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Adipose tissue mitochondrial dysfunction and cardiometabolic diseases: On the search for novel molecular targets

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ABSTRACT

Cardiometabolic diseases present an escalating global health and economic burden. Such a surge is driven by epidemic prevalence rates of metabolic disorders, such as obesity and type 2 diabetes, and their associated cardiovascular complications, majorly contributing to morbidity and mortality. A fundamental challenge impeding the effective management and therapy of these complications is a lack of clear understanding of the molecular mechanisms underpinning disease initiation and progression. Over the past decade, a role for metabolic disease-associated adipose tissue dysfunction and inflammation in evoking cardiovascular and renal deterioration emerged, together with a growing recognition of the positive impact of pharmacological tools modulating adipose tissue function. Adipose tissue is a plastic endocrine organ whose homeostasis is essentially dependent on the intercellular communication of its comprising cellular components. Yet, despite being a

Abbreviations: β-AR, Beta adrenergic receptor; AAC, ADP/ATP carrier; ACEI, Angiotensin converting enzyme inhibitor; Acly, ATP citrate lyase; ADH1, Alcohol dehydrogenase 1; Akt, Protein kinase B; AMPK, AMP-activated protein kinase; ANT, Adenine nucleotide translocase; ApoE, Apolipoprotein E; ARBs, Angiotensin II receptor blockers; AT, Adipose tissue; AT1R, Angiotensin 1 receptor; ATP, Adenosine tri-phosphate; BAT, Brown adipose tissue; BCAAs, Branched-chain amino acids; BCAT2, Branched chain amino acids transaminase 2; BMI, Body mass index; BNIP3, BCL2/E1B 19 KDa-interacting protein; CAD, Coronary artery disease; cAMP, Cyclic AMP; CD36, Cluster of differentiation 36; CHRNA2, Cholinergic receptor nicotinic alpha 2 subunit; CIDEA, Cell death inducing DFFA like effector A; CISD1, CDGSH iron sulfur domain 1; CKB, Creatine kinase B; CKD, Chronic kidney disease; CrT, Creatine transporter; CVDs, Cardiovascular diseases; DIO, Diet-induced obesity; Dnm2, Dynamin 2; DRP1, Dynamin-related protein 1; ECM, Extracellular matrix; eNOS, Endothelial nitric oxide synthase; EpiCAT, Epicardial adipose tissue; ER, Endoplasmic reticulum; ERR-α, Estrogen-related receptor alpha; FAO, Fatty acid oxidation; FFA, Free fatty acid; Fis1, Mitochondrial fission 1; FUNDC1, FUN14 domain-containing protein 1; GATM, Glycine amidinotransferase; GPR3, G-protein coupled receptor 3; HFD, High fat diet; HIF-1α, Hypoxia-inducible factor 1 alpha; HSL, Hormone sensitive lipase; IFN-γ, Interferon gamma; IL, Interleukin; IR, Insulin resistance; KCNK3, Potassium two pore domain channel subfamily K member 3; LC3, Microtubule-associated protein 1A/1B-light chain 3; LPL, Lipoprotein lipase; MCP-1, Monocyte chemoattractant protein 1; MCU, Mitochondrial calcium uniporter; MFF, Mitochondrial fission factor; MFN, Mitofusin; mGPD, Mitochondrial glycerol phosphate dehydrogenase; MiD, Mitochondrial dynamics protein; miR, MicroRNA; MPC, Mitochondrial pyruvate carrier; mtDNA, Mitochondrial DNA; NADH, Nicotinamide adenine dinucleotide; NF-κB, Nuclear factor kappa light chain enhancer activated B cells; NFE2L2, NFE2 like BZIP transcription factor 2; NLRP3, NLR family pyrin domain containing 3; NRF, Nuclear respiratory factor; OCT3, Organic cation transporter 3; OPA1, Optic atrophy 1; OXPHOS, Oxidative phosphorylation; ParaCAT, Paracardial adipose tissue; PeriCAT, Pericardial adipose tissue; PGC-1, Peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PINK1, PTEN-induced kinase 1; PKA, Protein kinase A; PLN, Phospholamban; PPAR, Peroxisome proliferator-activated receptor; PRAT, Perirenal adipose tissue; PRDM16, PR domain containing 16; PTEN, Phosphatase and tensin homolog; PVAT, Perivascular adipose tissue; Rac1, Rac family small GTPase 1; ROS, Reactive oxygen species; SAT, Subcutaneous adipose tissue; SERCA, Sarcoplasmic/endoplasmic reticulum calcium ATPase; Sirt, Sirtuin; Smad3, Smad family member 3; STAT3, Signal transducer and activator of transcription 3; T2D, Type 2 diabetes; TFAM, Mitochondrial transcription factor A; TGF-β1, Transforming growth factor beta 1; TMEM26, Transmembrane protein 26; TNAP, Tissue non-specific alkaline phosphatase; TNF-α, Tumor necrosis factor alpha; TOM70, Translocase of outer mitochondrial membrane 70; UCP1, Uncoupling protein 1; VAT, Visceral adipose tissue; VEGF, Vascular endothelial growth factor; WAT, White adipose issue.

