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2024 McGarry Symposium

Literature Overview Touchstone Diabetes Center UTSW Medical Center 3/11/2024

Paul Cohen, M.D., Ph.D.
The Rockefeller University

Henry Ginsberg, M.D., [illegible].D.
Columbia University

[illegible]cyn, Ph.D.
Stanford University

Martin Myers, Jr., Ph.D.
University of Michigan

Cell Metabolism 36, 1–18, April 2, 2024

Cell Metabolism

CellPress

Article

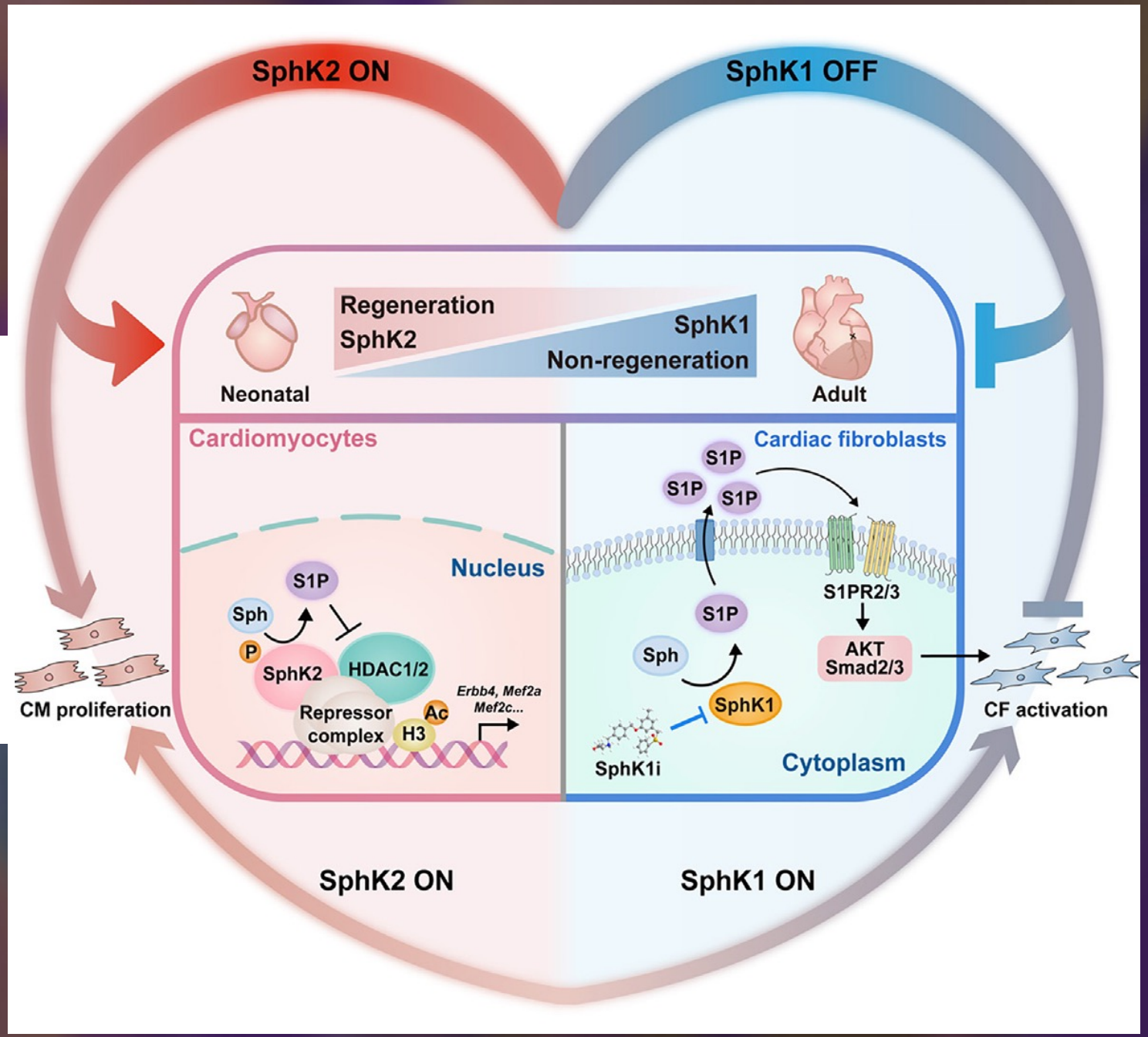
Sphingolipid metabolism controls mammalian heart regeneration

Xiaoqian Ji,[1,2,3,4,11] Zihao Chen,[1,3,4,11] Qiyuan Wang,[1,3,4,11] Bin Li,[1,3,4] Yan Wei,[1,3,4] Yun Li,[5,6,7] Jianqing Lin,[1,3,4] Weisheng Cheng,[1,3,4] Yijie Guo,[1,3,4] Shilin Wu,[1,3,4] Longkun Mao,[1,3,4] Yuzhou Xiang,[1,3,4] Tian Lan,[8] Shanshan Gu,[1,3,4] Meng Wei,[1,3,4] Joe Z. Zhang,[2] Lan Jiang,[5,6,7] Jia Wang,[9] Jin Xu,[10] and Nan Cao[1,3,4,12,*]

[1]Advanced Medical Technology Center, Zhongshan School of Medicine and the First Affiliated Hospital, Sun Yat-Sen University, Guangdong 510080, China

Utilization of lipids as energy substrates after birth causes cardiomyocyte (CM) cell-cycle arrest and loss of regenerative capacity in mammalian hearts. Beyond energy provision, proper management of lipid composition is crucial for cellular and organismal health, but its role in heart regeneration remains unclear. Here, we demonstrate widespread sphingolipid metabolism remodeling in neonatal hearts after injury and find that SphK1 and SphK2, isoenzymes producing the same sphingolipid metabolite sphingosine-1-phosphate (S1P), differently regulate cardiac regeneration. SphK2 is downregulated during heart development and determines CM proliferation via nuclear S1P-dependent modulation of histone acetylation. Reactivation of SphK2 induces adult CM cell-cycle re-entry and cytokinesis, thereby enhancing regeneration. Conversely, SphK1 is upregulated during development and promotes fibrosis through an S1P autocrine mechanism in cardiac fibroblasts. By fine-tuning the activity of each SphK isoform, we develop a therapy that simultaneously promotes myocardial repair and restricts fibrotic scarring to regenerate the infarcted adult hearts.

- Injury induces robust sphingolipid metabolism dynamics in the neonatal mouse hearts
- SphK2 promotes CM proliferation via nuclear S1P-dependent histone acetylation
- SphK1 depletion limits autocrine activation of CFs by S1P and promotes regeneration
- Introduction of the neonatal SphK1/SphK2 pattern induces adult heart regeneration



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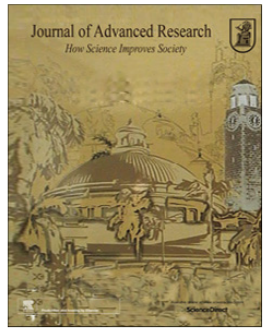

AdipoRon ameliorates the progression of heart failure with preserved ejection fraction via mitigating lipid accumulation and fibrosis

Wuping Tan [a,b,c,d,e,f,g,1], Yijun Wang [a,b,c,d,e,f,g,1], Siyi Cheng [a,b,c,d,e,f,g,1], Zhihao Liu [a,b,c,d,e,f,g,1], Mengjie Xie [a,b,c,d,e,f,g], Lingpeng Song [a,b,c,d,e,f,g], Qinfang Qiu [a,b,c,d,e,f,g], Xiaofei Wang [a,b,c,d,e,f,g], Zeyan Li [a,b,c,d,e,f,g], Tianyuan Liu [a,b,c,d,e,f,g], Fuding Guo [a,b,c,d,e,f,g,*], Jun Wang [h,*], Xiaoya Zhou [a,b,c,d,e,f,g,*]

