Journal of Family Medicine

Open Access

Austin Publishing Group

Research Article

# Post-translational Regulation of Mitochondrial Dynamics in Pancreatic β-Cells: Bridging Proteostatic Adaptations to Metabolic Reprogramming in Type 2 Diabetes

**Li X[1], Jiang H[2], Chan LWC[3], Fei S[4], Shao B[5], Li S[2], Liu X[6] and Yang S[2]***

[1]Department of Pathophysiology, School of Basic Medical Sciences, Hubei University of Medicine, Shiyan 442000, PR China

[2]Department of Laboratory Medicine, Huangshi Maternity and Children's Health Hospital, Affiliated Maternity and Children's Health Hospital of Hubei Polytechnic University, Huangshi Key Laboratory of Birth Defects Prevention, Huangshi, 435000, Hubei, PR China

[3]Department of Health Technology and Informatics, Hong Kong Polytechnic University, Hong Kong 99077, Hong Kong

[4]Pediatrics department, Huangshi maternal and Child Health Care Hospital, Affiliated Maternity and Children's Health Hospital of Hubei Polytechnic University, Huangshi Key Laboratory of Birth Defects Prevention, Huangshi, Hubei, 435003, PR China

[5]Department of Intensive Care Unit, Huangshi Maternity and Children's Health Hospital, Affiliated Maternity and Children's Health Hospital of Hubei Polytechnic University, Huangshi Key Laboratory of Birth Defects Prevention, Huangshi, 435000, Hubei, PR China

[6]Department of Ultrasound Medicine Huangshi Maternity and Children's Health Hospital, Affiliated Maternity and Children`s Health Hospital of Hubei Polytechnic University, Huangshi Key Laboratory of Birth Defects Prevention, Huangshi, 435000, Hubei, PR China

***Corresponding author:** Sijun Yang, Department of Laboratory Medicine, Huangshi Maternity and Children's Health Hospital, Affiliated Maternity and Children`s Health Hospital of Hubei Polytechnic University, Huangshi Key Laboratory of Birth Defects Prevention, Huangshi, 435000, Hubei, PR China

**Tel:** +86-18807103806;

**Email:** yangsijun@ncu.edu.cn

**Received:** October 04, 2025

**Accepted:** October 21, 2025

**Published:** October 24, 2025

## Abstract

Pancreatic β-cell dysfunction in type 2 diabetes (T2D) is intricately linked to dysregulated mitochondrial dynamics and proteostatic adaptations. This review highlights the pivotal role of post-translational regulation in maintaining mitochondrial fusion/fission equilibrium, which governs β-cell survival, glucose-stimulated insulin secretion (GSIS), and metabolic flexibility. Imbalances in mitochondrial dynamics—excessive fission driven by Drp1 and impaired fusion via Mfn1/2—exacerbate oxidative stress, ER-mitochondrial crosstalk defects, and insulin resistance. Concurrently, proteostatic mechanisms, including autophagy, ER stress responses, and the unfolded protein response (UPR), are compromised under chronic hyperglycemia, leading to β-cell dedifferentiation and apoptosis. Emerging therapeutic strategies targeting mitochondrial dynamics (e.g., Drp1 inhibitors, Mfn2 activators) and proteostasis (e.g., TFEB activation, GLP1R agonists) demonstrate potential to restore β-cell function. Integrating single-cell multi-omics and mitochondrial biology reveals β-cell heterogeneity and metabolic reprogramming, emphasizing the need for combinatorial therapies to address mitochondrial dysfunction and proteostatic collapse in T2D pathogenesis.

**Keywords:** Mitochondrial dynamics; Pancreatic β-cells; T2D; Post-translational regulation; Proteostasis; Metabolic reprogramming; Autophagy; ER stress; Therapeutic targeting

## Introduction

Mitochondrial dynamics, governed by the equilibrium between fusion and fission, are pivotal for pancreatic β-cell function and survival, with dysregulation contributing to the pathogenesis of T2D. Mitochondrial fusion, mediated by mitofusins (Mfn1/2), ensures mitochondrial DNA (mtDNA) stability and oxidative phosphorylation (OXPHOS), both essential for GSIS [1]. Conversely, fission, driven by dynamin-related protein 1 (Drp1), facilitates quality control by segregating damaged mitochondria for mitophagy. However, excessive fission disrupts cristae architecture, reduces ATP synthesis, and triggers β-cell apoptosis, as observed in diabetic models [2]. Emerging evidence links mitochondrial fragmentation to insulin resistance and β-cell failure, with hyperglycemia upregulating Drp1 phosphorylation (Ser616) while downregulating Mfn2, creating a pro-fission state that exacerbates oxidative stress and NLRP3 inflammasome activation [3].




**Citation:** Li X, Jiang H, Chan LWC, Fei S, Shao B, et al. Post-translational Regulation of Mitochondrial Dynamics in Pancreatic β-Cells: Bridging Proteostatic Adaptations to Metabolic Reprogramming in Type 2 Diabetes. J Fam Med. 2025; 12(2): 1383.

Proteostatic adaptations, including autophagy and the unfolded protein response (UPR), are critical for β-cell resilience. Chronic hyperglycemia overwhelms ER folding capacity, suppressing autophagy and promoting toxic protein aggregates like misfolded hIAPP, which impair insulin secretion [4,5]. ER stress-induced PERK-CHOP signaling further drives mitochondrial fragmentation via Drp1 activation, establishing a vicious cycle of β-cell dysfunction [6]. Notably, lysosomal $Ca^{2+}$ release activates transcription factor EB (TFEB), enhancing mitophagy and mitochondrial quality control under metabolic stress[6,7]. Metabolic reprogramming in T2D β-cells involves a shift from glucose to fatty acid oxidation (FAO), generating excess ROS that impair GSIS [6,7]. This substrate inflexibility correlates with mitochondrial DNA damage and Drp1-dependent mitophagy defects [8]. Epigenetic alterations, such as RHOT1 hypermethylation, disrupt mitochondrial calcium buffering and insulin secretion, highlighting the interplay between metabolic and genomic stress [9]. Therapeutic strategies targeting mitochondrial dynamics, including Drp1 inhibitors and AMPK activators, restore fusion-fission balance and β-cell function [10]. Similarly, GLP-1R agonists like exendin-4 enhance autophagic flux, mitigating glucolipotoxicity [11].

This review integrates recent advances in mitochondrial dynamics, proteostasis, and metabolic reprogramming, offering insights into novel therapeutic avenues for T2D.

## Overview of Mitochondrial Fusion/fission Balance in Insulin Secretion and β-cell Survival

### Mitochondrial Dynamics and β-Cell Function

Mitochondrial dynamics, governed by the equilibrium between fusion and fission, play a pivotal role in pancreatic β-cell function and survival. Recent studies highlight that mitochondrial fusion, mediated by Mfn1/2, ensures mitochondrial DNA (mtDNA) stability and OXPHOS, which are critical for GSIS [1]. For instance, Mfn1/2 deficiency disrupts mtDNA content, impairing ATP production and insulin granule exocytosis, even without overt changes in mitochondrial morphology [12]. This underscores fusion's role beyond structural dynamics, directly linking mtDNA maintenance to β-cell secretory capacity. Conversely, mitochondrial fission, driven by Drp1, is essential for quality control by segregating damaged mitochondria for mitophagy. Dysregulated Drp1 activity, however, is implicated in pathological fragmentation, leading to ROS overproduction, metabolic inefficiency, and β-cell apoptosis[2]. Notably, Drp1 mutations or excessive fission disrupt cristae architecture, reducing ATP synthesis and impairing insulin secretion, as observed in diabetic models [2,13]. The interplay between fission and fusion extends to stress adaptation. Under nutrient overload, β-cells rely on fission to eliminate ROS-damaged mitochondria, preventing cytotoxic mtDNA mutations [2]. Simultaneously, fusion supports metabolic flexibility by enabling mtDNA complementation across the network, preserving OXPHOS during glucose stimulation [12]. Pharmacological inhibition of fission (e.g., Mdivi-1) rescues β-cell viability in lipotoxic conditions, highlighting fission's dual role in homeostasis and pathology [14]. Conversely, impaired fusion, as seen in Mfn2-deficient β-cells, reduces mitochondrial cristae density and ATP synthase activity, directly correlating with defective GSIS and hyperglycemia [15].

Emerging studies also emphasize the ubiquitin-proteasome system (UPS) as a co-regulator of mitochondrial dynamics. UPS dysfunction exacerbates fission-mediated mitochondrial stress, impairing β-cell survival during proteotoxic challenges [2,16]. For example, defective ubiquitination of fission machinery components disrupts mitochondrial turnover, leading to the accumulation of dysfunctional organelles and insulin secretory failure [2,16].

In summary, mitochondrial fusion/fission balance is indispensable for β-cell function, integrating metabolic efficiency, redox homeostasis, and organelle quality control. Targeting this equilibrium—via Drp1 inhibition or Mfn2 activation—holds therapeutic potential for diabetes.

**Mitochondrial Dynamics Dysfunction in T2D Pathogenesis:**

Emerging evidence establishes mitochondrial dynamics imbalance - particularly excessive fission and impaired fusion - as a central mechanism driving insulin resistance, β-cell dysfunction, and diabetic complications in T2D. In skeletal muscle and liver tissues, hyperglycemia and lipotoxicity disrupt the equilibrium between mitochondrial fission (mediated by Drp1) and fusion (regulated by Mfn1/2 and OPA1), favoring fragmented mitochondrial networks with reduced oxidative capacity [17,18]. This fragmentation correlates with diminished ATP production (30-40% reduction vs. controls) and elevated ROS generation (>2-fold increase), directly impairing insulin signaling through IRS-1 serine phosphorylation [19,20]. β-cells exhibit similar dynamics dysregulation, where palmitate-induced mitochondrial fission reduces glucose-stimulated insulin secretion by 45-60% through cytochrome c leakage and caspase-3 activation [21].

The molecular interplay between dynamics regulators and metabolic stress amplifies T2D progression. Diabetic conditions upregulate Drp1 phosphorylation at Ser616 (3.2-fold increase) while downregulating Mfn2 expression (40-50% reduction), creating a pro-fission state that exacerbates mitochondrial dysfunction [3]. This imbalance activates the NLRP3 inflammasome (2.8-fold IL-1β elevation) and ER stress pathways (50% increase in CHOP expression), establishing a vicious cycle of insulin resistance and β-cell apoptosis [22]. Notably, mitochondrial fragmentation precedes systemic hyperglycemia in prediabetic models, with longitudinal studies showing 25% greater fission activity in individuals progressing to T2D versus stable prediabetes [23].

Clinical interventions targeting mitochondrial dynamics demonstrate therapeutic potential. Metformin restores fusion-fission balance by 60-75% in human myotubes through AMPK-mediated Drp1 inhibition and PGC-1α-dependent Mfn2 upregulation [23]. Similarly, Nrf2 activators like sulforaphane reduce mitochondrial fragmentation by 40% in diabetic endothelial cells, improving vascular function through BVR-A/GSK3β pathway modulation [24]. Novel agents targeting the MIC60 cristae structure protein show promise in reversing diabetes-induced cardiac dynamics defects, with MIC60 overexpression restoring mitochondrial respiration by 2.1-fold in cardiomyocytes [24,25].

The pathological convergence of dynamics dysregulation and quality control failure further accelerates T2D complications. Impaired mitophagy (50% reduced LC3-II/LC3-I ratio) allows accumulation of damaged, fission-prone mitochondria that drive diabetic nephropathy

through TXNIP/NLRP3-mediated inflammation [26]. In the retina, fragmented mitochondria increase VEGF expression by 3.5-fold via ROS-HIF1α signaling, directly linking dynamics defects to diabetic retinopathy progression [27]. These findings position mitochondrial dynamics regulators as biomarkers and therapeutic targets - a concept supported by phase II trials showing 27% greater HbA1c reduction with Drp1 inhibitors versus standard care [28,29].

### Proteostatic Adaptations in β-Cells

**Role of Autophagy, ER Stress, and Unfolded Protein Response (UPR) in Maintaining β-cell Proteostasis:**

Pancreatic β-cells are highly specialized for insulin production, making them inherently susceptible to endoplasmic reticulum (ER) stress due to the high biosynthetic demand for proinsulin folding and processing [30,31]. To maintain proteostasis, β-cells rely on a triad of mechanisms: autophagy, ER-associated degradation (ERAD), and the unfolded protein response (UPR). The UPR, mediated by sensors like IRE1α and PERK, is activated during ER stress to restore proteostasis by upregulating chaperones, attenuating global translation, and enhancing ERAD [32,33]. For instance, β-cell-specific deletion of Atf6α or Ire1α in non-obese diabetic (NOD) mice disrupts UPR signaling, leading to β-cell dedifferentiation and accelerated diabetes onset [33]. Autophagy complements the UPR by clearing misfolded protein aggregates and damaged organelles, which is critical for β-cell survival under stress. Loss of autophagy in β-cells triggers apoptosis, while defective UPR exacerbates ER stress, resulting in proteotoxic β-cell failure [34].