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principal regulator of adipose tissue metabolic activity, changes in aspects of adipose tissue mitochondrial biogenesis, dynamics, and bioenergetics in the context of cardiometabolic disorders have not garnered the necessary attention. Here, we gather the available evidence on the contribution of mitochondrial dysfunction to that of the adipose tissue in metabolic diseases, and to the ensuing cardiovascular deterioration. The involved molecular pathways are highlighted together with potential targets for intervention. The effects of several drug classes with known beneficial impact on adipose tissue remodeling and mitochondrial dysfunction in such a context are discussed. Finally, future research aspects in this domain are explored.

1. Introduction

Adipose tissue (AT) is not merely a passive store of excess calories but an endocrine organ, whose functionality is tightly regulated by components of the nervous, the vascular, and the immune systems [1]. The endocrine function of the AT is ascribed to the secretion of white AT (WAT) and brown AT (BAT) adipokines and batokines that modulate cardiometabolic diseases through paracrine and endocrine signaling. WAT comprises mitochondria-poor unilocular adipocytes that specialize in energy storage while BAT is formed of mitochondria-rich multilocular adipocytes that dissipate energy through non-shivering thermogenesis [2,3]. WAT is further subclassified into subcutaneous (SAT) and visceral AT (VAT). The accumulation of VAT is consistently associated with cardiovascular risk and cardiometabolic diseases in humans [3]. VAT comprises distinct adipose depots that are relevant to the development of cardiometabolic diseases such as the perivascular (PVAT), the perirenal (PRAT), and the epicardial (EpiCAT) ATs. Contrastingly, BAT expansion has been associated with a lower prevalence of cardiometabolic diseases, and the presence of BAT in humans independently correlates with a lower risk for the development of type 2 diabetes (T2D), dyslipidemia, coronary artery disease (CAD), hypertension, cerebrovascular disease, and congestive heart failure [4,5]. Moreover, it was demonstrated that SAT exhibits a greater potential than VAT for browning, a process by which white adipocytes acquire a brown-like phenotype and participate in energy dissipation to promote metabolic homeostasis [6]. Metabolic homeostasis comprises opposing processes promoting energy acquisition and energy expenditure. Increased energy acquisition due to caloric excess drives an imbalance of these processes and culminates in AT expansion and inflammation. Although the precise molecular mechanisms driving obesity-associated AT inflammation are not fully understood, AT inflammation is associated with the development of insulin resistance (IR), obesity, T2D, and cardiovascular diseases (CVDs). Although recently contested, ample evidence implicates hyperinsulinemia as a driver of adipocyte hypertrophy, localized hypoxia, and inflammation [7-10]. These pathological manifestations profoundly alter adipocyte mitochondrial homeostasis [11]. Importantly, these alterations are not reversed in the VAT of mice and humans following the remission of obesity and insulin resistance, suggesting that obesity promotes lasting mitochondrial dysfunction that compromises AT metabolic plasticity.