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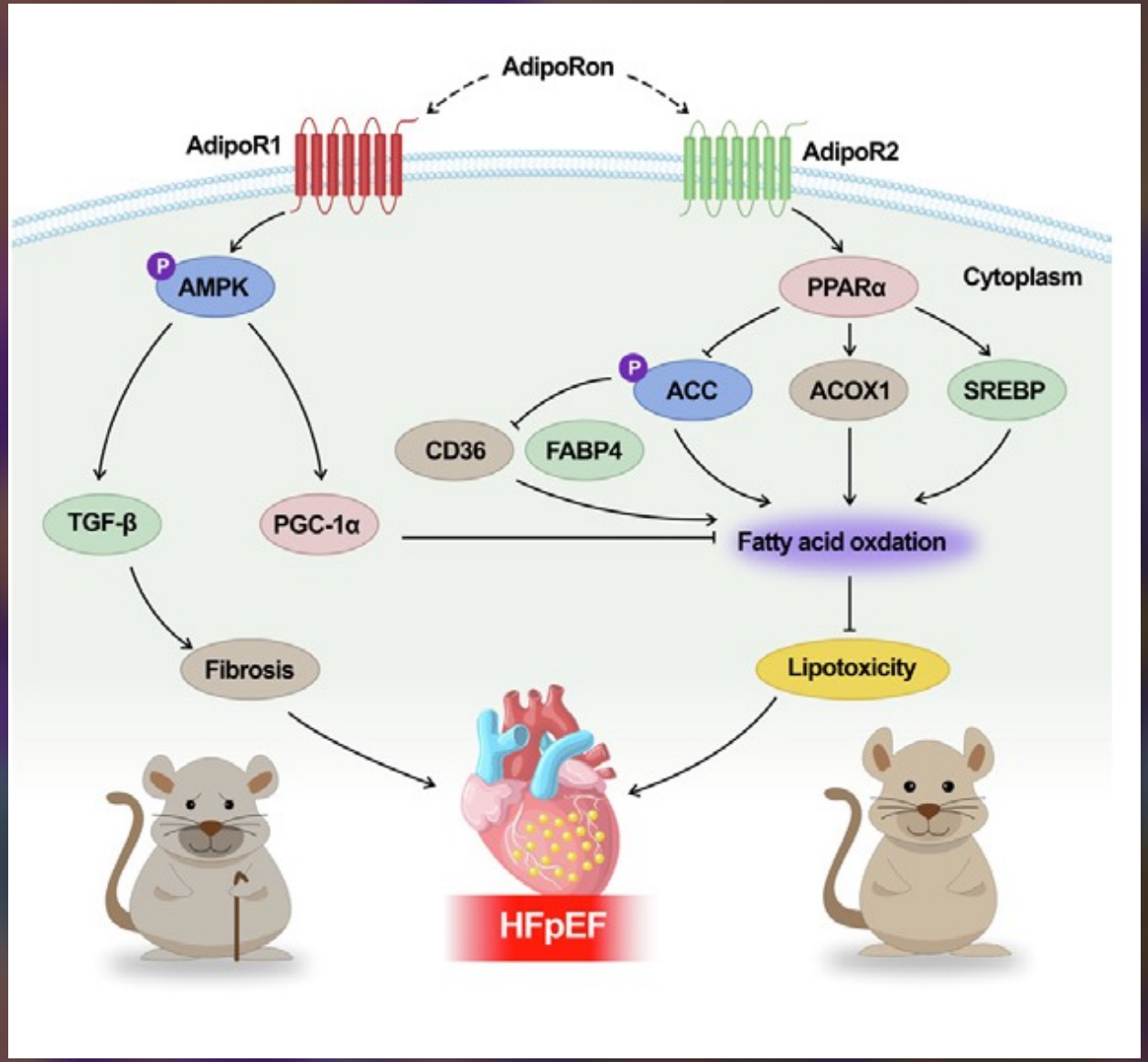
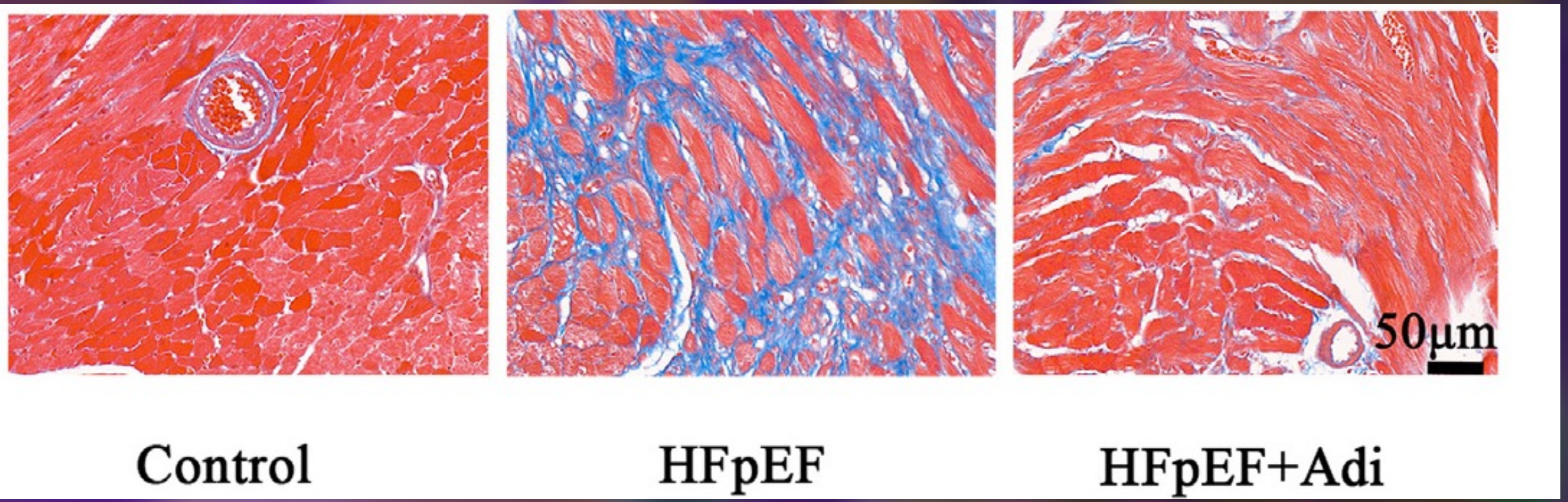
HIGHLIGHTS

- Adiponectin receptors (AdipoR) was downregulated in heart failure with preserved ejection fraction (HFpEF) mice.
- Impaired fatty acid oxidation (FAO) with increased fatty acid transport caused excess lipid accumulation in HFpEF mice.
- AdipoRon alleviated HFpEF phenotype partly via ameliorating cardiac lipid accumulation and fibrosis.
- AdipoRon ameliorated cardiac fibrosis partially via the regulation of AdipoR1/AMPKα /TGF-β pathways.
- AdipoRon restored fatty acid metabolism partially through AdipoR2/PPARα signaling pathways.



Objectives: We aimed to investigate the cardioprotective roles of AdipoRon, the adiponectin receptor agonist, in regulating lipid accumulation in the two-hit HFpEF model.
Methods: HFpEF mouse model was induced using 60 % high-fat diet plus L-NAME drinking water. Then, AdipoRon (50 mg/kg) or vehicle were administered by gavage to the two-hit HFpEF mouse model once daily for 4 weeks. Cardiac function was evaluated using echocardiography, and Postmortem analysis included RNA-sequencing, untargeted metabolomics, transmission electron microscopy and molecular biology methods.
Results: Our study presents the pioneering evidence that AdipoR was downregulated and impaired fatty acid oxidation in the myocardia of HFpEF mice, which was associated with lipid metabolism as indicated by untargeted metabolomics. AdipoRon, orally active synthetic adiponectin receptor agonist, could upregulate AdipoR1/2 (independently of adiponectin) and reduce lipid droplet accumulation, and alleviate fibrosis to restore HFpEF phenotypes. Finally, AdipoRon primarily exerted its effects through restoring the balance of myocardial fatty acid intake, transport, and oxidation via the downstream AMPKα or PPARα signaling pathways. The protective effects of AdipoRon in HFpEF mice were reversed by compound C and GW6471, inhibitors of AMPKα and PPARα, respectively.
Conclusions: AdipoRon ameliorated the HFpEF phenotype by promoting myocardial fatty acid oxidation, decreasing fatty acid transport, and inhibiting fibrosis via the upregulation of AdipoR and the activation of AdipoR1/AMPKα and AdipoR2/PPARα-related downstream pathways. These findings underscore the therapeutic potential of AdipoRon in HFpEF. Importantly, all these parameters get restored in the context of continued mechanical and metabolic stressors associated with HFpEF.