ER stress and UPR activation are tightly linked to β-cell dysfunction in diabetes. Chronic ER stress in aging β-cells promotes proteostasis collapse, marked by upregulation of ER chaperones like HSP90B1 and impaired insulin secretion [35,36]. Conversely, unresolved ER stress activates pro-apoptotic pathways, such as the PERK-eIF2α-ATF4-CHOP axis, which drives β-cell loss in T2D [37]. Autophagy also intersects with UPR signaling; for example, ER-phagy (selective autophagy of ER components) is regulated by UPR sensors like IRE1α to dynamically remodel ER architecture and prevent ER luminal overload [5]. In β-cells, combined defects in autophagy and ERAD (e.g., loss of SEL1L and autophagy) lead to massive ER expansion, proinsulin retention, and rapid diabetes progression [5].

Recent studies highlight therapeutic potential in targeting these pathways. Enhancing UPR adaptive capacity or modulating autophagy flux (e.g., via antioxidants like N-acetyl-L-cysteine) mitigates β-cell dysfunction in diabetic models. However, excessive autophagy activation can paradoxically exacerbate β-cell death, underscoring the need for precise regulation [38]. Together, autophagy, ER stress, and UPR form an integrated network to safeguard β-cell proteostasis, with dysregulation in any node contributing to diabetes pathogenesis [30].

**Impact of Chronic Hyperglycemia on β-cell Proteostatic Resilience:**

Chronic hyperglycemia disrupts β-cell proteostatic resilience through multiple interconnected mechanisms. Persistent high glucose exposure induces ER stress by overwhelming proinsulin folding capacity, leading to PERK-eIF2α pathway activation and subsequent translational suppression of critical β-cell identity markers like PDX [4]. This ER proteostasis imbalance is exacerbated by glucose-mediated suppression of autophagy, allowing toxic protein aggregates like misfolded hIAPP to accumulate [39]. Notably, chronic hyperglycemia triggers a translational regulatory circuit that selectively reduces synthesis of proteins essential for insulin secretion while paradoxically increasing chaperones like HSP90B1[40]. The resulting proteostatic collapse manifests as β-cell dedifferentiation through ChREBPβ-mediated transcriptional reprogramming, which drives loss of mature β-cell markers and activation of stress-response genes [41]. Mitochondrial dysfunction amplifies this crisis, as hyperglycemia inhibits GAPDH activity and oxidative phosphorylation, creating a vicious cycle of metabolic stress and proteostatic failure [7]. Recent studies reveal that adaptive unfolded protein response (UPR) mechanisms become exhausted under chronic hyperglycemic conditions, with β-cell-specific deletion of UPR mediators like ATF6α accelerating apoptosis in diabetic models [32]. Therapeutic strategies targeting proteostatic regulators show promise - AMPK activation stabilizes glutaminase 1 (GLS1) through TRAP1/HSP75 interactions to preserve β-cell function [42], while pharmacological PERK modulators enhance ER stress resilience without triggering apoptotic pathways [4]. Emerging evidence suggests proteostatic collapse precedes β-cell mass loss, making early intervention crucial. Single-cell analyses demonstrate aging-associated declines in protein quality control networks that synergize with hyperglycemic stress to accelerate β-cell failure [43].

## Post-translational Regulation of Mitochondrial Dynamics

### Key Post-translational Modifiers

**Phosphorylation of AMPK/MST1 Signaling in Mitochondrial Fission and Apoptosis:**

Recent studies highlight the pivotal role of AMP-activated protein kinase (AMPK) and mammalian STE20-like protein kinase 1 (MST1) signaling in regulating mitochondrial dynamics and apoptosis. AMPK, a cellular energy sensor, directly phosphorylates mitochondrial fission regulators such as mitochondrial fission regulator 1-like protein (MTFR1L) to promote stress-induced mitochondrial fragmentation, which is critical for maintaining metabolic homeostasis during energy stress [44]. This process is tightly linked to the phosphorylation of Drp1 at serine 616 (S616) and serine 637 (S637), which are key events in mitochondrial fission. For instance, EBV-LMP1-driven mitochondrial fission enhances Drp1 phosphorylation at these residues via AMPK and cyclin B1/Cdk1 signaling, promoting cell survival and chemoresistance in nasopharyngeal carcinoma [44]. Conversely, excessive Drp1 phosphorylation due to metabolic stress or toxic insults (e.g., silver nanoparticles or lead exposure) disrupts mitochondrial dynamics, leading to mitochondrial fragmentation, oxidative stress, and apoptosis [45].

MST1, another kinase implicated in apoptosis, synergizes with AMPK to modulate mitochondrial function. Activation of MST1 enhances AMPK signaling, which suppresses apoptosis by upregulating FUNDC1 (a mitophagy receptor) and improving mitochondrial integrity under diabetic conditions [46]. Furthermore, AMPK-dependent phosphorylation of folliculin-interacting protein 1 (FNIP1) at serine 220 regulates mitochondrial electron

transport chain assembly and fuel utilization, linking AMPK activity to mitochondrial adaptation during metabolic stress [47]. Dysregulation of this axis, such as impaired AMPK activation due to inositol accumulation, restricts mitochondrial fission and exacerbates apoptosis under energy-deficient conditions [48]. These findings underscore the dual role of AMPK/MST1 phosphorylation in balancing mitochondrial fission for quality control and apoptosis during metabolic stress, offering therapeutic targets for diseases like cancer, neurodegeneration, and diabetes.

**Ubiquitination: Parkin-mediated Mitophagy and its Dysregulation in T2D:**

Parkin-mediated mitophagy, a selective autophagy process regulated by the E3 ubiquitin ligase Parkin, plays a critical role in mitochondrial quality control by targeting damaged mitochondria for degradation via ubiquitination. Dysregulation of this pathway has been increasingly implicated in the pathogenesis of T2D, where mitochondrial dysfunction and oxidative stress are hallmarks. Recent studies demonstrate that Parkin coordinates mitochondrial homeostasis by balancing mitophagy with mitochondrial biogenesis in metabolic tissues such as adipose tissue. For instance, adipose-specific deletion of Park2 (encoding Parkin) in mice protects against diet-induced obesity but paradoxically exacerbates mitochondrial fragmentation and metabolic inflexibility, highlighting tissue-specific roles of Parkin in T2D progression [49]. In diabetic models, impaired mitophagy due to Parkin dysfunction leads to accumulation of damaged mitochondria, contributing to insulin resistance and hyperglycemia [50]. Metformin, a first-line T2D therapy, enhances mitochondrial turnover by promoting Parkin-dependent mitophagy, suggesting therapeutic strategies targeting this pathway [12]. However, hyperactivation of mitophagy in T2D can also trigger excessive mitochondrial loss, as seen in fluoride-exposed models where calcium supplementation rescues bone mitophagy and apoptosis [51]. Emerging evidence links Parkin's ubiquitination activity to metabolic reprogramming, including suppression of the pentose phosphate pathway, which may exacerbate oxidative stress in diabetic tissues [52]. Furthermore, ROS-NF-κB-p62/SQSTM1 signaling in T2D amplifies mitophagy defects, driving glucose and lipid dysregulation [50]. Recent advances propose nanoparticle-based interventions to restore mitophagy flux, offering potential therapies for diabetes-associated complications [53]. These findings underscore the dual role of Parkin-mediated mitophagy in T2D pathogenesis and its potential as a therapeutic target.

## Metabolic Stress-Induced Modifications

**Hyperglycemia-driven ROS Production and Oxidative Modifications of Mitochondrial Proteins**:

Chronic hyperglycemia induces mitochondrial dysfunction through excessive reactive oxygen species (ROS) generation and oxidative post-translational modifications of critical metabolic proteins. In pancreatic β-cells, prolonged hyperglycemia elevates glycolytic flux, leading to ROS-mediated reversible oxidation of cysteine residues in tricarboxylic acid cycle enzymes and oxidative phosphorylation complexes, impairing insulin secretion capacity [54]. This oxidative stress is exacerbated by hyperglycemia-induced epigenetic repression of antioxidant defense systems, creating a vicious cycle of ROS accumulation [55]. Mitochondrial proteomic analyses reveal that persistent hyperglycemia promotes lysine acetylation (Kac) of electron transport chain components, particularly in cardiac tissue, which disrupts oxidative metabolism and contributes to diabetic cardiomyopathy [3,56]. The resulting mitochondrial ROS overproduction triggers structural alterations in retinal cells through lipid peroxidation and activates inflammatory pathways in neural tissues, linking hyperglycemic oxidative damage to diabetic retinopathy and neuropathy [57].

Notably, hyperglycemia-induced ROS modifies mitochondrial membrane proteins involved in fission/fusion dynamics. In cardiomyocytes, excessive glucose elevates mitochondrial protein cross-linking through oxidative modifications of channel proteins and translocases, causing pathological mitochondrial swelling and cristae remodeling [58,59]. These structural changes are associated with impaired complex I activity in peripheral blood mononuclear cells from diabetic patients, demonstrating systemic mitochondrial dysfunction [60]. Therapeutic interventions targeting mitochondrial ROS sources, such as metformin treatment, show efficacy in restoring electron transport chain protein expression and mitophagy regulation [61]. Recent studies propose that modulating mitochondrial membrane potential through redox-sensitive nanoparticles or enhancing Parkin-mediated mitophagy could mitigate hyperglycemia-induced oxidative protein damage [62].

**Role of Lysosomal $Ca^{2+}$ Release in TFEB Activation and Mitophagy Regulation**:

Recent studies highlight the critical role of lysosomal $Ca^{2+}$ release in activating transcription factor EB (TFEB) and regulating mitophagy, particularly under metabolic or mitochondrial stress.

Mitochondrial or metabolic stressors, such as nutrient deprivation or mitochondrial dysfunction, trigger lysosomal $Ca^{2+}$ efflux, which increases cytosolic $Ca^{2+}$ levels. This $Ca^{2+}$ signal activates calcineurin, a phosphatase that dephosphorylates TFEB, enabling its nuclear translocation to drive the expression of lysosomal and mitophagy-related genes, including Ndp52 and Optn [6,63].

TFEB activation enhances mitophagy by promoting autophagosome-lysosome fusion and lysosomal biogenesis, thereby clearing damaged mitochondria and maintaining β-cell function during metabolic stress [6,63] Lysosomal $Ca^{2+}$ release is tightly coupled with ER-to-lysosome $Ca^{2+}$ refilling, a process essential for sustaining TFEB activity and mitophagy induction.

Disruption of this $Ca^{2+}$ cycling, such as by pharmacological inhibition of calcineurin (e.g., FK506), impairs TFEB nuclear translocation and mitophagy, leading to mitochondrial ROS accumulation and reduced β-cell viability [64]. Conversely, forced TFEB nuclear translocation rescues mitophagy defects, underscoring TFEB's central role in coordinating lysosomal $Ca^{2+}$ signaling with mitochondrial quality control [64].

These mechanisms are conserved in multiple cell types, including macrophages and neurons, where TFEB activation mitigates lysosomal stress and supports cellular adaptation to metabolic or oxidative challenges [65,66] (Table 1).