Emerging transcriptomic data highlights compositional and spatial cellular heterogeneity among different adipose depots and among adipocytes of a given adipose depot [12,13]. Moreover, mouse adipocyte mitochondrial proteomic analysis demonstrated tissue-specific substantial quantitative and qualitative differences [14]. While mitochondria of white adipocytes support anabolic cellular pathways, mitochondria of brown adipocytes resemble those of skeletal muscles. Interestingly, anatomically distinct white subcutaneous and visceral adipocytes exhibit marked variation in their mitochondrial content [15]. Owing to adipocyte and stromovascular cell heterogeneity, adipose depots display differential susceptibility to insulin-induced expansion and obesity-associated inflammation, and thus differentially contribute to cardiometabolic diseases. Of relevance, PVAT and PRAT inflammation were shown to occur in prediabetic rats in isolation of systemic inflammation, obesity, and hyperglycemia [16,17]. Moreover, EpiCAT was shown to exhibit a pro-inflammatory signature in CAD patients irrespective of diabetes and obesity, while the latter was suggested to exacerbate the proinflammatory activity of EpiCAT infiltrating immune cells [18-20]. In contrast to other VAT depots, PVAT, PRAT and EpiCAT exhibit an intrinsically beige phenotype, the contribution of which to the modulation of AT inflammation and cardiovascular deterioration is poorly understood [16,21]. Therefore, targeting dysfunctional pathways within these select adipose depots in metabolic diseases has been put forward as a potential disease-modifying approach in cardiometabolic diseases.

AT mitochondrial dysfunction arising from impaired mitochondrial homeostasis rather than AT expansion-associated hypoxia might be the primary cause of AT inflammation and IR. As these mechanisms parallelly induce AT dysfunction [22], investigation into mitochondrial dysfunction-induced AT inflammation and the ensuing cardiovascular derangements in the context of metabolic diseases is warranted. Mitochondrial dysfunction leads to an array of metabolic diseases including obesity, IR, and diabetes [23,24]. For instance, excessive lipid accumulation in adipocytes impairs mitochondrial function manifested by defective fatty acid oxidation (FAO) and elevated oxidative stress, leading to mitochondrial DNA (mtDNA) damage and impaired insulin signaling [25]. Obese and insulin resistant individuals exhibit reduced adipocyte mtDNA content, mtDNA-encoded transcripts, mitochondrial mass, and oxidative phosphorylation (OXPHOS) proteins [26,27]. Additionally, mitochondrial dysfunction encompasses important features including increased uncoupling of the electron transport chain, reduced OXPHOS, and altered mitochondrial turnover and dynamics. Mechanistic investigation into the mitochondrial dysfunction in adipose depots relevant to the development of cardiometabolic diseases, such as PVAT, PRAT, and EpiCAT is lacking. Here we thoroughly describe the aspects of metabolic impairment-associated AT mitochondrial dysfunction. We also explore the frameworks by which AT mitochondrial dysfunction contributes to the development of cardiometabolic derangements and discuss possible pharmacological and non-pharmacological approaches to modify the underlying pathological pathways.

2. Mitochondrial turnover and mitochondrial dynamics

2.1. Mitochondrial biogenesis is impaired in metabolic diseases

Mitochondrial biogenesis ensures mitochondrial self-renewal, maintenance of mtDNA, augmentation of oxidative capacity, and diminishment of pathological oxidative stress [28]. Stoichiometric mitochondrial biogenesis is governed by regulatory pathways altering gene expression, protein translation, protein function and transport, and metabolite levels. mtDNA transcription is primarily promoted by the peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) protein family (PGC-1α, PGC-1β, and PGG-1), the master regulator of mitochondrial biogenesis of which is PGC-1α [29]. PGC-1α activation is followed by the stimulation of the transcription factors nuclear respiratory factors (NRF-1/2), nuclear factor erythroid 2-like 2 (NFE2L2), and estrogen-related receptor (ERR-α), which subsequently increase the expression of mitochondrial transcription factor A (TFAM). TFAM promotes mtDNA replication and transcription [30,31]. Other regulatory components of mitochondrial biogenesis include mammalian target of rapamycin (mTOR) and endoplasmic reticulum (ER) stress signaling,

TOM70-dependent mitochondrial protein import, mitochondrial cristae remodeling factors, and lipid remodeling [28].