50μm
Control
HFpEF
HFpEF+Adi

J. Clin. Med. **2024**, *13*, 1195. https://doi.org/10.3390/jcm13051195

Journal of
Clinical Medicine

MDPI

Review

Myocardial Metabolism in Heart Failure with Preserved Ejection Fraction

John Aaron Henry [1,2,*], Liam S. Couch [1] and Oliver J. Rider [1]

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Metabolic disturbances play a crucial role in heart failure with preserved ejection fraction (HFpEF), presenting a unique opportunity for both understanding and treating this condition. Cardiometabolic risk factors, notably obesity and diabetes, significantly impact cardiac substrate utilisation. This leads to reduced myocardial ATP production and subsequent diastolic dysfunction. The insulin resistance triggered by these comorbidities tends to diminish glucose utilisation, resulting in an increased reliance on fatty acids as a primary fuel source. The progression from risk factor to HFpEF may be marked by the heart's diminished capacity to increase fatty acid metabolism, creating a mismatch between supply and utilisation. This imbalance can lead to myocardial steatosis and lipotoxicity. Consequently, targeting myocardial metabolism emerges as a promising approach in HFpEF treatment. Preliminary studies in animal models and human HFpEF patients have begun to explore ways to modify and enhance metabolism of fatty acids, glucose, and ketone bodies. However, further extensive research is essential to fully decipher the metabolic alterations in HFpEF and to uncover novel therapeutic targets.

Original Article
Basic Research

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dmj
DIABETES & METABOLISM JOURNAL

Check for updates

Alantolactone Attenuates Renal Fibrosis via Inhibition of Transforming Growth Factor β/Smad3 Signaling Pathway

Kyeong-Min Lee[1,*], Yeo Jin Hwang[1,*], Gwon-Soo Jung[2]

[1]Division of Biotechnology, Daegu Gyeongbuk Institute of Science and Technology, Daegu,
[2]New Drug Development Center, Daegu-Gyeongbuk Medical Innovation Foundation, Daegu, Korea

Background: Renal fibrosis is characterized by the accumulation of extracellular matrix proteins and interstitial fibrosis. Alantolactone is known to exert anticancer, anti-inflammatory, antimicrobial and antifungal effects; however, its effects on renal fibrosis remains unknown. Here, we investigated whether alantolactone attenuates renal fibrosis in mice unilateral ureteral obstruction (UUO) and evaluated the effect of alantolactone on transforming growth factor (TGF) signaling pathway in renal cells.

Methods: To evaluate the therapeutic effect of alantolactone, cell counting kit-8 (CCK-8) assay, histological staining, Western blot analysis, and real-time quantitative polymerase chain reaction were performed in UUO kidneys *in vivo* and in TGF-β-treated renal cells *in vitro*.

Results: Alantolactone (0.25 to 4 μM) did not affect the viability of renal cells. Mice orally administered 5 mg/kg of alantolactone daily for 15 days did not show mortality or liver toxicity. Alantolactone decreased UUO-induced blood urea nitrogen and serum creatinine levels. In addition, it significantly alleviated renal tubulointerstitial damage and fibrosis and decreased collagen type I, fibronectin, and α-smooth muscle actin (α-SMA) expression in UUO kidneys. In NRK-49F cells, alantolactone inhibited TGF-β-stimulated expression of fibronectin, collagen type I, plasminogen activator inhibitor-1 (PAI-1), and α-SMA. In HK-2 cells, alantolactone inhibited TGF-β-stimulated expression of collagen type I and PAI-1. Alantolactone inhibited UUO-induced phosphorylation of Smad3 in UUO kidneys. In addition, it not only decreased TGF-β secretion but also Smad3 phosphorylation and translocation to nucleus in both kidney cell lines.

Conclusion: Alantolactone improves renal fibrosis by inhibiting the TGF-β/Smad3 signaling pathway in obstructive nephropathy. Thus, alantolactone is a potential therapeutic agent for chronic kidney disease.

Original Article
Basic Research

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DIABETES & METABOLISM JOURNAL

Check for updates

DWN12088, A Prolyl-tRNA Synthetase Inhibitor, Alleviates Hepatic Injury in Nonalcoholic Steatohepatitis

Dong-Keon Lee[1,2,*], Su Ho Jo[1,*], Eun Soo Lee[1], Kyung Bong Ha[1], Na Won Park[1], Deok-Hoon Kong[2], Sang-In Park[2], Joon Seok Park[3], Choon Hee Chung[1]

[1]Department of Internal Medicine and Research Institute of Metabolism and Inflammation, Yonsei University Wonju College of Medicine, Wonju,
[2]Division of Research Program, Scripps Korea Antibody Institute, Chuncheon,
[3]Drug Discovery Center, Daewoong Pharmaceutical Co. Ltd., Seoul, Korea

Background: Nonalcoholic steatohepatitis (NASH) is a liver disease caused by obesity that leads to hepatic lipoapoptosis, resulting in fibrosis and cirrhosis. However, the mechanism underlying NASH is largely unknown, and there is currently no effective therapeutic agent against it. DWN12088, an agent used for treating idiopathic pulmonary fibrosis, is a selective prolyl-tRNA synthetase (PRS) inhibitor that suppresses the synthesis of collagen. However, the mechanism underlying the hepatoprotective effect of DWN12088 is not clear. Therefore, we investigated the role of DWN12088 in NASH progression.

Methods: Mice were fed a chow diet or methionine-choline deficient (MCD)-diet, which was administered with DWN12088 or saline by oral gavage for 6 weeks. The effects of DWN12088 on NASH were evaluated by pathophysiological examinations, such as real-time quantitative reverse transcription polymerase chain reaction, immunoblotting, biochemical analysis, and immunohistochemistry. Molecular and cellular mechanisms of hepatic injury were assessed by *in vitro* cell culture.

Results: DWN12088 attenuated palmitic acid (PA)-induced lipid accumulation and lipoapoptosis by downregulating the Rho-kinase (ROCK)/AMP-activated protein kinase (AMPK)/sterol regulatory element-binding protein-1c (SREBP-1c) and protein kinase R-like endoplasmic reticulum kinase (PERK)/α subunit of eukaryotic initiation factor 2 (eIF2α)/activating transcription factor 4 (ATF4)/C/EBP-homologous protein (CHOP) signaling cascades. PA increased but DWN12088 inhibited the phosphorylation of nuclear factor-κB (NF-κB) p65 (Ser536, Ser276) and the expression of proinflammatory genes. Moreover, the DWN12088 inhibited transforming growth factor β (TGFβ)-induced pro-fibrotic gene expression by suppressing TGFβ receptor 1 (TGFβR1)/Smad2/3 and TGFβR1/glutamyl-prolyl-tRNA synthetase (EPRS)/signal transducer and activator of transcription 6 (STAT6) axis signaling. In the case of MCD-diet-induced NASH, DWN12088 reduced hepatic steatosis, inflammation, and lipoapoptosis and prevented the progression of fibrosis.

Conclusion: Our findings provide new insights about DWN12088, namely that it plays an important role in the overall improvement of NASH. Hence, DWN12088 shows great potential to be developed as a new integrated therapeutic agent for NASH.

Molecular Biology Reports (2024) 51:206
https://doi.org/10.1007/s11033-023-08918-z

ORIGINAL ARTICLE

COL6A3 enhances the osteogenic differentiation potential of BMSCs by promoting mitophagy in the osteoporotic microenvironment

Kun Wang[1,2,3] · Xin Peng[2] · Rui Zhang[2] · Xiaotao Wu[1,2] · Lu Mao[1,2]