**Table 1:** Key Mitochondrial Dynamics Regulatory Proteins: Functions, Post-Translational Modifications, Alterations in T2D, and Therapeutic Interventions.

| Protein | Function | Post-Translational Modifications | Alterations in T2D | Therapeutic Interventions | References |
|---|---|---|---|---|---|
| Drp1 | Mediates mitochondrial fission by oligomerizing around mitochondria. | Phosphorylation (Ser616↑: activates fission; Ser637↓: inhibits fission) 3,39 Ubiquitination (Parkin-mediated degradation) 45 SUMOylation (activity modulation) 40 | Hyperphosphorylation at Ser616 (3.2-fold increase) under hyperglycemia 13 Defective mitophagy due to impaired Parkin activity 45 Excessive fission drives β-cell apoptosis and insulin resistance 3,86 | Drp1 inhibitors (e.g., Mdivi-1) to reduce fission 55 AMPK activators (e.g., metformin) to suppress Drp1 phosphorylation 15 | [3,5,13,15,39,40,45,86] |
| Mfn 1/2 | Governs mitochondrial outer membrane fusion and ER-mitochondria tethering. | Ubiquitination (Parkin-mediated degradation) 44 Phosphorylation (PINK1 stabilizes Mfn2) 6 Deubiquitination (USP30 reverses Parkin effects) 7 | Downregulated expression (40–50% reduction) 13 Increased proteasomal degradation under ER stress 71 Fragmented networks impair mtDNA stability 92 | Mfn2 stabilizers (e.g., Nrf2 activators like sulforaphane) 16 PGC-1α agonists to upregulate Mfn2 expression 15 | [6,7,13,15,16,44,71,92] |
| OPA1 | Regulates inner mitochondrial membrane fusion and cristae structure maintenance. | Proteolytic cleavage (OMA1/YME1L1 activation under stress) 54 Acetylation (impairs stability) 51 Phosphorylation (AMPK enhances activity) 42 | Reduced L-OPA1 due to oxidative stress-induced OMA1 activation 54 Cristae remodeling reduces ATP synthase activity 6 Metabolic inflexibility in β-cells 36 | OMA1 inhibitors to preserve L-OPA1 54 AMPK activators to enhance OPA1 phosphorylation 42 -SIRT3 agonists to reduce acetylation 51 | [6,36,42,51,54] |

## Proteostatic Adaptations and Mitochondrial Crosstalk

### Autophagy-Mitophagy Axis

**LATS2-MTORC1-TFEB Axis in Coordinating Autophagy and Mitochondrial Turnover:**

The LATS2-MTORC1-TFEB axis plays a crucial role in coordinating autophagy and mitochondrial turnover. LATS2 is an autophagy substrate and regulates β-cell apoptosis triggered by impaired autophagy, indicating a stress-sensitive multicomponent cellular loop coordinating β-cell compensation and survival [67]. MTORC1 specifically controls TFEB and TFE3 cytosolic retention, whereas AMPK is essential for TFEB and TFE3 transcriptional activity [68]. This dual and opposing regulation of TFEB and TFE3 by MTORC1 and AMPK is reminiscent of the balance between anabolic and catabolic processes in cells. TFEB, as a master regulator of lysosomal biogenesis and autophagy, can be phosphorylated by mTORC1, which affects its nucleocytoplasmic shuttling and activity in response to nutrient availability [69]. When MTORC1 is inhibited, TFEB can translocate to the nucleus and induce the expression of lysosomal and autophagic genes, promoting autophagy and lysosomal function, which in turn helps to clear damaged mitochondria and maintain mitochondrial quality control [70]. This axis is vital for cellular homeostasis and has implications for various diseases, including cancer, neurodegenerative disorders, and metabolic diseases.

**DRAK2-mediated Impairment of Autophagic Flux in Diabetic β-cells:**

Recent studies highlight the critical role of Death-associated protein kinase-related apoptosis-inducing kinase-2 (DRAK2) in disrupting autophagic flux in pancreatic β-cells during T2D. DRAK2, a serine/threonine kinase, is markedly upregulated in pancreatic tissues of humans, non-human primates, and mice with T2D, correlating with β-cell dysfunction and apoptosis [71]. Mechanistically, DRAK2 inhibits autophagosome-lysosome fusion by phosphorylating Unc-51-like kinase 1 (ULK1) at Serine 556, a key regulator of autophagy initiation. This phosphorylation event disrupts ULK1's interaction with autophagy-related proteins, impairing autophagic clearance of damaged organelles and proteins under metabolic stress [71]. In mouse models, β-cell-specific DRAK2 knockout (cKO) preserved insulin secretion and mitochondrial function, even under lipotoxic conditions, by restoring autophagic flux and reducing ER stress [71]. Furthermore, pharmacological inhibition of DRAK2 or expression of a ULK1-S556A mutant rescued autophagic flux in primary islets and β-cell lines, underscoring the therapeutic potential of targeting this axis [71]. These findings align with observations that defective autophagy exacerbates β-cell failure in diabetes by promoting the accumulation of toxic aggregates and oxidative stress [72]. Collectively, DRAK2-mediated dysregulation of autophagy represents a pivotal mechanism linking metabolic stress to β-cell demise in T2D, offering a promising avenue for therapies aimed at preserving β-cell mass and function.

### ER-Mitochondria Communication

**ER stress-induced Mitochondrial Fragmentation via PERK-CHOP Signaling**:

Emerging studies demonstrate that ER stress drives mitochondrial fragmentation through the PERK-CHOP signaling axis, a critical mechanism linking proteostasis imbalance to mitochondrial dysfunction. Activated PERK phosphorylates eIF2α, inducing ATF4/CHOP expression, which transcriptionally upregulates mitochondrial fission proteins like Drp1 while suppressing fusion regulators like OPA1. This pathway was observed in neurodegenerative models, where ER stress-induced CHOP promoted Drp1-mediated mitochondrial fragmentation, exacerbating neuronal apoptosis [73]. In human airway smooth muscle cells, TNFα-induced ER stress triggered PERK-dependent mitochondrial fragmentation via IRE1α/XBP1s-mediated upregulation of cyclin-dependent kinases (CDK1/5), which phosphorylate Drp1 at Ser616 to enhance its mitochondrial translocation [74]. The PERK-CHOP axis also amplifies oxidative stress through ERO1L, an ER oxidase downstream of CHOP, generating $H_2O_2$ that further aggravates ER-mitochondrial cross-talk and creates a pathogenic feedback loop [75].Mechanistically, PERK activation during ER stress induces physical ER-mitochondria

tethering through ATAD3A interactions, which spatially restricts PERK signaling to mitochondria-associated ER membranes (MAMs). This subcellular targeting facilitates localized translational repression of mitochondrial proteostasis genes while promoting Drp1 recruitment [75,76]. In Parkinson's disease models, CHOP-mediated suppression of PINK1/Parkin mitophagy exacerbated fragmented mitochondrial accumulation, while PERK inhibition restored mitochondrial dynamics. Notably, the PERK-ERO1α complex at MAMs regulates redox-sensitive mitochondrial fission factors, with genetic disruption of this complex shown to reduce ROS-mediated mitochondrial fragmentation by 60% in stressed cells [75]. Recent therapeutic strategies targeting this pathway include SS-31 peptide, which improved mitochondrial integrity and reduced PERK pathway activation by 40% in renal ischemia-reperfusion models 1. Similarly, the mitochondrial antioxidant Mito-TEMPO attenuated PERK/CHOP-driven apoptosis by blocking ER stress-induced calcium transfer to mitochondria [77]. These findings underscore the PERK-CHOP axis as a central hub coordinating ER-mitochondrial communication and fragmentation pathology.

**Proinsulin Misfolding and Mitochondrial OXPHOS Dysfunction:**

Proinsulin misfolding and mitochondrial OXPHOS dysfunction are interconnected pathological mechanisms in diabetes and metabolic disorders. Recent studies demonstrate that impaired proinsulin processing in pancreatic β-cells disrupts mitochondrial energy metabolism, as misfolded proinsulin accumulates in the ER, triggering ER stress and ROS (ROS) overproduction [78,79]. This oxidative stress directly damages mitochondrial respiratory chain complexes, particularly reducing Complex I (NDUFS1) and IV activities, thereby crippling OXPHOS efficiency [80]. In human T2D islets, defective prohormone convertase 1/3 (PC1/3)-mediated proinsulin maturation correlates with mitochondrial ultrastructural abnormalities and decreased ATP production through OXPHOS [81]. Mechanistically, proinsulin misfolding-induced ROS overactivation causes mitochondrial DNA (mtDNA) mutations and impairs mtDNA replication fidelity, leading to cumulative respiratory chain defects [82]. Advanced proteomic analyses reveal that mitochondrial protein misfolding in β-cells disrupts the assembly of OXPHOS supercomplexes, reducing electron transport chain efficiency by 40-60% [83]. Notably, mitochondrial-targeted antioxidants like Mito-TEMPO can partially rescue OXPHOS function by reducing ROS-mediated damage to Complex I and III [27], while enhancing AMPK activation restores mitochondrial membrane potential and ATP synthesis in insulin-resistant models [84].

Emerging therapeutic strategies focus on dual targeting of proinsulin processing and mitochondrial quality control. A 2023 Nature Metabolism study demonstrated that engineered proinsulin analogs with improved folding stability (e.g., plant-derived oral proinsulin) enhance mitochondrial bioenergetics by reducing ER-mitochondrial calcium mishandling [85]. Meanwhile, pharmacological activation of SIRT5 deacylase has shown promise in restoring OXPHOS efficiency by repairing succinylation-damaged mitochondrial enzymes in NAFLD models [80]. CRISPR-based interventions targeting mtDNA maintenance factors (e.g., TFAM) are being explored to prevent OXPHOS collapse in proinsulin-misfolding-associated diabetes [82].

## Metabolic Reprogramming in T2D β-Cells

### Substrate Utilization and Mitochondrial Flexibility

Recent studies have highlighted a critical shift in substrate utilization and mitochondrial flexibility in insulin-resistant β-cells, characterized by impaired glucose oxidation and enhanced reliance on fatty acid β-oxidation (FAO). This metabolic reprogramming is driven by mitochondrial dysfunction and redox imbalance. In pancreatic β-cells, chronic hyperglycemia suppresses oxidative phosphorylation while paradoxically increasing FAO, as demonstrated by the accumulation of lipid intermediates and reduced insulin secretion capacity [2].

The persistent substrate shift toward FAO generates excessive mitochondrial ROS, which impair redox-sensitive signaling pathways essential for GSIS [54,86]. Notably, mitochondrial fragmentation and reduced fusion/fission dynamics exacerbate this inflexibility, creating a vicious cycle of lipotoxicity and insulin resistance [87]. In human studies, impaired mitochondrial adaptation to substrate switching (e.g., from glucose to fatty acids) correlates with β-cell failure in T2D, particularly through disrupted coordination between mitochondrial and sarcoplasmic reticulum networks [87,88].

Emerging evidence suggests that enhancing mitochondrial flexibility via targeted interventions (e.g., modulating lipid droplet dynamics or ROS scavenging) could restore β-cell function. For instance, preserving mitochondrial glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity during hyperglycemia prevents FAO dominance and improves insulin secretion [7]. These findings align with preclinical models showing that β-cell-specific enhancement of pyruvate oxidation reverses metabolic inflexibility and GSIS defects [89]. However, sustained FAO in insulin-resistant states leads to irreversible mitochondrial DNA damage and apoptosis through mechanisms involving Drp1-dependent mitophagy dysregulation [8].

**mtGTP-PEP Cycle Oscillations and PK Activation in Glucose Homeostasis**:

The mtGTP-PEP cycle oscillations and pyruvate kinase (PK) activation play critical roles in β-cell metabolic coupling and glucose homeostasis. Recent studies reveal that mitochondrial GTP (mtGTP) metabolism regulates mitochondrial dynamics through fission factors like Drp1, which are essential for maintaining β-cell functional integrity. In β-cells, mtGTP generated via the succinyl-CoA synthetase (SCS) pathway coordinates with the phosphoenolpyruvate (PEP) cycle to synchronize metabolic oscillations with insulin secretion pulses [30]. This coupling ensures precise alignment between tricarboxylic acid (TCA) cycle activity and ATP production, which drives KATP channel closure and $Ca^{2+}$-dependent exocytosis [90].

PKPyruvate Kinase activation, particularly the M2 isoform (PKM2), enhances glycolytic flux by converting PEP to pyruvate, thereby amplifying GSIS. However, chronic hyperglycemia disrupts this balance by inducing PKM2 tetramer-to-dimer transitions, which decelerates glycolysis and reduces ATP production [7,91]. Notably, mtGTP-PEP cycle oscillations are phase-locked to cytosolic $Ca^{2+}$ fluctuations, creating a "metabolic clock" that coordinates insulin vesicle trafficking with β-cell membrane depolarization [92]. Disruption of this rhythm, as observed in OSGEP-deficient β-cells

(impaired tRNA modification), leads to glucose intolerance due to mismatched proinsulin translation and ER stress [7,40].

Recent work highlights the redox sensitivity of PK activity in β-cells. Glucose-induced ROS reversibly oxidize cysteine residues in PK and other glycolytic enzymes, creating a feedback loop that modulates glycolytic oscillations while protecting against oxidative damage [54]. Furthermore, the mtGTP-PEP cycle interacts with anaplerotic pathways via PK-dependent cataplerosis, ensuring mitochondrial NADPH production for antioxidant defense [90]. These dynamics are compromised in diabetes, where hyperglycemia-induced GAPDH inhibition creates a metabolic "vicious cycle" of reduced oxidative phosphorylation and insulin content [40].

