target and penetrate mitochondria. In this study, we report a novel nanosome composed of dequalinium-DOTAP-DOPE(1,2 dioleoyl-3-trimethylammonium-propane-1,2-dioleoyl-sn-glycero-3-phosphoethanolamine) (DQA80s) as a potential mitochondria-targeting delivery vector. The functional DQAsome, DQA80s, showed enhanced transfection efficiency compared to a vector DQAsomes in HeLa cells.In addition, DQA80s/pDNA complexes exhibited rapid escape from the endosome into the cytosol. We observed the delivery of pDNA to mitochondria in living cells using flow cytometry, confocal microscopy, and TME imaging. More specifically, we confirmed our results by co-localization of hmtZsGreen constructs to mitochondria when delivered via DQAsomes and DQA80s in living cells. The mitochondria-targeting DQAsomes and DQA80s induced mitochondrial dysfunction through depolarization of mitochondrial membrane potential. Our data demonstrate that DQA80s show promise for use as a mitochondria-targeted carrier system for treatment of mitochondria diseases in vivo.

Keywords nanosome, DQAsome, Mitochondria-targeted gene, DQA80s

P42

Zbtb7c and SIRT1 repression: implications in high-fat diet and agedependent obesity

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The aging or high-fat diet-fed mice showed an increase in Zbtb7c expression in liver and white adipose tissues. The knockout of the Zbtb7c gene caused a significant decrease in fat tissues in aging mice. The knockdown of Zbtb7c mRNA in 3T3-L1 preadipocyte resulted in potent inhibition of adipocyte differentiation.
SIRT1 mRNA is increased in those tissues of Zbtb7c KO mice, suggesting Zbtb7c may repress SIRT1. Indeed, Zbtb7c interacted with p53 and bound to the p53REs to repress the SIRT1 gene. Zbtb7c made p53 interact with the corepressor mSin3A-HADC1 complex at the downstream p53RE. Both the p53 binding at the p53RE1 and the Zbtb7c binding at the p53RE2 is critical in SIRT1 repression. In particular, the mutation in the downstream p53RE changed the regulation of the SIRT1 gene by p53 and Zbtb7c. p53 no longer repressed the SIRT1 and ZbTb7c potently activated transcription. By repressing the SIRT1 gene, Zbtb7c increased the acetylation of the two major regulators of lipid metabolism and adipogenesis, Pgc-1α and Pparγ, which resulted in repression of Pgc-1α target genes and activation of the Pparγ target genes. Our study provided a molecular target that can overexpress SIRT1 protein in the liver, pancreas, adipose tissues, which can be beneficial in the treatment of diabetes, obesity, longevity, etc.

Keywords

ZBTB7C, SIRT1, Lipid metabolism, beta oxidation, Histone acetylation

P43

Simulation of substrate-dependent changes of mitochondrial function using a computational mitochondria model

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Mitochondrial substrates are essential for generation of ATP in the process of oxidative phosphorylation. They enter the citric acid cycle to generate NADH and FADH2 which are the source of electrons in the oxidative phosphorylation. A set of substrates which can maximize the mitochondrial respiration, however, is still in pursuit. We constructed a computational interface to simulate the effects of substrate composition. The model of mitochondria includes the citric acid cycle, electron transport system, substrate transporters, and malate-aspartate shuttle. We tested the effects of substrate combination in the cytosolic space on the mitochondrial generation of NADH and membrane potential. In case of single substrate, none of them was effective. In case of double substrates, the combination of malate and glutamate was most effective. In case of triple substrate, the combination of malate, glutamate, and succinate or malate, pyruvate, and glutamate was equally effective in increasing NADH and membrane potential. Addition of inorganic phosphates amplified the generation of NADH in all cases. Our computational model and its interface would be very useful as both the educational tool and research aid

Notes

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3P-MACE, 3-point major adverse cardiovascular events; **4P-MACE**, 4-point major adverse cardiovascular events; **CI**, confidence interval; **CV**, cardiovascular; **HbA1c**, glycosylated haemoglobin; **RAAS**, renin-angiotensin-aldosterone system.

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