Abstract

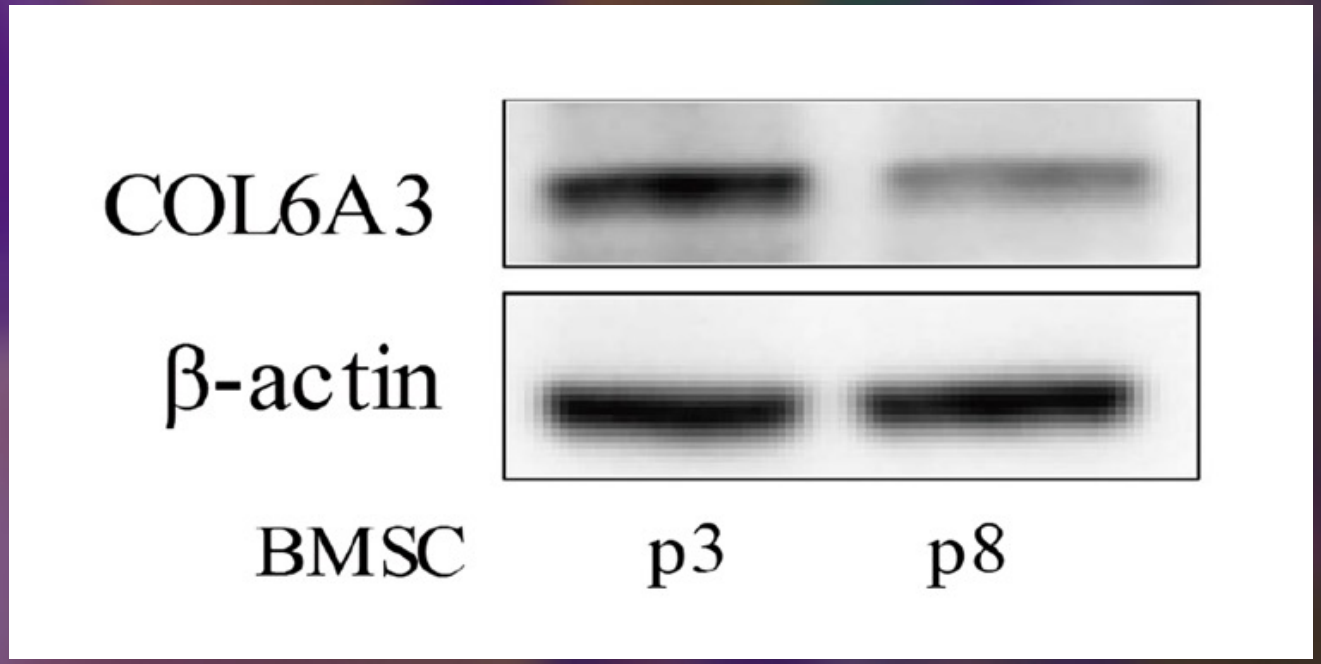
Background Bone marrow mesenchymal stem cells (BMSCs) have been widely recognized as a highly promising option for cell-based tissue engineering therapy targeting osteoporosis. However, the osteogenic differentiation of BMSCs is impeded by the limited viability and diminished capacity for bone formation within the osteoporotic microenvironment.

Methods In this study, the *COL6A3* gene was confirmed through an extensive analysis of the preceding single-cell sequencing database. The generation of an inflammatory microenvironment resembling osteoporotic cell transplantation was achieved by employing lipopolysaccharide (LPS). A lentivirus targeting the *COL6A3* gene was constructed, and a Western blotting assay was used to measure the marker proteins of osteogenesis, adipogenesis, and mitophagy. Immunofluorescence was utilized to observe the colocalization of mitochondria and lysosomes. The apoptosis rate of each group was evaluated using the TUNEL assay, and the mitochondrial membrane potential was assessed using JC-1 staining.

Results This investigation discovered that the impaired differentiation capacity and decreased viability of BMSCs within the inflammatory microenvironment were markedly ameliorated upon overexpression of the specific *COL6A3* gene. Moreover, the administration of *COL6A3* gene overexpression successfully mitigated the inhibitory impacts of LPS on mitophagy and the expression of inflammatory mediators, specifically inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), in BMSCs. To clarify the underlying mechanism, the role of mitophagy during the differentiation of *COL6A3* gene-modified BMSCs in the inflammatory microenvironment was evaluated using the mitophagy inhibitor Mdivi-1.

Conclusions In the context of lipopolysaccharide (LPS) stimulation, *COL6A3* enhances the differentiation of BMSCs into osteogenic and adipogenic lineages through the promotion of mitophagy and the maintenance of mitochondrial health. Our findings may provide a novel therapeutic approach utilizing stem cells in the treatment of osteoporosis.

GemmaPharma (Shanghai, China) provided lentiviruses that overexpressed the *COL6A3* gene as well as a negative control lentivirus. The second generation cells were placed in a



Macrophage-Derived Endotrophin Supports Tumor Migration Potentials in Thyroid Caner

Hyo Shik Shin, MS[1], Hana Kim, MD[2], Young Shin Song, MD, PhD[3], Hyun Jin Sun, MS[4], Young Mi Whang, PhD[4], Jiyoung Park, PhD[5], Do Joon Park, MD, PhD[1], Young Joo Park, MD,PhD[1], Sun Wook Cho, MD, PhD[1].

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human thyroid tissues was studied. Immunohistochemical staining showed that the ETP was expressed in papillary (PTC) or anaplastic (ATC) thyroid cancer tissues but not

their ETP expression, ETP^{low} and ETP^{High}. Tumor size was bigger and LN metastasis rates were higher in ETP^{High} than

Immunofluorescent staining showed that the expression of ETP and F4/80-postive macrophages were co-localized in the peritumoral area. Additionally, human monocytic

Treatment of CMs from co-cultures increased cell migration potentials than that of the single cell alone, and these effects were reduced by anti-ETP neutralizing antibody,

including MMP-9 and MMP-14. In conclusion, macrophage contributes ETP productions by modulating MMP expressions and ETP supports pro-metastatic potentials of human thyroid cancer cells in TMEs. Thus ETP can be a good therapeutic target for macrophage-enriched advanced thyroid cancers.

Original Article
Cardiovascular Risk/Epidemiology

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dmj
DIABETES & METABOLISM JOURNAL

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Psychotic Disorders and the Risk of Type 2 Diabetes Mellitus, Atherosclerotic Cardiovascular Diseases, and All-Cause Mortality: A Population-Based Matched Cohort Study

You-Bin Lee[1], Hyewon Kim[2], Jungkuk Lee[3], Dongwoo Kang[3], Gyuri Kim[1], Sang-Man Jin[1], Jae Hyeon Kim[1], Hong Jin Jeon[4], Kyu Yeon Hur[1]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul,

Background: The effects of psychotic disorders on cardiometabolic diseases and premature death need to be determined in Asian populations.
Methods: In this population-based matched cohort study, the Korean National Health Insurance Service database (2002 to 2018) was used. The risk of type 2 diabetes mellitus (T2DM), acute myocardial infarction (AMI), ischemic stroke, composite of all cardiometabolic diseases, and all-cause death during follow-up was compared between individuals with psychotic disorders treated with antipsychotics (n=48,162) and 1:1 matched controls without psychiatric disorders among adults without cardiometabolic diseases before or within 3 months after baseline.
Results: In this cohort, 53,683 composite cases of all cardiometabolic diseases (during median 7.38 years), 899 AMI, and 1,216 ischemic stroke cases (during median 14.14 years), 7,686 T2DM cases (during median 13.26 years), and 7,092 deaths (during median 14.23 years) occurred. The risk of all outcomes was higher in subjects with psychotic disorders than matched controls (adjusted hazard ratios [95% confidence intervals]: 1.522 [1.446 to 1.602] for T2DM; 1.455 [1.251 to 1.693] for AMI; 1.568 [1.373 to 1.790] for ischemic stroke; 1.595 [1.565 to 1.626] for composite of all cardiometabolic diseases; and 2.747 [2.599 to 2.904] for all-cause mortality) during follow-up. Similar patterns of associations were maintained in subgroup analyses but more prominent in younger individuals (P for interaction <0.0001) when categorized as those aged 18–39, 40–64, or ≥65 years.
Conclusion: Patients with psychotic disorders treated with antipsychotics were associated with increased risk of premature all-cause mortality and cardiometabolic outcomes in an Asian population. This relationship was more pronounced in younger individuals, especially aged 18 to 39 years.

company announcement

novo nordisk®

Semaglutide 1.0 mg demonstrates 24% reduction in the risk of kidney disease-related events in people with type 2 diabetes and chronic kidney disease in the FLOW trial

Bagsværd, Denmark, 5 March 2024 – Novo Nordisk today announced the headline results from the kidney outcomes trial FLOW. The announcement today follows the decision to stop the trial early due to efficacy, which was announced on 10 October 2023, based on a recommendation from an Independent Data Monitoring Committee. The double-blind trial compared injectable semaglutide 1.0 mg with placebo as an adjunct to standard of care for prevention of progression of kidney impairment and risk of kidney and cardiovascular mortality in people with type 2 diabetes and chronic kidney disease (CKD). The trial enrolled 3,533 people with type 2 diabetes and CKD.