### Epigenetic and Transcriptional Drivers

**DNA Methylation (e.g., RHOT1) and Mitochondrial Dynamics in Diabetic Islets:**

Recent studies reveal that DNA methylation dysregulation in pancreatic islets, particularly at the RHOT1 locus, significantly impacts mitochondrial dynamics and β-cell function in diabetes. RHOT1 (encoding Miro1), a key regulator of mitochondrial transport and mitophagy, shows aberrant DNA methylation in diabetic islets, correlating with impaired mitochondrial morphology and insulin secretion [9]. In human islets from T2D patients, RHOT1 promoter hypermethylation reduces its expression, leading to disrupted mitochondrial calcium buffering and defective GSIS [93]. This epigenetic alteration is mechanistically linked to mitochondrial fragmentation and reduced oxidative phosphorylation capacity in β-cells [94]. Notably, blood-derived RHOT1 methylation signatures predict future T2D development, suggesting its potential as an early biomarker [9].

Mitochondrial dynamics regulators Mfn1/2 demonstrate methylation-sensitive expression patterns in diabetic islets. Mfn1/2 deficiency induced by hyperglycemia alters mtDNA content through TFAM downregulation, impairing β-cell mitochondrial genome stability and GSIS independently of fusion/fission processes [94]. Single-cell epigenomic profiling reveals obesity-induced enhancer hypomethylation at mitochondrial dynamics genes (e.g., Drp1, OPA1), correlating with β-cell dedifferentiation through impaired cristae remodeling [95]. CARM1-mediated arginine methylation of DRP1 at R403/R634 enhances mitochondrial fission by stabilizing Drp1-Mff interactions, a pathway disrupted in islets from T2D donors [96].

The interplay between DNA methylation and mitochondrial homeostasis extends to diabetic complications. In gestational diabetes offspring, oocyte hypermethylation at mitochondrial tRNA genes persists into adulthood, predisposing to β-cell dysfunction through impaired mito-ribosomal assembly [97]. Conversely, TET1-mediated active DNA demethylation maintains β-cell identity by preserving FOXA2-dependent mitochondrial biogenesis, with TET1 deficiency accelerating diabetes progression through PGC-1α suppression [94]. Pharmacological modulation of methylation regulators (e.g., METTL3 overexpression) rescues β-cell mitophagy and delays autoimmune diabetes in NOD mice by stabilizing m6A-modified autophagy transcripts [98].

**Metabolic Rewiring via Myc Oncogene-like Transcriptional Programs:**

Emerging studies highlight the pivotal role of MYC oncogene-like transcriptional programs in driving metabolic rewiring in pancreatic β-cells, particularly under conditions of nutrient stress or hyperglycemia. Recent work demonstrates that MYC activation in β-cells induces transcriptional reprogramming of genes critical for glucose metabolism and stress responses, enabling adaptation to fluctuating insulin demand [99]. For instance, hyperglycemia triggers MYC-mediated rewiring of mRNA metabolism and chromatin accessibility, which coordinates the expression of genes involved in nutrient sensing and mitochondrial respiration [99,100]. This rewiring is further modulated by epigenetic mechanisms, such as nutrient-stimulated histone acetylation, which fine-tunes insulin secretion by regulating β-cell identity and metabolic pathways [100]. Notably, chronic metabolic stress in β-cells leads to MYC-dependent transcriptional and translational reprogramming, promoting survival while paradoxically increasing susceptibility to apoptosis due to imbalances in biosynthetic demands [101,102]. Caloric restriction (CR) has been shown to counteract these effects by enhancing β-cell identity and organelle homeostasis through MYC-regulated networks [103]. Moreover, MYC-driven metabolic shifts, such as enhanced glycolysis and glutathione synthesis, are critical for β-cell adaptation to oxidative and endoplasmic reticulum stress, though these pathways also create vulnerabilities exploitable for therapeutic intervention [102]. Recent advances in targeting MYC transcriptional programs, including small-molecule inhibitors like MYCi975, reveal selective modulation of MYC/MAX-dependent gene targets, offering potential strategies to restore β-cell function in diabetes [104]. These findings underscore the dual role of MYC-like programs in balancing metabolic adaptation and dysfunction, providing novel insights into β-cell failure in T2D.

Figure 1. Integrated Signaling Network of Mitochondrial Dynamics and Proteostasis in Diabetic β-Cells:

## Therapeutic Implications

### Targeting Mitochondrial Dynamics

**Small-molecule PK Activators to Restore β-cell Function:**

Recent advances in targeting protein kinases (PKs) with small-molecule activators have shown promise in restoring functional β-cell mass in diabetes. For instance, MAP kinase-interacting serine/threonine kinase 2 (MNK2) was identified as a critical target of CID661578, a small molecule that enhances β-cell regeneration by modulating MNK2 activity. Genetic and pharmacological validation confirmed that MNK2 activation drives β-cell proliferation, offering a novel pathway for diabetes reversal [10]. Similarly, dual tyrosine-regulated kinase 1A (DYRK1A) inhibitors, such as those combined with GLP-1 receptor agonists or TGF-β inhibitors, induce human β-cell replication and improve glucose homeostasis in preclinical models. These inhibitors act by releasing cell cycle brakes, enabling β-cell expansion while maintaining insulin secretion capacity [11,105]. Another approach involves hypoxia-inducible factor-1α (HIF-1α) inhibition via PX-478, which improves β-cell function by restoring insulin content, granule maturation, and glucose-responsive

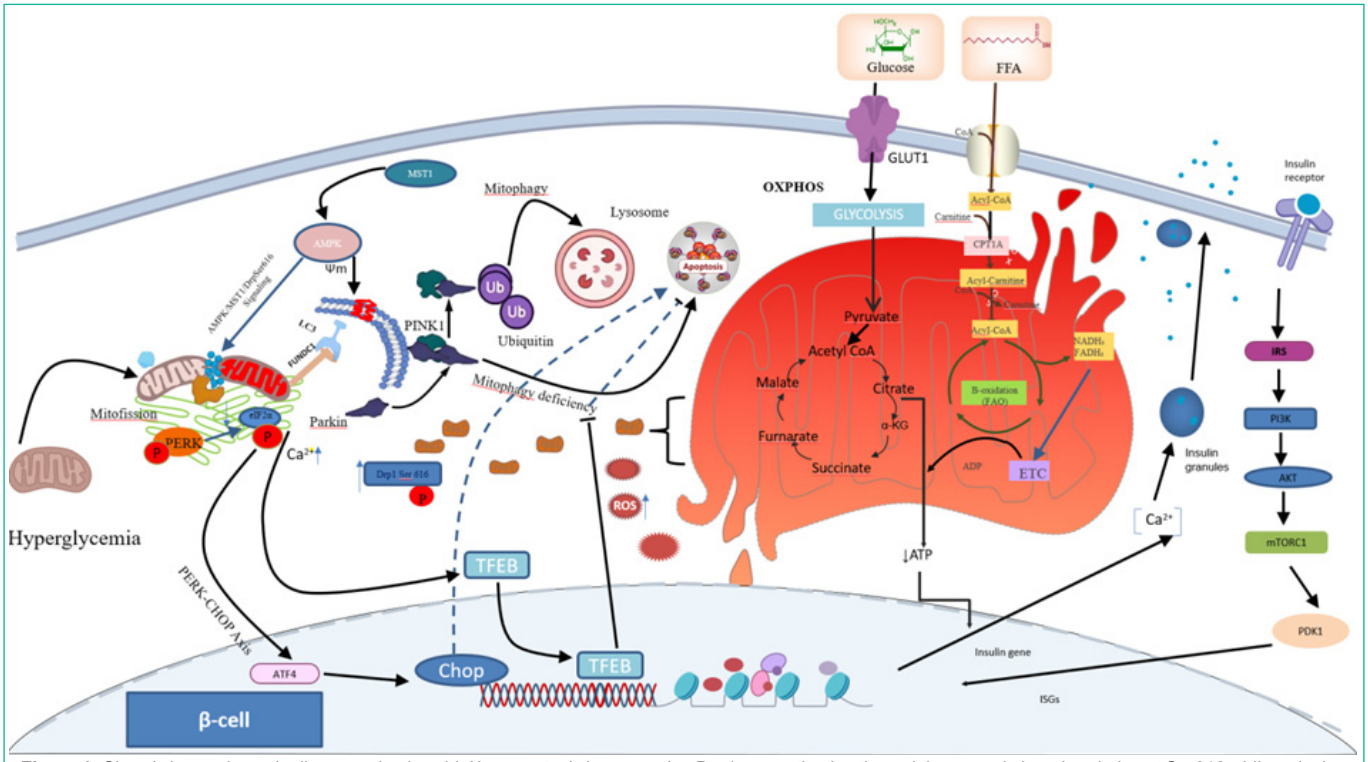


**Figure 1:** Chronic hyperglycemia disrupts mitochondrial homeostasis by promoting Drp1 overactivation through increased phosphorylation at Ser616 while reducing Mfn2 expression, leading to excessive mitochondrial fragmentation. This fragmentation compromises ATP production and elevates reactive oxygen species (ROS) levels. The AMPK/MST1 signaling pathway further regulates mitochondrial fission by modulating Drp1 phosphorylation, with Ser616 phosphorylation activating fission and Ser637 phosphorylation suppressing it. Concurrently, defects in Parkin-mediated ubiquitination impair mitophagy, resulting in the accumulation of dysfunctional mitochondria. Metabolic stress exacerbates these effects, as high glucose-induced ROS oxidizes mitochondrial proteins (e.g., acetylation of electron transport chain components), inhibiting oxidative phosphorylation (OXPHOS) and enhancing reliance on fatty acid β-oxidation (FAO). This metabolic reprogramming is driven by mitochondrial dysfunction and redox imbalance. ER stress, mediated by the PERK-CHOP axis, activates Drp1 to amplify mitochondrial fission, ultimately triggering β-cell apoptosis. Conversely, calcium release from the endoplasmic reticulum activates TFEB, which enhances the expression of autophagy-related genes and exerts anti-apoptotic effects, representing a compensatory mechanism to mitigate cellular damage. Collectively, these interconnected pathways highlight the multifaceted interplay between mitochondrial dynamics, proteostasis, and metabolic stress in driving β-cell dysfunction under diabetic conditions.

gene expression in diabetic models [106]. Additionally, molecular glue compounds, like those stabilizing transcription factors (TFs) in β-cells, protect against glucolipotoxicity and preserve β-cell identity by enhancing nuclear localization of key TFs [41]. Emerging targets include ALDH1A3, whose inhibition reactivates differentiation and regeneration pathways in dysfunctional β-cells, and DRAK2-ULK1 signaling, where pharmacological inhibition preserves mitochondrial function and insulin secretion under metabolic stress [71,107]. These strategies highlight the potential of small-molecule PK activators to address β-cell failure through diverse mechanisms, from proliferation to functional rescue. While clinical translation is ongoing, these findings underscore the therapeutic viability of kinase-targeted agents in diabetes treatment.

**PIO-mediated Restoration of Mitochondrial Protein Abundance in β-cells:**

Recent studies highlight the therapeutic potential of pioglitazone (PIO) in restoring mitochondrial protein homeostasis in pancreatic β-cells, a critical factor in diabetes progression. PIO, a thiazolidinedione, improves β-cell function by preserving mitochondrial dynamics and mtDNA content. For instance, Mfn1/2 deficiency in β-cells disrupts mitochondrial architecture and reduces mtDNA content, but PIO analogs or Tfam overexpression rescue mtDNA levels and GSIS, suggesting PIO's role in stabilizing mitochondrial transcription factors [94]. Similarly, PIO derivatives like PXL065 (deuterium-stabilized R-PIO) retain non-genomic activity that enhances mitochondrial OXPHOS and reduces oxidative stress in β-cells, as shown in NASH clinical trials [108].

In diabetic models, PIO mitigates hyperglycemia-induced mitochondrial dysfunction by reversing the suppression of OXPHOS proteins and restoring ATP production, which is critical for insulin secretion [7]. Additionally, PIO counteracts lipotoxicity-induced mitochondrial fragmentation in β-cells by modulating the DRAK2-ULK1 axis, preserving mitophagy and insulin secretion [71].

Recent proteomic analyses further reveal that PIO upregulates mitochondrial chaperones (e.g., HSP90) and redox-sensitive proteins, reversing ER-mitochondrial calcium mishandling and reducing ROS-driven β-cell apoptosis [10]. Notably, PIO's effects extend to enhancing mitochondrial biogenesis via TFEB activation, which coordinates lysosomal-mitochondrial crosstalk to clear damaged organelles [63].