Mitochondrial biogenesis drives adipogenesis, adipocyte differentiation, and thermogenesis. Cells lacking both PGC-1α and PGC-1β exhibit completely abolished mitochondrial biogenesis, while mice lacking both PGC-1α and PGC-1β exhibit rescued mitochondrial biogenesis and adipocyte thermogenesis through the allelic compensation of PGC-1α4 [32-35]. The expression of TFAM is markedly increased during brown adipogenesis and the forced expression of TFAM in brown adipocyte precursors enhance mtDNA replication [36]. One study showed that adiponectin promoter-driven adipocyte-specific deletion of TFAM in mice promotes lipodystrophy, IR, hypertension, cardiac hypertrophy, and cardiac dysfunction [37]. Another study suggested that aP2 promoter-driven adipocyte-specific deletion of TFAM enhanced mitochondrial oxidative capacity and uncoupling leading to increased energy expenditure and protection against diet-induced obesity (DIO) [38]. This discrepancy is likely due to the use of different genetic systems to manipulate TFAM expression. While adiponectin promoter-driven deletion of TFAM is detrimental to mitochondrial complex IV expression and activity, it is likely that aP2 promoter-driven deletion of TFAM reduces complex IV to levels below the threshold to produce failure of the electron transport chain. Impaired mitochondrial biogenesis is a hallmark of obesity, T2D, and their complications [39]. Morbidly obese patients exhibit SAT with reduced PGC-1α expression, while the pharmacological induction of the latter in diabetes enhances mitochondrial biogenesis [40,41].

2.2. Mitophagy at the crossroad of adipogenesis and thermogenesis

Mitophagy comprises the autophagic degradation and recycling of mitochondrial fragments [42]. Mitophagy occurs through two different mechanisms, either through direct, ubiquitin-independent mitophagy that depends on the interaction of Microtubule-associated protein 1A/1B-light chain 3 (LC3) with mitochondrial outer proteins such as BCL2/E1B 19 KDa-interacting protein (BNIP3) and FUN14 domain-containing protein 1 (FUNDC1) [43,44], or adapter-mediated, ubiquitin-dependent mitophagy that is achieved by phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1), which upon reduced mitochondrial membrane potential, stabilizes on the mitochondrial outer membrane and recruits the E3 ubiquitin ligase Parkin. Parkin ubiquitinates outer mitochondrial proteins and destines them for degradation [45]. Importantly, adipocyte BNIP3 expression is downregulated in IR and Fundc1-deficient mice exhibit a higher propensity for DIO [46-48]. White adipocytes exhibit a higher mitophagic flux than their beige and brown counterparts [49,50]. Particularly, the induction of AT browning and adipocyte thermogenesis are associated with reduced parkin-mediated mitophagy [51,52]. Adipocyte thermogenic stimulation represses parkin expression via noradrenergic and peroxisome proliferator-activated receptor alpha (PPARα)-mediated pathways involving enhanced intracellular lipolysis in brown adipocytes [53]. Mitophagy suppression promotes inflammasome activation, AT inflammation, and the progression of metabolic disease [54]. Moreover, mice with either global or brown adipocyte-specific deficiency in PINK1 exhibit dysfunctional BAT and an obesity-prone phenotype [55]. Similarly, adipocyte-specific deletion of p62 renders mice obese and thermogenically impaired [56].