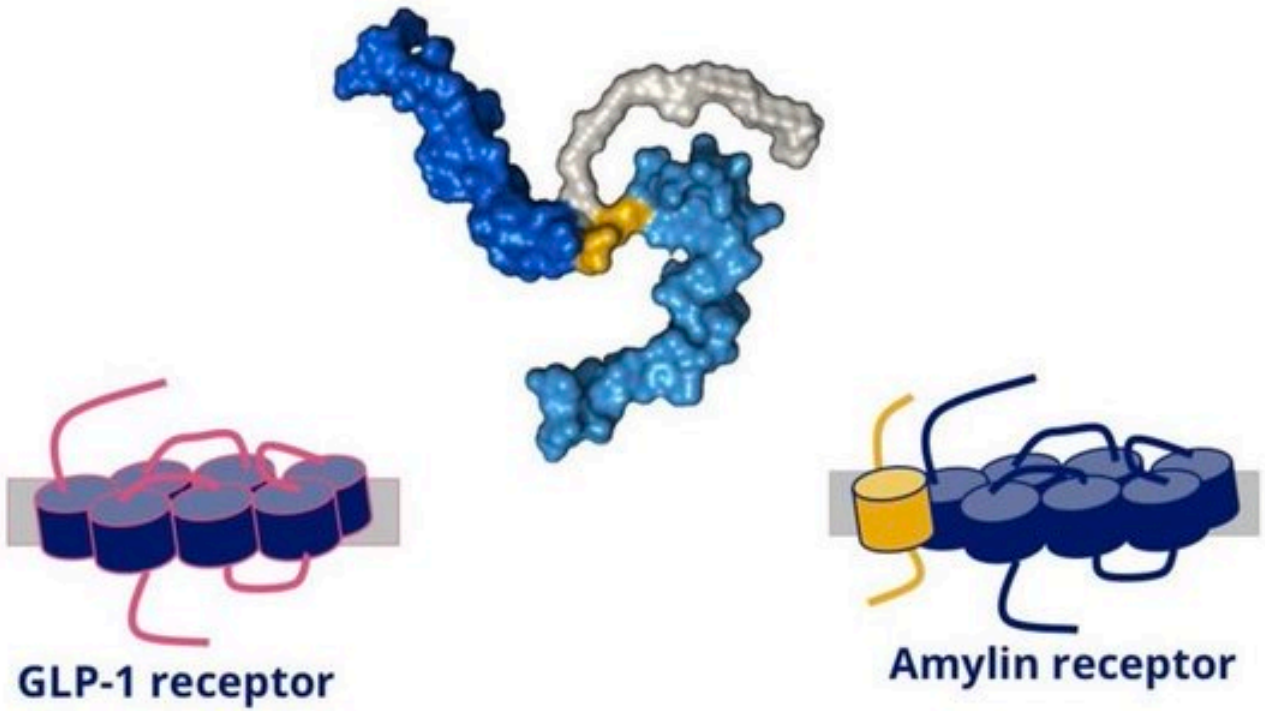
FORBES > BUSINESS

BREAKING

Ozempic Maker's New Weight Loss Pill Beats Wegovy In Early Trial — What To Know About Novo Nordisk's Amycretin

GLP-1 and amylin.

Amycretin is a GLP-1 and amylin receptor co-agonist intended for oral delivery



Utilising the SNAC technology

SCIENCE ADVANCES | RESEARCH ARTICLE

BIOCHEMISTRY

Structure-guided discovery of a single-domain antibody agonist against human apelin receptor

Yanbin Ma[1], Yao Ding[1], Xianqiang Song[1], Xiaochuan Ma[1], Xun Li[1], Ning Zhang[1], Yunpeng Song[1], Yaping Sun[1], Yuqing Shen[2], Wenge Zhong[1]*, Liaoyuan A. Hu[1], Yingli Ma[1], Mei-Yun Zhang[1†]

Developing antibody agonists targeting the human apelin receptor (APJ) is a promising therapeutic approach for the treatment of chronic heart failure. Here, we report the structure-guided discovery of a single-domain antibody (sdAb) agonist JN241-9, based on the cocrystal structure of APJ with an sdAb antagonist JN241, the first cocrystal structure of a class A G protein–coupled receptor (GPCR) with a functional antibody. As revealed by the structure, JN241 binds to the extracellular side of APJ, makes critical contacts with the second extracellular loop, and inserts the CDR3 into the ligand-binding pocket. We converted JN241 into a full agonist JN241-9 by inserting a tyrosine into the CDR3. Modeling and molecular dynamics simulation shed light on JN241-9–stimulated receptor activation, providing structural insights for finding agonistic antibodies against class A GPCRs.

Cell Metabolism 36, 1–17, May 7, 2024

Cell Metabolism

CellPress
OPEN ACCESS

Article

Hepatic malonyl-CoA synthesis restrains gluconeogenesis by suppressing fat oxidation, pyruvate carboxylation, and amino acid availability

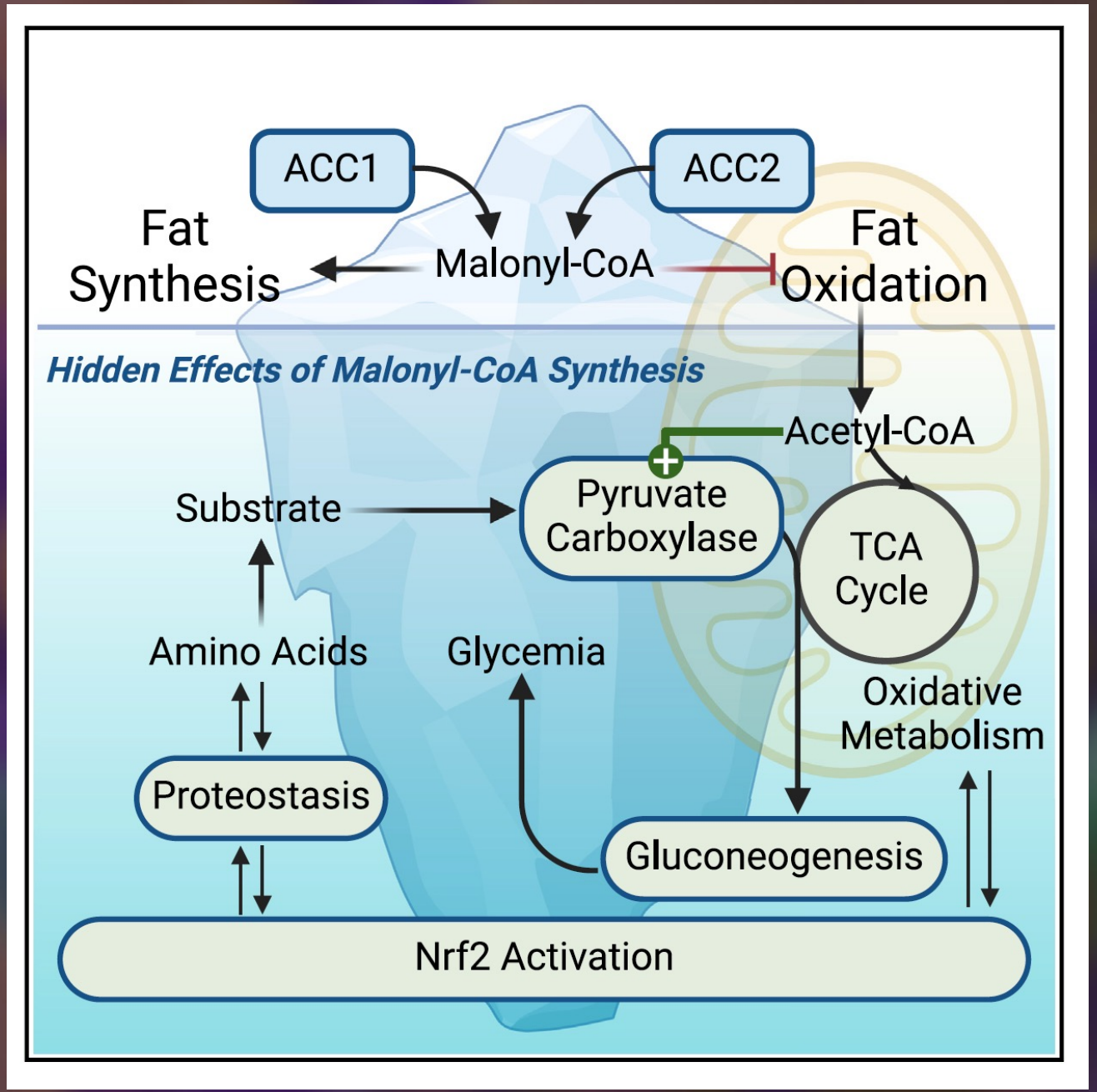
Stanislaw Deja,[1,2] Justin A. Fletcher,[1,3] Chai-Wan Kim,[1] Blanka Kucejova,[1] Xiaorong Fu,[1,5] Monika Mizerska,[1] Morgan Villegas,[1] Natalia Pudelko-Malik,[1,10] Nicholas Browder,[1] Melissa Inigo-Vollmer,[1] Cameron J. Menezes,[7] Prashant Mishra,[7] Eric D. Berglund,[4] Jeffrey D. Browning,[3,4] John P. Thyfault,[8] Jamey D. Young,[9] Jay D. Horton,[1,4,5,*] and Shawn C. Burgess[1,6,11,*]