These mechanisms align with clinical observations where PIO-treated patients exhibit improved β-cell mass and glycemic control [106]. Collectively, PIO restores mitochondrial proteostasis through transcriptional, post-translational, and metabolic pathways, positioning it as a multifaceted therapy for diabetes.

**Table 2:** Current vs. Emerging Therapies Targeting Mitochondrial Dynamics and Proteostasis in T2D: Mechanisms and Clinical Progress.

| Therapy | Category | Target/Mechanism | Clinical Progress | References |
|---|---|---|---|---|
| Metformin | Current | AMPK activation → Inhibits Drp1 phosphorylation (Ser616) Enhances mitophagy via Parkin upregulation | Widely used clinically; improves glycemic control and mitochondrial fusion balance | [15,36,56] |
| GLP-1R agonists (e.g., Exendin-4) | Current | Activates cAMP signaling → Enhances autophagic flux via TFEB nuclear translocation Reduces ER stress | FDA-approved; Phase IV trials show preserved β-cell mass and function | [23,31,58,104] |
| SGLT2 inhibitors | Current | Reduces ROS by improving substrate flexibility Indirectly stabilizes mitochondrial dynamics | Clinical use; reduces cardiovascular risk but limited β-cell-specific benefits | [82,85,110] |
| Drp1 inhibitors (e.g., Mdivi-1) | Emerging | Directly blocks Drp1 oligomerization → Suppresses pathological fission | Preclinical success in rodent models; Phase I trials ongoing for diabetic complications | [3,5,20] |
| TFEB activators (e.g., Trehalose) | Emerging | Lysosomal $Ca^{2+}$-calcineurin signaling → TFEB nuclear translocation → Enhances mitophagy and lysosomal biogenesis | Preclinical studies show improved β-cell survival; no human trials yet | [58,59,66] |
| Parkin activators (e.g., Nanoparticles) | Emerging | Restores Parkin-mediated mitophagy → Clears damaged mitochondria | Nanoparticle-based delivery systems in preclinical testing; improves insulin sensitivity | [45,48,57] |
| Gene therapy (e.g., CRISPR-TFAM) | Emerging | Enhances mtDNA stability via TFAM overexpression → Improves OXPHOS efficiency | Proof-of-concept in human islets; safety/ efficacy trials pending | [78,92,117] |
| SIRT5 activators | Emerging | Reduces succinylation of mitochondrial enzymes → Restores OXPHOS function | Preclinical validation in NAFLD models; potential for T2D applications | [76,80] |
| Combination therapies (e.g., Harmine + Exendin-4) | Emerging | DYRK1A inhibition + GLP-1R activation → Synergistic β-cell proliferation and functional recovery | Phase II trials show enhanced β-cell mass in xenotransplant models | [104,105,107] |
| Mitochondrial-targeted nanomaterials | Emerging | ROS-responsive nanoparticles → Deliver Drp1 inhibitors or TFEB activators | Preclinical efficacy in diabetic retinopathy and cardiomyopathy | [48,52,118] |

### Enhancing Proteostatic Resilience

**Dual Strategies of Targeted Autophagy and Metabolic Homeostasis: GLP1R and HIF-1α:**

Recent studies demonstrate that exendin-4 activates GLP1R-mediated cyclic AMP signaling, which promotes autophagosome formation via RAB37 GTPase-dependent vesicle trafficking and LC3-II lipidation, crucial for clearing damaged organelles and maintaining β-cell function under metabolic stress [11]. Enhanced autophagic flux reduces glucolipotoxicity-induced β-cell apoptosis by degrading aggregated proteins and dysfunctional mitochondria, while preserving insulin granule integrity [31,38]. Notably, exendin-4 co-administration with DYRK1A inhibitors amplifies this pro-survival effect, increasing human β-cell mass 4-7-fold in diabetic models through coordinated autophagy-lysosomal activation[11]. However, excessive autophagic flux inhibition (e.g., via OGT-mediated O-GlcNAcylation defects) counteracts these benefits, emphasizing the therapeutic window for GLP1R agonist dosing [109]. Emerging evidence links GLP1R agonism to improved mitochondrial oxidative phosphorylation and reduced ER stress in β-cells, both autophagy-dependent processes critical for glycemic control [38]. These findings position GLP1R agonists as multimodal regulators of β-cell proteostasis through controlled autophagic flux modulation. In addition, in diabetic mice, sustained metabolic overload induces β-cell hypoxia, driving HIF-1α accumulation and impairing insulin secretion. PX-478, a selective HIF-1α inhibitor, restored glucose-stimulated insulin secretion in human islet organoids chronically exposed to high glucose by normalizing hypoxia-driven transcriptional programs [106]. Mechanistically, PX-478 improved β-cell maturity markers (e.g., increased insulin granule formation, upregulated PDX1/ MAFA expression) while suppressing dedifferentiation pathways [106]. In streptozotocin-induced diabetic mice, PX-478 treatment enhanced pancreatic insulin content by 2.1-fold and accelerated glucose homeostasis recovery, correlating with reduced HIF-1α-mediated glycolytic shift and oxidative stress [106]. Notably, HIF-1α inhibition preserved β-cell function without altering islet viability or proliferation [110], suggesting targeted metabolic reprogramming. These findings align with studies showing HIF-1α destabilization improves β-cell resilience under metabolic stress by reactivating mitochondrial oxidative phosphorylation and reducing ER stress [111]. While most evidence derives from preclinical models, ongoing trials (NCT04845183) are evaluating HIF-1α inhibitors in diabetes-associated complications, underscoring translational potential (Table 2). Figure 2. The Integrated Framework of Mitochondrial Dynamics, Proteostasis, and Metabolic Reprogramming in Diabetic β-cell Failure, Alongside Targeted Interventions to Preserve Function.

## Conclusion and Future Directions

The integration of single-cell transcriptomics and mitochondrial biology has unveiled critical insights into β-cell heterogeneity and its metabolic regulation, yet key questions remain unresolved. First, the temporal-spatial regulation of mitochondrial dynamics in β-cell subpopulations remains poorly understood. Recent studies highlight that β-cell subsets with elevated mitochondrial metabolism, marked by CD63 expression, exhibit enhanced oxidative phosphorylation and mitochondrial respiration, suggesting dynamic mitochondrial remodeling underpins functional diversity [8,112]. However, how mitochondrial fission/fusion balances proteostasis and metabolic demands during β-cell differentiation or stress responses—particularly in aging or diabetes—requires further exploration. For instance, mitochondrial dynamics regulators like DRP1 and OPA1, which influence stem cell regeneration via metabolic reprogramming [113], may similarly govern β-cell plasticity. Spatial multi-omics approaches, such as single-cell ATAC-seq combined

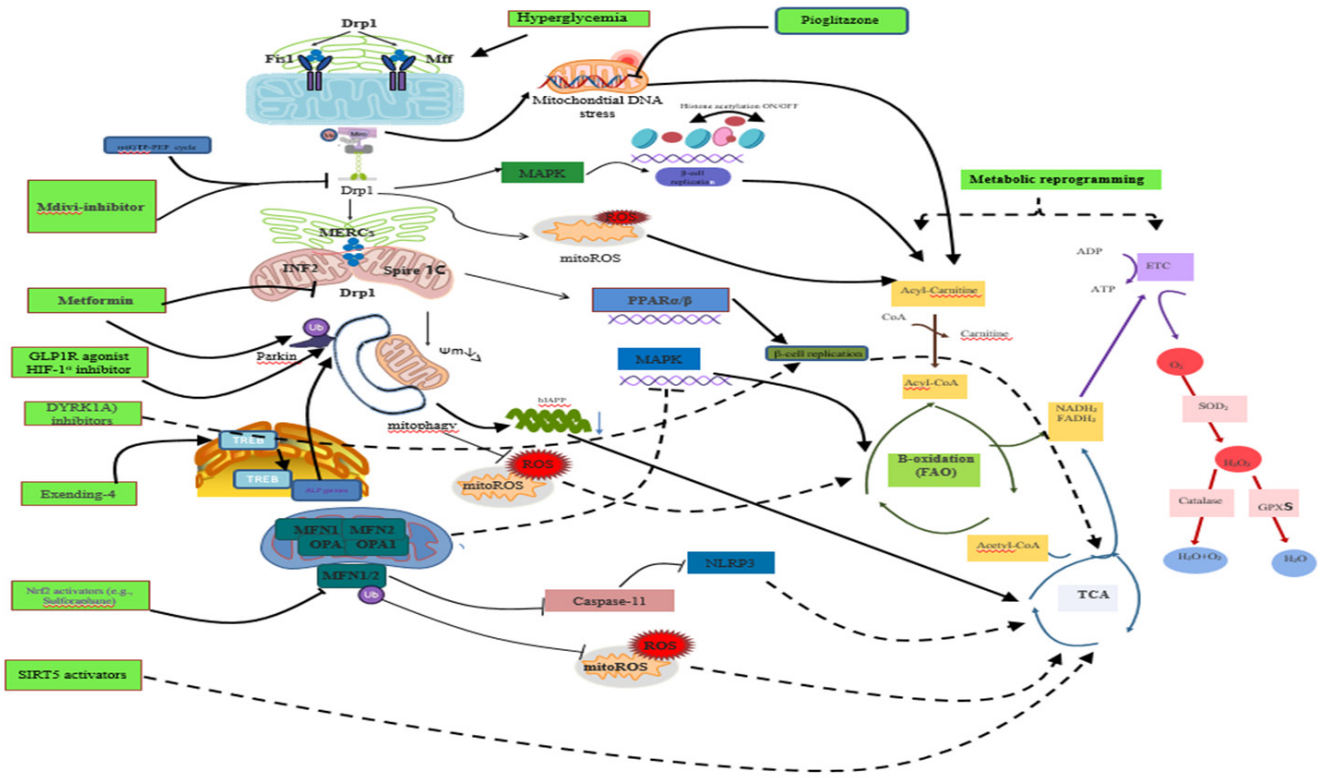


**Figure 2:** Chronic hyperglycemia disrupts pancreatic β-cell homeostasis by promoting mitochondrial fission through activation of dynamin-related protein 1 (Drp1) and impairing Parkin-mediated mitophagy, leading to excessive mitochondrial reactive oxygen species (mitoROS) accumulation and oxidative stress. This metabolic stress triggers a shift toward fatty acid β-oxidation (FAO) and disrupts the tricarboxylic acid (TCA) cycle, reducing ATP production and compromising glucose-stimulated insulin secretion. Concurrently, oxidative stress exacerbates β-cell damage via an imbalance in antioxidant systems (e.g., SOD, catalase, GPX) and activation of the NLRP3 inflammasome through Caspase-11. Epigenetic alterations, such as dynamic histone acetylation, further destabilize β-cell identity and function. To counteract these pathways, therapeutic strategies include: SIRT5 activators and Nrf2 activators (e.g., sulforaphane) to enhance antioxidant defenses; Mdivi-1 (a Drp1 inhibitor) and metformin (an AMPK activator) to restore mitochondrial fusion-fission balance; GLP-1 receptor agonists (e.g., exendin-4) and pioglitazone (a PPARγ agonist) to improve insulin secretion and metabolic flexibility; and DYRK1A inhibitors or HIF-1α inhibitors to prevent β-cell dedifferentiation and hypoxia-induced damage. This integrated framework highlights the interplay of mitochondrial dynamics, proteostasis, and metabolic reprogramming in diabetic β-cell failure, alongside targeted interventions to preserve function.

with mitochondrial DNA mutation tracking [114], could resolve how mitochondrial network remodeling coordinates with chromatin accessibility to drive β-cell adaptation or dysfunction in diabetes. Second, single-cell transcriptomics has emerged as a transformative tool for dissecting β-cell subpopulations with distinct metabolic states. Recent work identified T2D-associated β-cell subtypes characterized by stress-response gene activation and impaired mitochondrial OXPHOS [115]. Clusters with low electron transport chain (ETC) activity correlate with therapeutic resistance, emphasizing the need to map metabolic heterogeneity at single-cell resolution [116]. Emerging technologies like single-cell mitochondrial proteomics or spatial metabolomics could further resolve how mitochondrial stress gradients (e.g., localized ROS or mitophagy) influence β-cell fate. For example, ZnT8 loss-of-function accelerates β-cell maturation by enhancing mitochondrial energetic [117], suggesting metabolic state transitions are targetable. Machine learning frameworks integrating transcriptomic, chromatin, and metabolic data [115] will be critical to decode the regulatory logic of β-cell heterogeneity. Finally, combinatorial therapies targeting proteostasis and mitochondrial metabolism hold translational promise. Mitochondrial-targeted nanomaterials, which enhance fission/fusion dynamics [118], could synergize with proteostasis modulators like TFEB activators to restore β-cell function under metabolic stress [63,119]. Preclinical models demonstrate that mitochondrial stress primes resistance to proteasome inhibitors, necessitating regimens combining OXPHOS inhibitors (e.g., metformin) with ER stress mitigators [120]. Similarly, boosting mitophagy via lysosomal $Ca^{2+}$ modulation [63] or ceramide signaling [121] may protect β-cells from glucolipotoxicity. Future trials should prioritize patient stratification based on single-cell metabolic signatures to tailor combinatorial approaches [115,116] (Table 2).

## Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used kimi in order to improve English readability. After using this tool/service, the authors reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

### References

1. Sabouny, R., and Shutt, T.E. Reciprocal Regulation of Mitochondrial Fission and Fusion. Trends Biochem Sci. 2020; 45: 564-577.

2. Rosdah, A.A., Smiles, W.J., Oakhill, J.S., Scott, J.W., Langendorf, C.G., Delbridge, L.M.D., et al. New perspectives on the role of Drp1 isoforms in regulating mitochondrial pathophysiology. Pharmacol Ther. 2020; 213: 107594.

3. Zhang, L., Luo, Y., Lv, L., Chen, S., Liu, G., and Zhao, T. TRAP1 inhibits MARCH5-mediated MIC60 degradation to alleviate mitochondrial dysfunction and apoptosis of cardiomyocytes under diabetic conditions. Cell Death Differ. 2023; 30: 2336-2350.

4. Yong, J., Parekh, V.S., Reilly, S.M., Nayak, J., Chen, Z., Lebeaupin, C., et al. Chop/Ddit3 depletion in beta cells alleviates ER stress and corrects hepatic steatosis in mice. Sci Transl Med. 2011; 13.

5. Shrestha, N., Torres, M., Zhang, J., Lu, Y., Haataja, L., Reinert, R.B., et al. Integration of ER protein quality control mechanisms defines beta cell function and ER architecture. J Clin Invest. 2023; 133.

6. Park, K., Lim, H., Kim, J., Hwang, Y., Lee, Y.S., Bae, S.H., et al. Lysosomal Ca(2+)-mediated TFEB activation modulates mitophagy and functional adaptation of pancreatic beta-cells to metabolic stress. Nat Commun. 2022; 13: 1300.

7. Haythorne, E., Lloyd, M., Walsby-Tickle, J., Tarasov, A.I., Sandbrink, J., Portillo, I., et al. Altered glycolysis triggers impaired mitochondrial metabolism and mTORC1 activation in diabetic beta-cells. Nat Commun. 2022; 13: 6754.

8. Liu, B., Hua, D., Shen, L., Li, T., Tao, Z., Fu, C., et al. NPC1 is required for postnatal islet beta cell differentiation by maintaining mitochondria turnover. Theranostics. 2024; 14: 2058-2074.

9. Ronn, T., Ofori, J.K., Perfilyev, A., Hamilton, A., Pircs, K., Eichelmann, F., et al. Genes with epigenetic alterations in human pancreatic islets impact mitochondrial function, insulin secretion, and type 2 diabetes. Nat Commun. 2023; 14: 8040.

10. Karampelias, C., Watt, K., Mattsson, C.L., Ruiz, A.F., Rezanejad, H., Mi, J., et al. MNK2 deficiency potentiates beta-cell regeneration via translational regulation. Nat Chem Biol. 2022; 18: 942-953.

11. Rosselot, C., Li, Y., Wang, P., Alvarsson, A., Beliard, K., Lu, G., et al. Harmine and exendin-4 combination therapy safely expands human beta cell mass in vivo in a mouse xenograft system. Sci Transl Med. 2024; 16: eadg3456.

12. de Maranon, A.M., Diaz-Pozo, P., Canet, F., Diaz-Morales, N., Abad-Jimenez, Z., Lopez-Domenech, S., et al. Metformin modulates mitochondrial function and mitophagy in peripheral blood mononuclear cells from type 2 diabetic patients. Redox Biol. 2022; 53: 102342.

13. Oshima, Y., Verhoeven, N., Cartier, E., and Karbowski, M. The OMM-severed and IMM-ubiquitinated mitochondria are intermediates of mitochondrial proteotoxicity-induced autophagy in PRKN/parkin-deficient cells. Autophagy. 2021; 17: 3884-3886.

14. Yang, L., Li, X., Jiang, A., Li, X., Chang, W., Chen, J., and Ye, F. Metformin alleviates lead-induced mitochondrial fragmentation via AMPK/Nrf2 activation in SH-SY5Y cells. Redox Biol. 2020; 36: 101626.

15. Lopez-Vicario, C., Sebastian, D., Casulleras, M., Duran-Guell, M., Flores-Costa, R., Aguilar, F., et al.. Essential lipid autacoids rewire mitochondrial energy efficiency in metabolic dysfunction-associated fatty liver disease. Hepatology. 2023; 77: 1303-1318.

16. Nie, T., Tao, K., Zhu, L., Huang, L., Hu, S., Yang, R., et al. Chaperone-mediated autophagy controls the turnover of E3 ubiquitin ligase MARCHF5 and regulates mitochondrial dynamics. Autophagy. 2021; 17: 2923-2938.

17. Diaz-Vegas, A., Sanchez-Aguilera, P., Krycer, J.R., Morales, P.E., Monsalves-Alvarez, M., Cifuentes, M., et al. Is Mitochondrial Dysfunction a Common Root of Noncommunicable Chronic Diseases? Endocr Rev. 2020; 41.

18. Harrington, J.S., Ryter, S.W., Plataki, M., Price, D.R., and Choi, A.M.K. Mitochondria in health, disease, and aging. Physiol Rev. 2023; 103: 2349-2422.

19. Rocha, M., Apostolova, N., Diaz-Rua, R., Muntane, J., and Victor, V.M. Mitochondria and T2D: Role of Autophagy, ER Stress, and Inflammasome. Trends Endocrinol Metab. 2020; 31: 725-741.

20. Lopez-Soldado, I., Torres, A.G., Ventura, R., Martinez-Ruiz, I., Diaz-Ramos, A., Planet, E., et al. Decreased expression of mitochondrial aminoacyl-tRNA synthetases causes downregulation of OXPHOS subunits in type 2 diabetic muscle. Redox Biol. 2023; 61: 102630.

21. Siehler, J., Blochinger, A.K., Meier, M., and Lickert, H. Engineering islets from stem cells for advanced therapies of diabetes. Nat Rev Drug Discov. 2021; 20: 920-940.

22. Yong, J., Johnson, J.D., Arvan, P., Han, J., and Kaufman, R.J. Therapeutic opportunities for pancreatic beta-cell ER stress in diabetes mellitus. Nat Rev Endocrinol. 2021; 17: 455-467.

23. Chen, Z., Radjabzadeh, D., Chen, L., Kurilshikov, A., Kavousi, M., Ahmadizar, F., et al. Association of Insulin Resistance and Type 2 Diabetes With Gut Microbial Diversity: A Microbiome-Wide Analysis From Population Studies. JAMA Netw Open. 2021; 4: e2118811.

24. Dai, X., Wang, K., Fan, J., Liu, H., Fan, X., Lin, Q., et al. Nrf2 transcriptional upregulation of IDH2 to tune mitochondrial dynamics and rescue angiogenic function of diabetic EPCs. Redox Biol. 2022; 56: 102449.

25. Chang, X., Li, Y., Cai, C., Wu, F., He, J., Zhang, Y., Zhong, J., Tan, Y., Liu, R., Zhu, H., and Zhou, H. (2022). Mitochondrial quality control mechanisms as molecular targets in diabetic heart. Metabolism. 2022; 137, 155313.

26. Tang, C., Cai, J., Yin, X.M., Weinberg, J.M., Venkatachalam, M.A., and Dong, Z. (2021). Mitochondrial quality control in kidney injury and repair. Nat Rev Nephrol 17, 299-318.

27. Huang, L., Chen, Z., Chen, R., Lin, L., Ren, L., Zhang, M., and Liu, L. (2022). Increased fatty acid metabolism attenuates cardiac resistance to beta-adrenoceptor activation via mitochondrial reactive oxygen species: A potential mechanism of hypoglycemia-induced myocardial injury in diabetes. Redox Biol 52, 102320.

28. Vacurova, E., Trnovska, J., Svoboda, P., Skop, V., Novosadova, V., Reguera, D.P., Petrezselyova, S., Piavaux, B., Endaya, B., Spoutil, F., et al. (2022). Mitochondrially targeted tamoxifen alleviates markers of obesity and type 2 diabetes mellitus in mice. Nat Commun 13, 1866.

29. Gancheva, S., Kahl, S., Pesta, D., Mastrototaro, L., Dewidar, B., Strassburger, K., Sabah, E., Esposito, I., Weiss, J., Sarabhai, T., et al. (2022). Impaired Hepatic Mitochondrial Capacity in Nonalcoholic Steatohepatitis Associated With Type 2 Diabetes. Diabetes Care 45, 928-937.

30. Chen, X., Shi, C., He, M., Xiong, S., and Xia, X. (2023). Endoplasmic reticulum stress: molecular mechanism and therapeutic targets. Signal Transduct Target Ther 8, 352.

31. Wu, T., Shao, Y., Li, X., Wu, T., Yu, L., Liang, J., Zhang, Y., Wang, J., Sun, T., Zhu, Y., et al. (2023). NR3C1/Glucocorticoid receptor activation promotes pancreatic beta-cell autophagy overload in response to glucolipotoxicity. Autophagy 19, 2538-2557.

32. Lee, H., Sahin, G.S., Chen, C.W., Sonthalia, S., Canas, S.M., Oktay, H.Z., Duckworth, A.T., Brawerman, G., Thompson, P.J., Hatzoglou, M., et al. (2023). Stress-induced beta cell early senescence confers protection against type 1 diabetes. Cell Metab 35, 2200-2215.e2209.

33. Eizirik, D.L., Pasquali, L., and Cnop, M. (2020). Pancreatic beta-cells in type 1 and type 2 diabetes mellitus: different pathways to failure. Nat Rev Endocrinol 16, 349-362.

34. Shrestha, N., Liu, T., Ji, Y., Reinert, R.B., Torres, M., Li, X., Zhang, M., Tang, C.A., Hu, C.A., Liu, C., et al. (2020). Sel1L-Hrd1 ER-associated degradation maintains beta cell identity via TGF-beta signaling. J Clin Invest 130, 3499-3510.

35. Li, J., Zheng, Y., Yan, P., Song, M., Wang, S., Sun, L., Liu, Z., Ma, S., Izpisua Belmonte, J.C., Chan, P., et al. (2021). A single-cell transcriptomic atlas of primate pancreatic islet aging. Natl Sci Rev 8, nwaa127.

36. Hetz, C., and Dillin, A. (2024). Central role of the ER proteostasis network in healthy aging. Trends Cell Biol.

37. Zhu, Q., Liu, Z., Wang, Y., Song, E., and Song, Y. (2021). Endoplasmic reticulum stress manipulates autophagic response that antagonizes polybrominated diphenyl ethers quinone induced cytotoxicity in microglial BV2 cells. J Hazard Mater 411, 124958.

38. Shao, Y., Zhang, Y., Zou, S., Wang, J., Li, X., Qin, M., Sun, L., Yin, W., Chang, X., Wang, S., et al. (2024). (-)-Epigallocatechin 3-gallate protects pancreatic beta-cell against excessive autophagy-induced injury through promoting FTO degradation. Autophagy 20, 2460-2477.

39. Wirth, F., Heitz, F.D., Seeger, C., Combaluzier, I., Breu, K., Denroche, H.C., Thevenet, J., Osto, M., Arosio, P., Kerr-Conte, J., et al. (2023). A human antibody against pathologic IAPP aggregates protects beta cells in type 2 diabetes models. Nat Commun 14, 6294.

40. Cheruiyot, A., Hollister-Lock, J., Sullivan, B., Pan, H., Dreyfuss, J.M., Bonner-Weir, S., and Schaffer, J.E. (2023). Sustained hyperglycemia specifically targets translation of mRNAs for insulin secretion. J Clin Invest 134.

41. Katz, L.S., Visser, E.J., Plitzko, K.F., Pennings, M.A.M., Cossar, P.J., Tse, I.L., Kaiser, M., Brunsveld, L., Ottmann, C., and Scott, D.K. (2025). Molecular glues of the regulatory ChREBP/14-3-3 complex protect beta cells from glucolipotoxicity. Nat Commun 16, 2110.