2.3. Mitochondrial fusion and fission: Altered mitochondrial dynamics drive adipose tissue dysfunction

Mitochondrial fusion is controlled by three evolutionary conserved dynamin-related GTPases, mitofusin 1 (Mfn1), mitofusin 2 (Mfn2), and optic atrophy 1 (OPA1) [57]. Both Mfn1 and Mfn2 reside in the outer mitochondrial membrane, while the long-form OPA1 localizes to the inner mitochondrial membrane [57]. Overexpressing Mfn1, Mfn2, or Opa1 induces mitochondrial elongation, while their deficiencies in cells promote mitochondrial fragmentation [58,59]. Obese human subjects and mice exhibit reduced Mfn2 and Opa1 expression in the AT and mice with adipocyte-specific deletion of Mfn2 exhibit enhanced adiposity and body weight gain even when on standard chow [60-62]. Transgenic mice overexpressing Opa1 exhibited enhanced AT expandability, AT browning, and insulin sensitivity, while mice with adipocyte-specific deletion of Opa1 exhibited the opposite phenotype [62,63]. Despite being required for BAT thermogenesis, Opa1 deletion specifically in brown adipocytes rendered mice resistant to DIO due to BAT-derived fibroblast growth factor 21(FGF21)-mediated compensatory browning of WAT [64]. Similarly, brown adipocyte-specific deletion of Mfn2 caused BAT lipohypertrophy and cold intolerance in standard chow-fed mice, but paradoxically improved insulin sensitivity and resistance to obesity in DIO mice independent of thermogenesis [65]. This is attributed to gender-specific remodeling of BAT mitochondrial function secondary to Mfn2 deletion. While female mice exhibited enhanced lipid oxidation in BAT, male mice exhibited enhanced BAT glycolytic activity [65].

Mitochondrial fission is initiated at ER tubule-mitochondria contact sites and is carried out by the cytosolic GTPase Dynamin-related protein 1 (Drp1) following its recruitment by the adaptor proteins fission protein 1 (Fis1), mitochondrial fission factor (MFF), and mitochondrial dynamics proteins MiD49 and MiD51 [66]. The deletion of either Drp1 or MFF lead to the emergence of hypertubular mitochondria [67,68], while the overexpression of MFF lead to the formation of fragmented mitochondrial networks [68]. The overexpression of MiDs resulted in mitochondrial elongation through the sequestration of Drp1 [69], whereas low levels of MiDs induced mitochondrial fission [70-72]. The canonical GTPase Dnm2 has been proposed to drive the final step of the outer mitochondrial membrane scission [73]. This has been however contested and Drp1 was suggested to be capable of constricting and severing the mitochondrial membrane [74]. Mechanisms underpinning inner mitochondrial membrane constriction are not well characterized and no machinery has been associated to date with inner mitochondrial membrane division. Nevertheless, it has been proposed that inner mitochondrial membrane division is calcium-dependent and occurs at ER-mitochondria contact sites prior to Drp1 recruitment and outer mitochondrial membrane constriction [75]. DRP1 is highly expressed in BAT compared to WAT, and its expression further increases during brown adipogenesis [76]. Cold-exposure in mice and beta-adrenergic receptor (β-AR) stimulation in cultured brown adipocytes enhances PKA-dependent phosphorylation of DRP-1 and lipolysis-induced mitochondrial depolarization-associated cleavage of OPA1 prior to mitochondrial membrane depolarization, which promotes the rapid fragmentation of mitochondria [77]. Moreover, DRP-1 translocates to the ER and regulates lipid droplet multilocularity downstream of PKA activation in response to β-AR stimulation [78]. Paradoxically, DIO mice carrying a homozygous DRP-1 S600A knockin mutation, in which S600 cannot be phosphorylated, display improved glucose tolerance and thermogenesis compared to standard chow-fed mice [79]. This is likely due to BAT-mediated compensatory thermogenic induction evidenced by BAT exhibiting larger mitochondria, enhanced respiratory capacity, and increased FAO. Moreover, mice with adipocyte-specific deletion of DRP-1 displayed impaired cold-induced BAT lipolysis, thermogenesis, and energy expenditure [78].

3. Mitochondrial bioenergetics are compromised in metabolic disease

One of the main roles played by the mitochondria is the production of energy through oxidative phosphorylation. Obesity and diabetes are associated with reduced mitochondrial oxidative capacity, which is mediated in part through an impairment in the assembly of the mitochondrial respiratory complexes [80-82]. Compared to adipocytes of lean subjects, obese subjects exhibit hypertrophied adipocytes with reduced basal respiration and increased oxidative stress [83-86].