[1]Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, TX 75390-9046, USA

Acetyl-CoA carboxylase (ACC) promotes prandial liver metabolism by producing malonyl-CoA, a substrate for *de novo* lipogenesis and an inhibitor of CPT-1-mediated fat oxidation. We report that inhibition of ACC also produces unexpected secondary effects on metabolism. Liver-specific double ACC1/2 knockout (LDKO) or pharmacologic inhibition of ACC increased anaplerosis, tricarboxylic acid (TCA) cycle intermediates, and gluconeogenesis by activating hepatic CPT-1 and pyruvate carboxylase flux in the fed state. Fasting should have marginalized the role of ACC, but LDKO mice maintained elevated TCA cycle intermediates and preserved glycemia during fasting. These effects were accompanied by a compensatory induction of proteolysis and increased amino acid supply for gluconeogenesis, which was offset by increased protein synthesis during feeding. Such adaptations may be related to Nrf2 activity, which was induced by ACC inhibition and correlated with fasting amino acids. The findings reveal unexpected roles for malonyl-CoA synthesis in liver and provide insight into the broader effects of pharmacologic ACC inhibition.

Highlights

- ACC inhibition increases gluconeogenesis in fed mice by activating CPT-1 and PC flux
- ACC inhibition unexpectedly increases anaplerosis and gluconeogenesis in fasted mice
- Adaptive changes in proteostasis mediate ACC's unexpected effects during fasting
- Hepatic Nrf2 is activated by ACC inhibition and may play a role in its adaptive effects



Cell Metabolism
Previews

CellPress

UCP1 and CKB are parallel players in BAT

Meng Dong,[1] Ziyu Cheng,[1,2] and Wanzhu Jin[1,2,*]
[1]Key Laboratory of Animal Ecology and Conservation Biology, Institute of Zoology, Chinese Academy of Sciences, 1 West Beichen Road No. 5, Chaoyang District, Beijing 100101, China
[2]University of the Chinese Academy of Sciences, Beijing 100049, China
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https://doi.org/10.1016/j.cmet.2024.01.016

It is generally believed that the contributions of the UCP1-independent thermogenic pathways are secondary to UCP1-mediated thermogenesis in BAT. Now, Rahbani et al. demonstrate *in vivo* that adaptive thermogenesis in brown adipose tissue is regulated by UCP1 and CKB in parallel.

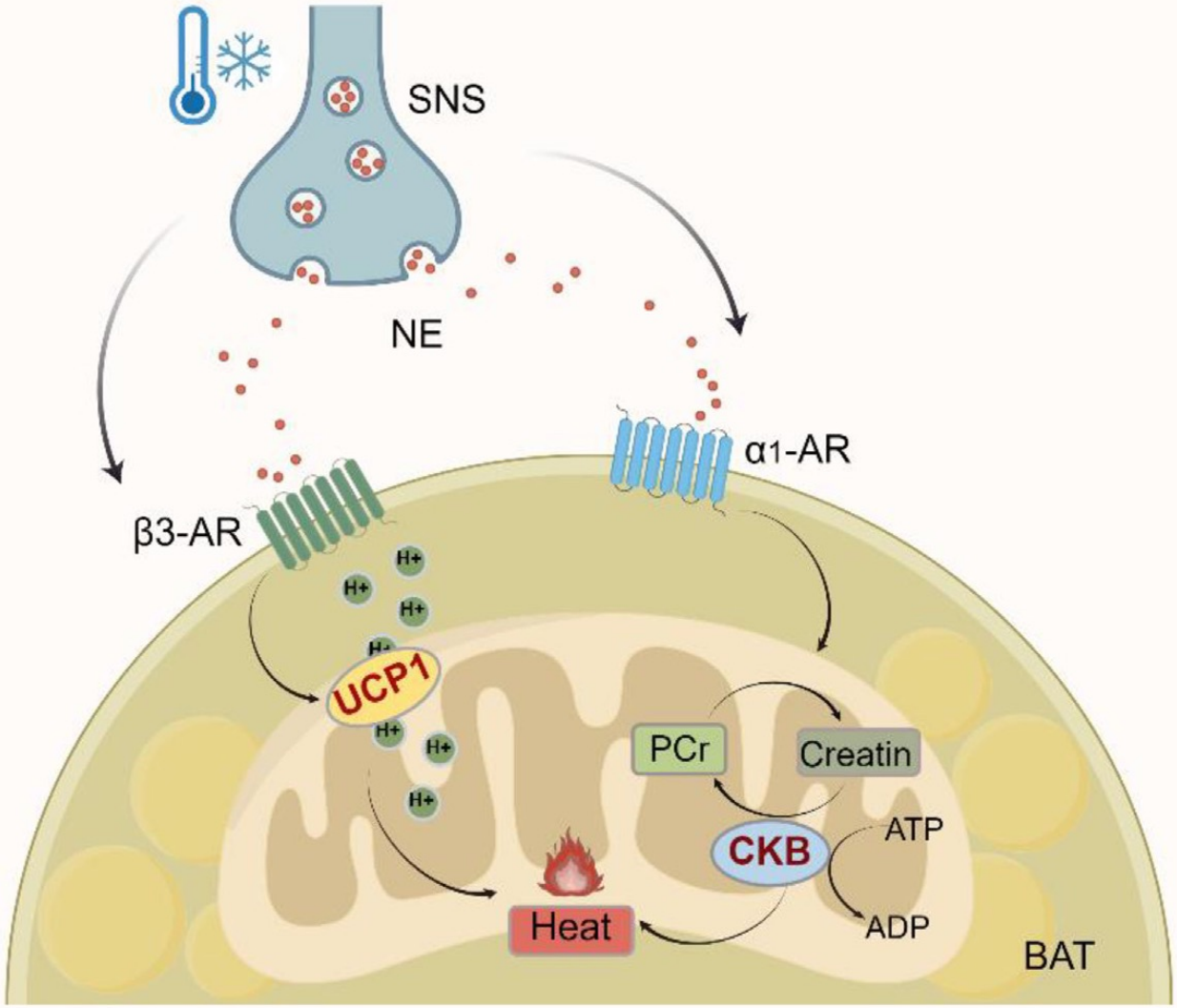


Figure 1. UCP1 and CKB regulate the adaptive thermogenesis process in parallel
Norepinephrine (NE) secreted by the sympathetic nervous system (SNS) that, in response to cold stimulation, acts on UCP1 and CKB via β3-AR and α1-AR receptors, respectively. Brown adipose tissue (BAT) utilizes non-paralogous protein redundancy to support robustness to promote cold-induced energy dissipation through UCP1 and CKB.