42. Karunakaran, U., Elumalai, S., Moon, J.S., and Won, K.C. (2021). Pioglitazone-induced AMPK-Glutaminase-1 prevents high glucose-induced pancreatic beta-cell dysfunction by glutathione antioxidant system. Redox Biol 45, 102029.

43. Shrestha, S., Erikson, G., Lyon, J., Spigelman, A.F., Bautista, A., Manning Fox, J.E., Dos Santos, C., Shokhirev, M., Cartailler, J.P., Hetzer, M.W., et al. (2022). Aging compromises human islet beta cell function and identity by decreasing transcription factor activity and inducing ER stress. Sci Adv 8, eabo3932.

44. Tilokani, L., Russell, F.M., Hamilton, S., Virga, D.M., Segawa, M., Paupe, V., Gruszczyk, A.V., Protasoni, M., Tabara, L.C., Johnson, M., et al. (2022). AMPK-dependent phosphorylation of MTFR1L regulates mitochondrial morphology. Sci Adv 8, eabo7956.

45. Chang, X., Niu, S., Shang, M., Li, J., Guo, M., Zhang, W., Sun, Z., Li, Y., Zhang, R., Shen, X., et al. (2023). ROS-Drp1-mediated mitochondria fission contributes to hippocampal HT22 cell apoptosis induced by silver nanoparticles. Redox Biol 63, 102739.

46. Cai, Y., Yang, E., Yao, X., Zhang, X., Wang, Q., Wang, Y., Liu, J., Fan, W., Yi, K., Kang, C., and Wu, J. (2021). FUNDC1-dependent mitophagy induced by tPA protects neurons against cerebral ischemia-reperfusion injury. Redox Biol 38, 101792.

47. Xiao, L., Yin, Y., Sun, Z., Liu, J., Jia, Y., Yang, L., Mao, Y., Peng, S., Xie, Z., Fang, L., et al. (2024). AMPK phosphorylation of FNIP1 (S220) controls mitochondrial function and muscle fuel utilization during exercise. Sci Adv 10, eadj2752.

48. Hsu, C.C., Zhang, X., Wang, G., Zhang, W., Cai, Z., Pan, B.S., Gu, H., Xu, C., Jin, G., Xu, X., et al. (2021). Inositol serves as a natural inhibitor of mitochondrial fission by directly targeting AMPK. Mol Cell 81, 3803-3819. e3807.

49. Moore, T.M., Cheng, L., Wolf, D.M., Ngo, J., Segawa, M., Zhu, X., Strumwasser, A.R., Cao, Y., Clifford, B.L., Ma, A., et al. (2022). Parkin regulates adiposity by coordinating mitophagy with mitochondrial biogenesis in white adipocytes. Nat Commun 13, 6661.

50. He, F., Huang, Y., Song, Z., Zhou, H.J., Zhang, H., Perry, R.J., Shulman, G.I., and Min, W. (2021). Mitophagy-mediated adipose inflammation contributes to type 2 diabetes with hepatic insulin resistance. J Exp Med 218.

51. Hu, Y., Li, Y., Li, M., Zhao, T., Zhang, W., Wang, Y., He, Y., Zhao, H., Li, H., Wang, T., et al. (2024). Calcium supplementation attenuates fluoride-induced bone injury via PINK1/Parkin-mediated mitophagy and mitochondrial apoptosis in mice. J Hazard Mater 465, 133411.

52. Agarwal, E., Goldman, A.R., Tang, H.Y., Kossenkov, A.V., Ghosh, J.C., Languino, L.R., Vaira, V., Speicher, D.W., and Altieri, D.C. (2021). A cancer ubiquitome landscape identifies metabolic reprogramming as target of Parkin tumor suppression. Sci Adv 7.

53. Wang, S., Wang, Z., Zang, Z., Liang, X., Jia, B., Ye, T., Lan, Y., and Shi, X. (2025). A Mitochondrion-Targeting Piezoelectric Nanosystem for the Treatment of Erectile Dysfunction via Autophagy Regulation. Adv Mater 37, e2413287.

54. Holendova, B., Salovska, B., Benakova, S., and Plecita-Hlavata, L. (2024). Beyond glucose: The crucial role of redox signaling in beta-cell metabolic adaptation. Metabolism 161, 156027.

55. Kang, Q., and Yang, C. (2020). Oxidative stress and diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. Redox Biol 37, 101799.

56. Davidson, M.T., Grimsrud, P.A., Lai, L., Draper, J.A., Fisher-Wellman, K.H., Narowski, T.M., Abraham, D.M., Koves, T.R., Kelly, D.P., and Muoio, D.M. (2020). Extreme Acetylation of the Cardiac Mitochondrial Proteome Does Not Promote Heart Failure. Circ Res 127, 1094-1108.

57. Zhang, Y., Zhang, H., Zhao, F., Jiang, Z., Cui, Y., Ou, M., Mei, L., and Wang, Q. (2023). Mitochondrial-targeted and ROS-responsive nanocarrier via nose-to-brain pathway for ischemic stroke treatment. Acta Pharm Sin B 13, 5107-5120.

58. Lee, C., Nam, J.S., Lee, C.G., Park, M., Yoo, C.M., Rhee, H.W., Seo, J.K., and Kwon, T.H. (2021). Analysing the mechanism of mitochondrial oxidation-induced cell death using a multifunctional iridium(III) photosensitiser. Nat Commun 12, 26.

59. Dubois, M., Boulghobra, D., Rochebloine, G., Pallot, F., Yehya, M., Bornard, I., Gayrard, S., Coste, F., Walther, G., Meyer, G., et al. (2024). Hyperglycemia triggers RyR2-dependent alterations of mitochondrial calcium homeostasis in response to cardiac ischemia-reperfusion: Key role of DRP1 activation. Redox Biol 70, 103044.

60. Cacace, J., Luna-Marco, C., Hermo-Argibay, A., Pesantes-Somogyi, C., Hernandez-Lopez, O.A., Pelecha-Salvador, M., Banuls, C., Apostolova, N., de Miguel-Rodriguez, L., Morillas, C., et al. (2025). Poor glycaemic control in type 2 diabetes compromises leukocyte oxygen consumption rate, OXPHOS complex content and neutrophil-endothelial interactions. Redox Biol 81, 103516.

61. Yao, L., Liang, X., Liu, Y., Li, B., Hong, M., Wang, X., Chen, B., Liu, Z., and Wang, P. (2023). Non-steroidal mineralocorticoid receptor antagonist finerenone ameliorates mitochondrial dysfunction via PI3K/Akt/eNOS signaling pathway in diabetic tubulopathy. Redox Biol 68, 102946.

62. Cho, J.H., Chae, C.W., Lim, J.R., Jung, Y.H., Han, S.J., Yoon, J.H., Park, J.Y., and Han, H.J. (2024). Sodium butyrate ameliorates high glucose-suppressed neuronal mitophagy by restoring PRKN expression via inhibiting the RELA-HDAC8 complex. Autophagy 20, 1505-1522.

63. Park, K., and Lee, M.S. (2022). Essential role of lysosomal Ca2+-mediated TFEB activation in mitophagy and functional adaptation of pancreatic beta-cells to metabolic stress. Autophagy 18, 3043-3045.

64. Park, K., Sonn, S.K., Seo, S., Kim, J., Hur, K.Y., Oh, G.T., and Lee, M.S. (2023). Impaired TFEB activation and mitophagy as a cause of PPP3/calcineurin inhibitor-induced pancreatic beta-cell dysfunction. Autophagy 19, 1444-1458.

65. Lopez-Hernandez, T., Puchkov, D., Krause, E., Maritzen, T., and Haucke, V. (2020). Endocytic regulation of cellular ion homeostasis controls lysosome biogenesis. Nat Cell Biol 22, 815-827.

66. Chamoli, M., Rane, A., Foulger, A., Chinta, S.J., Shahmirzadi, A.A., Kumsta, C., Nambiar, D.K., Hall, D., Holcom, A., Angeli, S., et al. (2023). A drug-like molecule engages nuclear hormone receptor DAF-12/FXR to regulate mitophagy and extend lifespan. Nat Aging 3, 1529-1543.

67. Yuan, T., Annamalai, K., Naik, S., Lupse, B., Geravandi, S., Pal, A., Dobrowolski, A., Ghawali, J., Ruhlandt, M., Gorrepati, K.D.D., et al. (2021). The Hippo kinase LATS2 impairs pancreatic beta-cell survival in diabetes through the mTORC1-autophagy axis. Nat Commun 12, 4928.

68. Paquette, M., El-Houjeiri, L., L, C.Z., Puustinen, P., Blanchette, P., Jeong, H., Dejgaard, K., Siegel, P.M., and Pause, A. (2021). AMPK-dependent phosphorylation is required for transcriptional activation of TFEB and TFE3. Autophagy 17, 3957-3975.

69. Cui, Z., Napolitano, G., de Araujo, M.E.G., Esposito, A., Monfregola, J., Huber, L.A., Ballabio, A., and Hurley, J.H. (2023). Structure of the lysosomal mTORC1-TFEB-Rag-Ragulator megacomplex. Nature 614, 572-579.

70. Zhu, L., Yuan, Y., Yuan, L., Li, L., Liu, F., Liu, J., Chen, Y., Lu, Y., and Cheng, J. (2020). Activation of TFEB-mediated autophagy by trehalose attenuates mitochondrial dysfunction in cisplatin-induced acute kidney injury. Theranostics 10, 5829-5844.

71. Lu, Y., Xu, J., Li, Y., Wang, R., Dai, C., Zhang, B., Zhang, X., Xu, L., Tao, Y., Han, M., et al. (2024). DRAK2 suppresses autophagy by phosphorylating ULK1 at Ser(56) to diminish pancreatic beta cell function upon overnutrition. Sci Transl Med 16, eade8647.

72. Nguyen, H.T., Wiederkehr, A., Wollheim, C.B., and Park, K.S. (2024). Regulation of autophagy by perilysosomal calcium: a new player in beta-cell lipotoxicity. Exp Mol Med 56, 273-288.

73. Almeida, L.M., Pinho, B.R., Duchen, M.R., and Oliveira, J.M.A. (2022). The PERKs of mitochondria protection during stress: insights for PERK modulation in neurodegenerative and metabolic diseases. Biol Rev Camb Philos Soc 97, 1737-1748.

74. Dasgupta, D., Mahadev Bhat, S., Creighton, C., Cortes, C., Delmotte, P., and Sieck, G.C. (2024). Molecular mechanisms underlying TNFalpha-induced mitochondrial fragmentation in human airway smooth muscle cells. Am J Physiol Lung Cell Mol Physiol 326, L190-l205.

75. Bassot, A., Chen, J., Takahashi-Yamashiro, K., Yap, M.C., Gibhardt, C.S., Le, G.N.T., Hario, S., Nasu, Y., Moore, J., Gutierrez, T., et al. (2023). The endoplasmic reticulum kinase PERK interacts with the oxidoreductase ERO1 to metabolically adapt mitochondria. Cell Rep 42, 111899.

76. Brar, K.K., Hughes, D.T., Morris, J.L., Subramanian, K., Krishna, S., Gao, F., Rieder, L.S., Uhrig, S., Freeman, J., Smith, H.L., et al. (2024). PERK-ATAD3A interaction provides a subcellular safe haven for protein synthesis during ER stress. Science 385, eadp7114.

77. Jin, Y., Huynh, D.T.N., and Heo, K.S. (2022). Ginsenoside Rh1 inhibits tumor growth in MDA-MB-231 breast cancer cells via mitochondrial ROS and ER stress-mediated signaling pathway. Arch Pharm Res 45, 174-184.

78. Meier, D.T., Rachid, L., Wiedemann, S.J., Traub, S., Trimigliozzi, K., Stawiski, M., Sauteur, L., Winter, D.V., Le Foll, C., Bregere, C., et al. (2022). Prohormone convertase 1/3 deficiency causes obesity due to impaired proinsulin processing. Nat Commun 13, 4761.

79. Liu, Y., Yang, X., Zhou, J., Yang, H., Yang, R., Zhu, P., Zhou, R., Wu, T., Gao, Y., Ye, Z., et al. (2024). OSGEP regulates islet beta-cell function by modulating proinsulin translation and maintaining ER stress homeostasis in mice. Nat Commun 15, 10479.

80. Salomone, F., Pipitone, R.M., Longo, M., Malvestiti, F., Amorini, A.M., Distefano, A., Casirati, E., Ciociola, E., Iraci, N., Leggio, L., et al. (2024). SIRT5 rs12216101 T>G variant is associated with liver damage and mitochondrial dysfunction in patients with non-alcoholic fatty liver disease. J Hepatol 80, 10-19.