Nevertheless, this has been recently contested as it was suggested that the reduction of tissue weight-normalized mitochondrial respiratory capacity in HFD-fed mice is abolished when adipocyte size or number were considered [87]. Moreover, it is suggested that metabolically unhealthy obese individuals exhibit enhanced mitochondrial respiration in comparison to metabolically healthy obese individuals as a compensatory mechanism to IR [88]. Putting these findings into context, it should be highlighted that impaired adipocyte mitochondrial respiratory capacity is likely insufficient to drive systemic glucose intolerance in murine models of obesity [89]. As mitochondrial dysfunction and mitochondrial oxidative stress occur in tandem, disentangling the individual roles of these processes is difficult, especially that impaired adipocyte mitochondrial function induces IR independent of mitochondrial ROS production [90]. Intricate cellular pathways, particularly in brown and beige adipocytes, uncouple cellular respiration either directly through competitive dissipation of the protonmotive force or indirectly through the futile consumption of generated ATP [6].

3.1. Mitochondrial uncoupling and adaptive thermogenesis

Mitochondria possess a unique mechanism for uncoupling of cellular respiration from ATP synthesis in brown and beige adipocytes [6]. The most prominent pathway for mitochondrial uncoupling is attributed to the presence of uncoupling protein 1 (UCP1), an inner mitochondrial membrane protein which, in response to adrenergic stimulation [91,92], dissipates the proton gradient generated across the inner mitochondrial membrane and promotes the production of heat in beige and brown adipocytes. Norepinephrine signals through β-AR and via cAMP and PKA to activate the adipocytic lipolytic cascade, which directly enhances UCP1-mediated mitochondrial uncoupling and provides reducing equivalents to maintain the protonmotive force [93-95]. Thermogenically-active adipocytes as well as AT stromovascular cells such as alternatively-activated macrophages secrete paracrine factors enhancing AT sympathetic innervation and sympathetic neurons neurite outgrowth [96-98]. Murine models of genetic and DIO exhibit significant reduction of SAT and BAT sympathetic innervation [99]. Recent evidence highlights the occurrence of adrenergic signaling-independent pathways activating BAT thermogenesis including signaling through the constitutively active G-protein coupled receptor 3 (GPR3) and the cholinergic receptor nicotinic alpha 2 subunit (CHRNA2) [100-102]. Adrenergic stimulation of lipolysis and thermogenesis is counterbalanced by the negative regulator KCNK3, a two-pore-domain potassium channel that antagonizes norepinephrine-induced membrane depolarization and downstream signaling [103]. Emerging evidence suggests the dispensability of UCP1 to cold-induced and diet-induced thermogenesis albeit being the most efficient and the most quantitatively significant thermogenic effector [6].

3.2. UCP1-independent thermogenic pathways

3.2.1. Futile creatine cycling

Creatine futile cycling represents the most prominent and well-characterized alternative thermogenic pathway in adipocytes [104]. Creatine futile cycling, that is the phosphorylation of creatine by creatine kinase B (CKB) in the mitochondrial matrix and the subsequent hydrolysis of phosphocreatine by tissue non-specific alkaline phosphatase (TNAP) prior to its shuttling outside the mitochondria, occurs following thermogenic stimulation-induced coordinated activation of α1- and β3 adrenergic receptors, and downstream of Gαs and Gαq signaling, respectively [105-107]. Mitochondrial patch clamp experiments revealed the occurrence of futile creatine cycling in UCP1-positive and UCP1-negative beige adipocytes [108]. Reducing creatine cellular availability in adipocytes either by deleting glycine amidinotransferase (GATM), the rate limiting enzyme of creatine biosynthesis, or the cell surface creatine transporter (CrT) renders mice unresponsive to thermogenic stimulation and prone to DIO [109,110]. Similarly, mice bearing adipocyte-specific deletion of CKB or TNAP exhibit diminished energy expenditure and increased predisposition to DIO. Moreover, it was recently demonstrated that impaired phosphocreatine metabolism in white adipocytes promote AT inflammation [111]. Of translational relevance, no evidence for acute cold-induced BAT thermogenic activation was observed following creatine supplementation to young, healthy, and lean vegetarian adults, who are characterized by low circulating levels of creatine [112]. This is consistent with animal experiments demonstrating the necessity of a certain metabolic imbalance to uncover the physiological relevance of creatine cycling-dependent thermogenesis, which highlights the necessity of future clinical trials examining the effects of creatine supplementation in metabolically dysfunctional individuals.