First, the authors found that the mRNA expression levels of several key genes in the Ca^{2+} futile cycling and TAG-fatty acid cycling also change in these mice, so do these pathways also regulate adaptive thermogenesis in parallel? Second,

Cell Metabolism 36, 526–540, March 5, 2024

CellPress

Cell Metabolism

Article

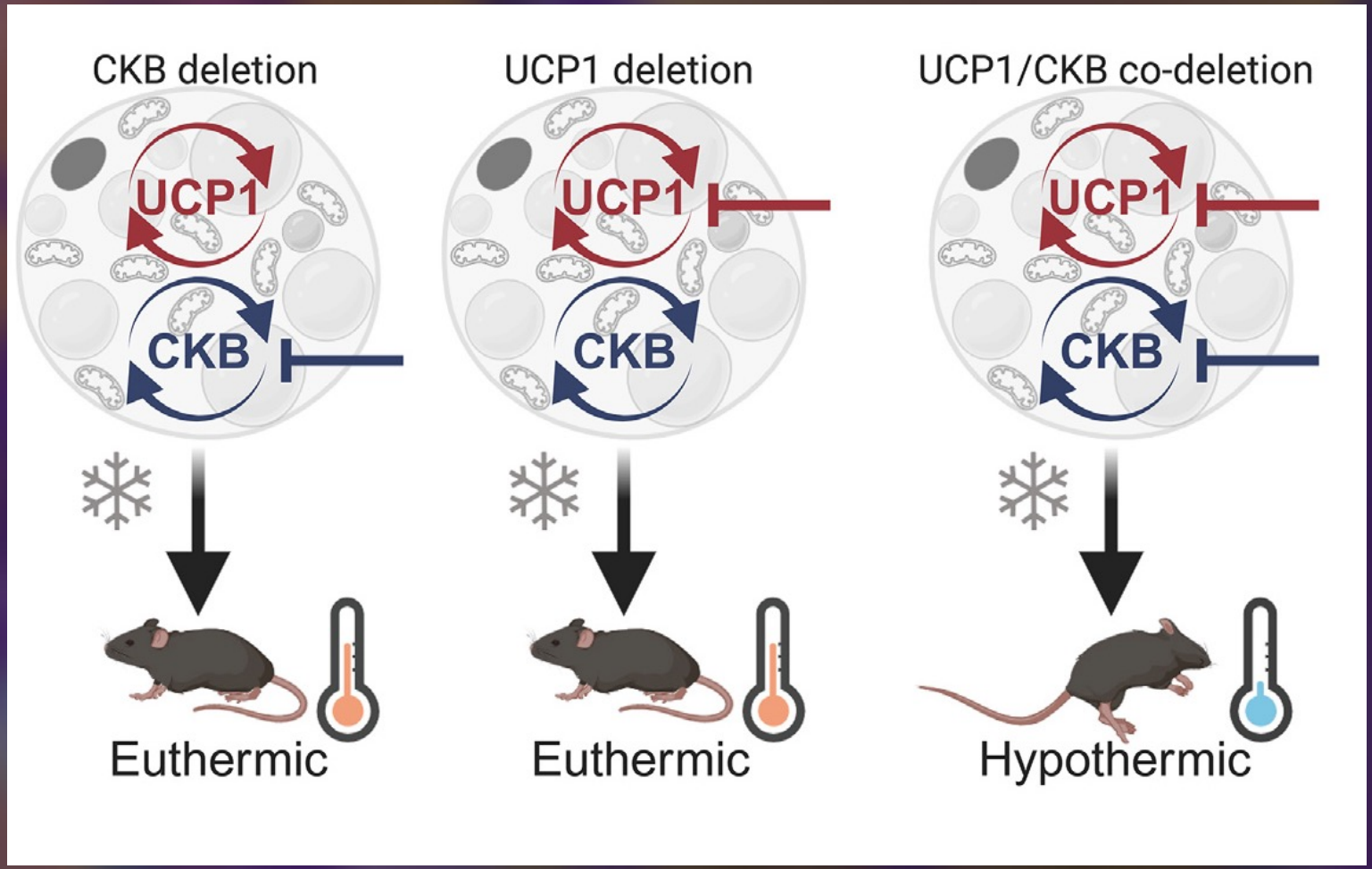
Parallel control of cold-triggered adipocyte thermogenesis by UCP1 and CKB

Janane F. Rahbani,[1,7] Jakub Bunk,[1,2,7] Damien Lagarde,[1] Bozena Samborska,[1] Anna Roesler,[1,2] Haopeng Xiao,[3,4] Abhirup Shaw,[1] Zafir Kaiser,[1,2] Jessica L. Braun,[5] Mia S. Geromella,[5] Val A. Fajardo,[5] Robert A. Koza,[6] and Lawrence Kazak[1,2,8,*]

[1]Rosalind and Morris Goodman Cancer Institute, McGill University, Montreal, QC H3A 1A3, Canada

Highlights

- Inducible adipocyte-specific *Ucp1* deletion evades secondary changes beyond UCP1
- Individually, UCP1 and CKB are dispensable for cold-stimulated thermogenesis
- UCP1 and CKB co-deletion causes hypothermia with near-full penetrance
- Quantitative contribution of UCP1-independent adipocyte thermogenesis is defined



PNAS 2024 Vol. 121 No. 10 e2318771121

PNAS RESEARCH ARTICLE | PHYSIOLOGY OPEN ACCESS

Mitochondrial uncoupling proteins protect human airway epithelial ciliated cells from oxidative damage

Akansha Jain[a,b,1], Bo Ram Kim[a,c,1], Wenjie Yu[a,c], Thomas O. Moninger[a], Philip H. Karp[a,c], Brett A. Wagner[d], and Michael J. Welsh[a,b,c,2]

Apical cilia on epithelial cells defend the lung by propelling pathogens and particulates out of the respiratory airways. Ciliated cells produce ATP that powers cilia beating by densely grouping mitochondria just beneath the apical membrane. However, this efficient localization comes at a cost because electrons leaked during oxidative phosphorylation react with molecular oxygen to form superoxide, and thus, the cluster of mitochondria creates a hotspot for oxidant production. The relatively high oxygen concentration overlying airway epithelia further intensifies the risk of generating superoxide. Thus, airway ciliated cells face a unique challenge of producing harmful levels of oxidants. However, surprisingly, highly ciliated epithelia produce less reactive oxygen species (ROS) than epithelia with few ciliated cells. Compared to other airway cell types, ciliated cells express high levels of mitochondrial uncoupling proteins, UCP2 and UCP5. These proteins decrease mitochondrial protonmotive force and thereby reduce production of ROS. As a result, lipid peroxidation, a marker of oxidant injury, decreases. However, mitochondrial uncoupling proteins exact a price for decreasing oxidant production; they decrease the fraction of mitochondrial respiration that generates ATP. These findings indicate that ciliated cells sacrifice mitochondrial efficiency in exchange for safety from damaging oxidation. Employing uncoupling proteins to prevent oxidant production, instead of relying solely on antioxidants to decrease postproduction oxidant levels, may offer an advantage for targeting a local area of intense ROS generation.

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Seipin localizes at endoplasmic-reticulum-mitochondria contact sites to control mitochondrial calcium import and metabolism in adipocytes

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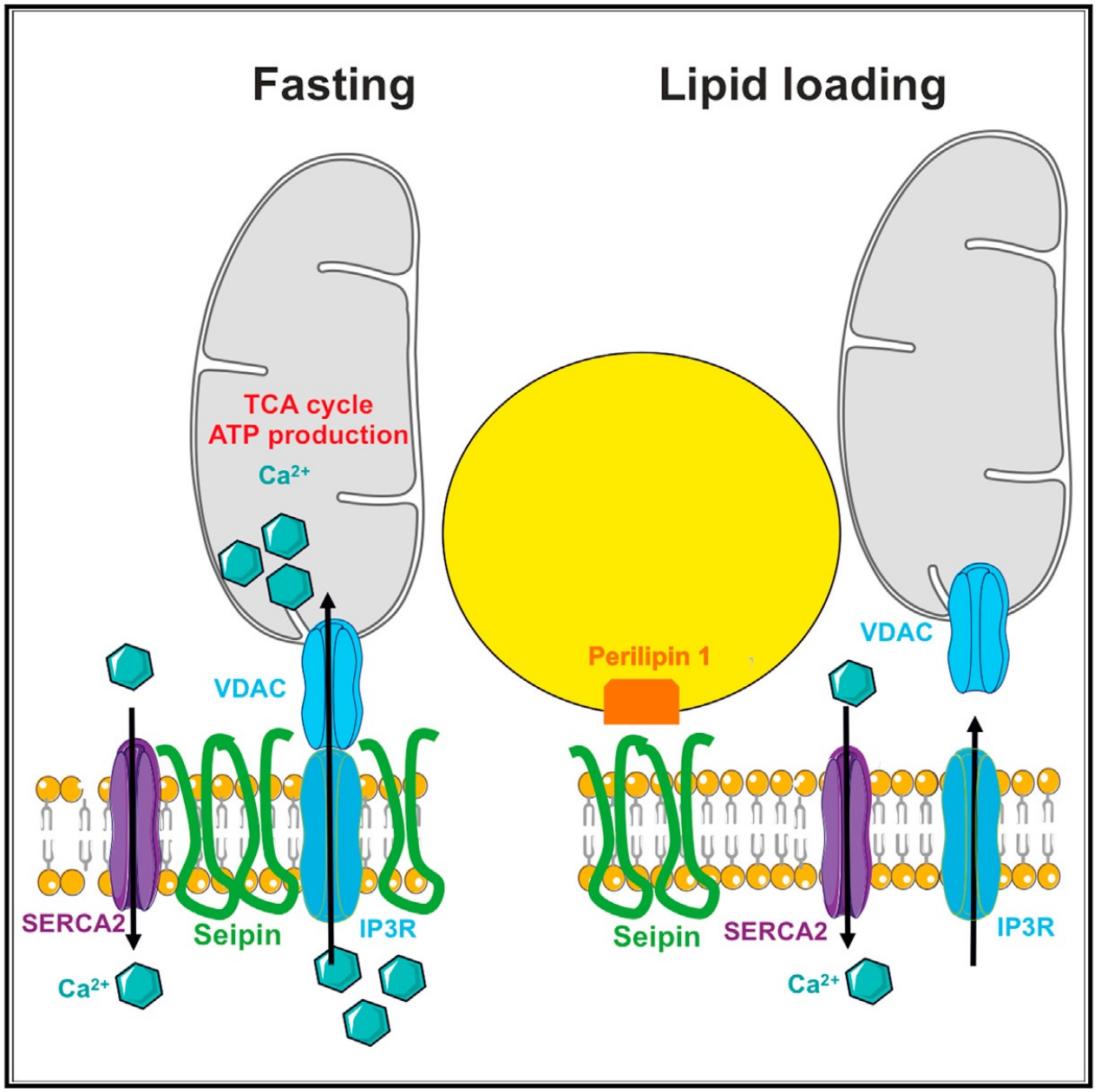
- Seipin is enriched at ER-MAMs
- Seipin interacts with MAM calcium regulators in a nutritionally regulated manner
- Adipocyte seipin deficiency impairs mitochondrial calcium import and ATP production
- Inducible seipin removal from adipose tissue leads to rapid mitochondrial dysfunction