81. Yeh, Y.T., Sona, C., Yan, X., Li, Y., Pathak, A., McDermott, M.I., Xie, Z., Liu, L., Arunagiri, A., Wang, Y., et al. (2023). Restoration of PITPNA in Type 2 diabetic human islets reverses pancreatic beta-cell dysfunction. Nat Commun 14, 4250.

82. Shi, X., Ma, C., Chen, N., Xu, M.M., Kambal, S., Cai, Z.F., Yang, Q., Adeola, A.C., Liu, L.S., Wang, J., et al. (2025). Selection Increases Mitonuclear DNA Discordance but Reconciles Incompatibility in African Cattle. Mol Biol Evol 42.

83. Meng, F., Jia, Z., Zheng, J., Ji, Y., Wang, J., Xiao, Y., Fu, Y., Wang, M., Ling, F., and Guan, M.X. (2022). A deafness-associated mitochondrial DNA mutation caused pleiotropic effects on DNA replication and tRNA metabolism. Nucleic Acids Res 50, 9453-9469.

84. Fiorenza, M., Onslev, J., Henriquez-Olguin, C., Persson, K.W., Hesselager, S.A., Jensen, T.E., Wojtaszewski, J.F.P., Hostrup, M., and Bangsbo, J. (2024). Reducing the mitochondrial oxidative burden alleviates lipid-induced muscle insulin resistance in humans. Sci Adv 10, eadq4461.

85. Daniell, H., Singh, R., Mangu, V., Nair, S.K., Wakade, G., and Balashova, N. (2023). Affordable oral proinsulin bioencapsulated in plant cells regulates blood sugar levels similar to natural insulin. Biomaterials 298, 122142.

86. Jaburek, M., Kloppel, E., Pruchova, P., Mozheitova, O., Tauber, J., Engstova, H., and Jezek, P. (2024). Mitochondria to plasma membrane redox signaling is essential for fatty acid beta-oxidation-driven insulin secretion. Redox Biol 75, 103283.

87. Castro-Sepulveda, M., Fernandez-Verdejo, R., Zbinden-Foncea, H., and Rieusset, J. (2023). Mitochondria-SR interaction and mitochondrial fusion/fission in the regulation of skeletal muscle metabolism. Metabolism 144, 155578.

88. Xourafa, G., Korbmacher, M., and Roden, M. (2024). Inter-organ crosstalk during development and progression of type 2 diabetes mellitus. Nat Rev Endocrinol 20, 27-49.

89. Sun, Q., Guven, B., Wagg, C.S., Almeida de Oliveira, A., Silver, H., Zhang, L., Chen, B., Wei, K., Ketema, E.B., Karwi, Q.G., et al. (2024). Mitochondrial fatty acid oxidation is the major source of cardiac adenosine triphosphate production in heart failure with preserved ejection fraction. Cardiovasc Res 120, 360-371.

90. Merrins, M.J., Corkey, B.E., Kibbey, R.G., and Prentki, M. (2022). Metabolic cycles and signals for insulin secretion. Cell Metab 34, 947-968.

91. Takhaveev, V., Ozsezen, S., Smith, E.N., Zylstra, A., Chaillet, M.L., Chen, H., Papagiannakis, A., Milias-Argeitis, A., and Heinemann, M. (2023). Temporal segregation of biosynthetic processes is responsible for metabolic oscillations during the budding yeast cell cycle. Nat Metab 5, 294-313.

92. Ren, H., Li, Y., Han, C., Yu, Y., Shi, B., Peng, X., Zhang, T., Wu, S., Yang, X., Kim, S., et al. (2022). Pancreatic alpha and beta cells are globally phase-locked. Nat Commun 13, 3721.

93. Chemla, A., Arena, G., Sacripanti, G., Barmpa, K., Zagare, A., Garcia, P., Gorgogietas, V., Antony, P., Ohnmacht, J., Baron, A., et al. (2025). Parkinson's disease mutant Miro1 causes mitochondrial dysfunction and dopaminergic neuron loss. Brain.

94. Sidarala, V., Zhu, J., Levi-D'Ancona, E., Pearson, G.L., Reck, E.C., Walker, E.M., Kaufman, B.A., and Soleimanpour, S.A. (2022). Mitofusin 1 and 2 regulation of mitochondrial DNA content is a critical determinant of glucose homeostasis. Nat Commun 13, 2340.

95. Wang, L., Wu, J., Sramek, M., Obayomi, S.M.B., Gao, P., Li, Y., Matveyenko, A.V., and Wei, Z. (2024). Heterogeneous enhancer states orchestrate beta cell responses to metabolic stress. Nat Commun 15, 9361.

96. Cho, Y., and Kim, Y.K. (2024). ROS-mediated cytoplasmic localization of CARM1 induces mitochondrial fission through DRP1 methylation. Redox Biol 73, 103212.

97. Guo, H.Y., Tang, S.B., Li, L.J., Lin, J., Zhang, T.T., Chao, S., Jin, X.W., Xu, K.P., Su, X.F., Yin, S., et al. (2025). Gestational diabetes mellitus causes genome hyper-methylation of oocyte via increased EZH2. Nat Commun 16, 127.

98. De Jesus, D.F., Zhang, Z., Brown, N.K., Li, X., Xiao, L., Hu, J., Gaffrey, M.J., Fogarty, G., Kahraman, S., Wei, J., et al. (2024). Redox regulation of m(6)A methyltransferase METTL3 in beta-cells controls the innate immune response in type 1 diabetes. Nat Cell Biol 26, 421-437.

99. Haemmerle, M.W., Scota, A.V., Khosravifar, M., Varney, M.J., Sen, S., Good, A.L., Yang, X., Wells, K.L., Sussel, L., Rozo, A.V., et al. (2024). RNA-binding protein PCBP2 regulates pancreatic beta cell function and adaptation to glucose. J Clin Invest 134.

100. Wortham, M., Liu, F., Harrington, A.R., Fleischman, J.Y., Wallace, M., Mulas, F., Mallick, M., Vinckier, N.K., Cross, B.R., Chiou, J., et al. (2023). Nutrient regulation of the islet epigenome controls adaptive insulin secretion. J Clin Invest 133.

101. Edwards-Hicks, J., Su, H., Mangolini, M., Yoneten, K.K., Wills, J., Rodriguez-Blanco, G., Young, C., Cho, K., Barker, H., Muir, M., et al. (2022). MYC sensitises cells to apoptosis by driving energetic demand. Nat Commun 13, 4674.

102. Chen, C.W., Guan, B.J., Alzahrani, M.R., Gao, Z., Gao, L., Bracey, S., Wu, J., Mbow, C.A., Jobava, R., Haataja, L., et al. (2022). Adaptation to chronic ER stress enforces pancreatic beta-cell plasticity. Nat Commun 13, 4621.

103. Dos Santos, C., Cambraia, A., Shrestha, S., Cutler, M., Cottam, M., Perkins, G., Lev-Ram, V., Roy, B., Acree, C., Kim, K.Y., et al. (2024). Calorie restriction increases insulin sensitivity to promote beta cell homeostasis and longevity in mice. Nat Commun 15, 9063.

104. Holmes, A.G., Parker, J.B., Sagar, V., Truica, M.I., Soni, P.N., Han, H., Schiltz, G.E., Abdulkadir, S.A., and Chakravarti, D. (2022). A MYC inhibitor selectively alters the MYC and MAX cistromes and modulates the epigenomic landscape to regulate target gene expression. Sci Adv 8, eabh3635.

105. Karakose, E., Wang, X., Wang, P., Carcamo, S., Demircioglu, D., Lambertini, L., Wood, O., Kang, R., Lu, G., Scott, D.K., et al. (2024). Cycling alpha cells in regenerative drug-treated human pancreatic islets may serve as key beta cell progenitors. Cell Rep Med 5, 101832.

106. Ilegems, E., Bryzgalova, G., Correia, J., Yesildag, B., Berra, E., Ruas, J.L., Pereira, T.S., and Berggren, P.O. (2022). HIF-1alpha inhibitor PX-478 preserves pancreatic beta cell function in diabetes. Sci Transl Med 14, eaba9112.

107. Son, J., Du, W., Esposito, M., Shariati, K., Ding, H., Kang, Y., and Accili, D. (2023). Genetic and pharmacologic inhibition of ALDH1A3 as a treatment of beta-cell failure. Nat Commun 14, 558.

108. Harrison, S.A., Thang, C., Bolze, S., Dewitt, S., Hallakou-Bozec, S., Dubourg, J., Bedossa, P., Cusi, K., Ratziu, V., Grouin, J.M., et al. (2023). Evaluation of PXL065 - deuterium-stabilized (R)-pioglitazone in patients with NASH: A phase II randomized placebo-controlled trial (DESTINY-1). J Hepatol 78, 914-925.

109. Pellegrini, F.R., De Martino, S., Fianco, G., Ventura, I., Valente, D., Fiore, M., Trisciuoglio, D., and Degrassi, F. (2023). Blockage of autophagosome-lysosome fusion through SNAP29 O-GlcNAcylation promotes apoptosis via ROS production. Autophagy 19, 2078-2093.

110. Wrublewsky, S., Glas, J., Carlein, C., Nalbach, L., Hoffmann, M.D.A., Pack, M., Vilas-Boas, E.A., Ribot, N., Kappl, R., Menger, M.D., et al. (2022). The loss of pancreatic islet NADPH oxidase (NOX)2 improves islet transplantation. Redox Biol 55, 102419.

111. Fagundes, R.R., Zaldumbide, A., and Taylor, C.T. (2024). Role of hypoxia-inducible factor 1 in type 1 diabetes. Trends Pharmacol Sci 45, 798-810.

112. Rubio-Navarro, A., Gomez-Banoy, N., Stoll, L., Dundar, F., Mawla, A.M., Ma, L., Cortada, E., Zumbo, P., Li, A., Reiterer, M., et al. (2023). A beta cell subset with enhanced insulin secretion and glucose metabolism is reduced in type 2 diabetes. Nat Cell Biol 25, 565-578.

113. Hong, X., Isern, J., Campanario, S., Perdiguero, E., Ramirez-Pardo, I., Segales, J., Hernansanz-Agustin, P., Curtabbi, A., Deryagin, O., Pollan, A., et al. (2022). Mitochondrial dynamics maintain muscle stem cell regenerative competence throughout adult life by regulating metabolism and mitophagy. Cell Stem Cell 29, 1298-1314.e1210.

114. Nitsch, L., Lareau, C.A., and Ludwig, L.S. (2024). Mitochondrial genetics through the lens of single-cell multi-omics. Nat Genet 56, 1355-1365.

115. Wang, G., Chiou, J., Zeng, C., Miller, M., Matta, I., Han, J.Y., Kadakia, N., Okino, M.L., Beebe, E., Mallick, M., et al. (2023). Integrating genetics with single-cell multiomic measurements across disease states identifies mechanisms of beta cell dysfunction in type 2 diabetes. Nat Genet 55, 984-994.

116. Sunassee, E.D., Deutsch, R.J., D'Agostino, V.W., Castellano-Escuder, P., Siebeneck, E.A., Ilkayeva, O., Crouch, B.T., Madonna, M.C., Everitt, J., Alvarez, J.V., et al. (2024). Optical imaging reveals chemotherapy-induced metabolic reprogramming of residual disease and recurrence. Sci Adv 10, eadj7540.

117. Ma, Q., Xiao, Y., Xu, W., Wang, M., Li, S., Yang, Z., Xu, M., Zhang, T., Zhang, Z.N., Hu, R., et al. (2022). ZnT8 loss-of-function accelerates functional maturation of hESC-derived beta cells and resists metabolic stress in diabetes. Nat Commun 13, 4142.

118. Fu, H., Cheng, J., Hu, L., Heng, B.C., Zhang, X., Deng, X., and Liu, Y. (2025). Mitochondria-targeting materials and therapies for regenerative engineering. Biomaterials 316, 123023.

119. Wu, L., Wang, L., Du, Y., Zhang, Y., and Ren, J. (2023). Mitochondrial quality control mechanisms as therapeutic targets in doxorubicin-induced cardiotoxicity. Trends Pharmacol Sci 44, 34-49.

120. Leow, D.M., Ng, Y.K., Wang, L.C., Koh, H.W., Zhao, T., Khong, Z.J., Tabaglio, T., Narayanan, G., Giadone, R.M., Sobota, R.M., et al. (2024). Hepatocyte-intrinsic SMN deficiency drives metabolic dysfunction and liver steatosis in spinal muscular atrophy. J Clin Invest 134.

121. Karampelias, C., and Lickert, H. (2024). Greasing the machinery toward maturation of stem cell-derived beta cells. Cell Stem Cell 31, 793-794.