3.2.2. Calcium cycling

An appreciation of the role of calcium cycling in adipocyte thermogenesis downstream of adrenergic stimulation is relatively recent [113-115]. The abundance of cytoplasmic calcium depends on its release from the sarcoplasmic/endoplasmic reticulum and its subsequent reuptake by the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA). Calcium cycling-mediated thermogenesis occurs in thermogenic adipocytes [116], and it was shown that the inhibition of SERCA2b impairs UCP1-independent beige adipocyte thermogenesis in mice and in humans [113]. As such, SERCA2 expression is downregulated in obese and diabetic subjects and ablating SERCA2 expression specifically in adipocytes renders mice mildly lipodystrophic and glucose intolerant [117]. Calcium cycling-mediated thermogenesis is tightly controlled and the induction of SERCA activity protects mice against DIO and IR [118]. It has been postulated that SERCA activity in adipocytes is regulated by the homopentameric protein phospholamban (PLN) [119,120]. However, PLN-deficient mice exhibit comparable propensity for the development of DIO in comparison to their wildtype counterparts, which could be explained in part by enhanced BAT UCP1-dependent thermogenesis [121,122]. Similarly, UCP1-deificient mice exhibit enhanced phospholamban phosphorylation and calcium cycling-dependent thermogenesis reflecting the complementarity among the thermogenic pathways [114]. In addition to the increase in cytosolic calcium abundance in response to adrenergic stimulation in beige and brown adipocytes, an increase in mitochondrial calcium concentration is also suggested to drive UCP1-independent thermogenesis [123,124]. It is suggested that this is achieved by an inner mitochondrial membrane localized SERCA in brown adipocytes. Indeed, UCP1-deficient mice display reduced mitochondrial calcium buffering and calcium overload which could in part explain enhanced calcium-dependent thermogenesis in these mice [125]. Moreover, adrenergic stimulation of BAT was shown to activate PKA-dependent mitochondrial calcium efflux through the mitochondrial sodium/calcium exchanger (NCLX) to limit mitochondrial calcium overload [126]. Although recent evidence indicated that adrenergic stimulation enhances UCP1 recruitment and activity by the mitochondrial calcium uniporter (MCU) [127], there exist discrepant effects of MCU deletion in brown adipocytes on mice thermogenesis and disposition to DIO [127,128].

3.2.3. Lipolysis/re-esterification cycling

An energetically futile cycle of lipolysis/re-esterification drives UCP1-indepdent futile consumption of cellular ATP based on the energy demand of triacylglycerol breakdown and acylglycerol synthesis downstream of adrenergic stimulation [129]. Cold exposure, adrenergic stimulation, and PPARγ agonism simultaneously enhance lipolysis and the synthesis of fatty acids [130-133]. Indeed, cold exposure enhances lipid cycling in WAT, and to a greater extent in BAT [134]. In brown adipocytes, FFAs are activated to acyl-CoA which either undergoes mitochondrial FAO or is re-esterified to a glycerol backbone that is provided from glycerol 3-phosphate through phosphorylation by glycerol kinase, a key enzyme in the replenishment of cellular triacylglycerol. In white adipocytes, glycerol 3-phosphate mainly