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Lipid droplets and cellular lipid flux

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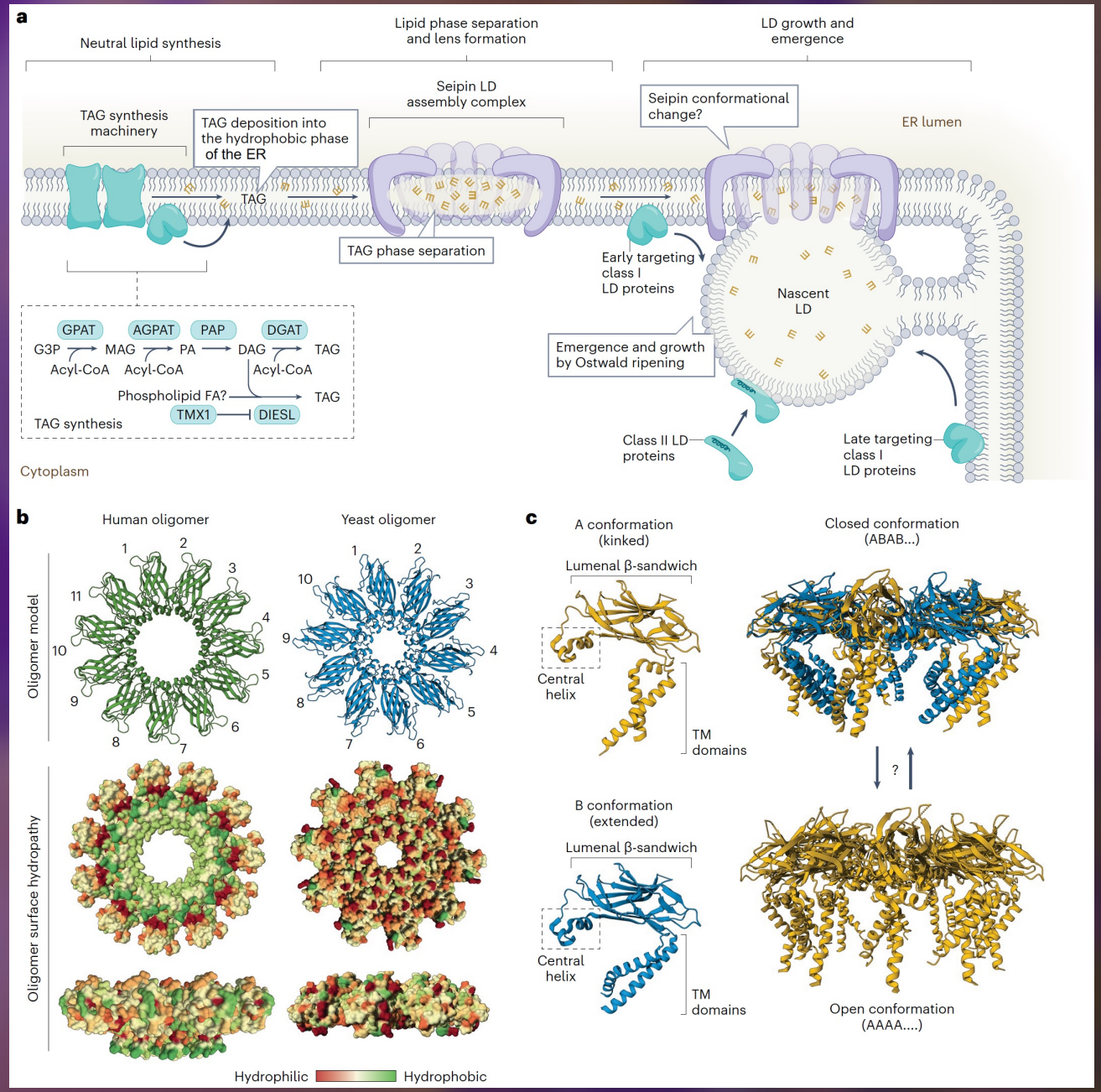
Lipid droplets are dynamic organelles that store neutral lipids, serve the metabolic needs of cells, and sequester lipids to prevent lipotoxicity and membrane damage. Here we review the current understanding of the mechanisms of lipid droplet biogenesis and turnover, the transfer of lipids and metabolites at membrane contact sites, and the role of lipid droplets in regulating fatty acid flux in lipotoxicity and cell death.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Neutral lipid synthesis
Lipid phase separation and lens formation
LD growth and emergence
TAG synthesis machinery
TAG deposition into the hydrophobic phase of the ER
Seipin LD assembly complex
Seipin conformational change?
ER lumen
TAG
TAG phase separation
Early targeting class I LD proteins
Nascent LD
Emergence and growth by Ostwald ripening
Class II LD proteins
Late targeting class I LD proteins
GPAT
AGPAT
PAP
DGAT
G3P
MAG
PA
DAG
TAG
Acyl-CoA
Acyl-CoA
Acyl-CoA
Phospholipid FA?
TMX1
DIESL
TAG synthesis
Cytoplasm
b
Human oligomer
Yeast oligomer
Oligomer model
Oligomer surface hydropathy
Hydrophilic
Hydrophobic
c
A conformation (kinked)
Lumenal β-sandwich
Central helix
TM domains
Closed conformation (ABAB...)
?
B conformation (extended)
Lumenal β-sandwich
Central helix
TM domains
Open conformation (AAAA....)

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Review article

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Futile lipid cycling: from biochemistry to physiology

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Anand Kumar Sharma, Radhika Khandelwal & Christian Wolfrum

In the healthy state, the fat stored in our body isn't just inert. Rather, it is dynamically mobilized to maintain an adequate concentration of fatty acids (FAs) in our bloodstream. Our body tends to produce excess FAs to ensure that the FA availability is not limiting. The surplus FAs are actively re-esterified into glycerides, initiating a cycle of breakdown and resynthesis of glycerides. This cycle consumes energy without generating a new product and is commonly referred to as the 'futile lipid cycle' or the glyceride/FA cycle. Contrary to the notion that it's a wasteful process, it turns out this cycle is crucial for systemic metabolic homeostasis. It acts as a control point in intra-adipocyte and inter-organ cross-talk, a metabolic rheostat, an energy sensor and a lipid diversifying mechanism. In this Review, we discuss the metabolic regulation and physiological implications of the glyceride/FA cycle and its mechanistic underpinnings.