originates from the aborted gluconeogenesis pathway leading to the production of dihydroxyacetone phosphate. In response to adrenergic stimulation, glycerol 3-phosphate is metabolized by the calcium-activated glycerol 3-phosphate dehydrogenase (mGPD) to donate electrons for the mitochondrial electron transport chain, which might limit substrate availability for acylglycerol re-esterification. Consistently, mGPD-deficient mice exhibit enhanced BAT thermogenesis despite a reduction in whole body energy expenditure [135]. Moreover, catecholamines redirect fatty acids for oxidation rather than re-esterification through the phosphorylation of STAT3 in adipocytes [136]. Lipid cycling can also be activated independent of adrenergic stimulation [137]. For example, although mitochondrial pyruvate carrier (MPC) inhibition impairs cold exposure-induced thermogenesis, the pharmacological and genetic inhibition of MPC in brown adipocytes activates lipid cycling in the absence of adrenergic stimulation [138,139]. Of clinical significance, it was demonstrated that a persistent low body weight in constitutionally thin human subjects is associated with higher WAT mitochondrial activity, an increased mitochondrial DNA content, and augmented futile lipid cycling in absence of WAT browning [140].

3.2.4. ADP/ATP carrier proton leak

The inner mitochondrial membrane protein ADP/ATP carrier (AAC) (also known as the adenine nucleotide translocase; ANT), which exchanges mitochondrial ATP for cytosolic ADP, induces proton cycling at high membrane potential in a UCP1-independent manner in all mitochondria [141,142]. AAC-mediated proton leak requires FFAs, is potentiated following cysteine residues oxidation, and is negatively regulated by the exchange activity of the carrier, suggesting tight control of proton conductance by cellular ATP abundance and the rate of ADP/ATP exchange [142-144]. Recent evidence suggests that common mitochondrial uncoupling protonophores and long-chain fatty acids binding sites overlap with the putative ADP/ATP-binding site [145]. Indeed, ANT2 and ANT3 expression increases during adipogenesis, and in response to insulin and PPARγ agonism to support oxidative metabolism, and human SAT exhibits higher ANT expression level in comparison to VAT [146]. Saturated fatty acid-stimulated ANT2-mediated uncoupling, early during the metabolic challenge, drives aberrant oxygen consumption, leading to hypoxia, evidenced by increased HIF-1α expression, and AT inflammation [147]. Deletion of adipocyte Ant2 improves obesity-induced AT hypoxia by decreasing adipocyte oxygen demand, without affecting mitochondrial number or mass [148]. The deletion of Ant2 is also associated with reduced AT inflammation and improved glucose tolerance and IR.

4. Mitochondrial dysfunction in adipose depots relevant to cardiometabolic diseases

4.1. Perivascular adipose tissue

PVAT environs most vasculature, including the aorta and coronary and subcutaneous arteries, and exhibits anatomically distinct phenotypical and functional characteristics, which complicates the translation trajectory of characterized PVAT multifaceted involvement in metabolic and cardiovascular diseases [21]. By virtue of its anatomical proximity to vasculature, PVAT intimately regulates the vascular function through paracrine and endocrine signaling pathways modulating anti-contractile vascular smooth muscle cell and endothelial cell functions, which are partially dependent on β3-AR activation [149-152]. In addition to being richly sympathetically innervated, PVAT contains functional catecholamines including norepinephrine that is stored by Organic cation transporter 3 (OCT3)-mediated uptake and vesicular monoamine transporter-mediated transport, independent of sympathetic nerves [153-155]. PVAT dysfunction has been associated with the development of hypertension, atherosclerosis, abdominal aortic aneurysms, coronary atherosclerosis, ischemic heart disease, and CAD [156-158]. One mechanism underlying PVAT dysfunction is increased mitochondrial oxidative stress. It was shown that PVAT mitochondrial respiration is impaired, while mitochondrial ROS production is enhanced in PVAT adipocytes of HFD-fed mice [159]. Moreover, redox imbalance characterized by increased oxidative stress and the concomitant reduction in antioxidant mechanisms in PVAT, is suggested to contribute to the loss of PVAT anticontractile activity [160-162]. Therefore, targeting PVAT oxidative stress with the use of antioxidant therapy has been put forward for the treatment of CVDs [163]. Nevertheless, mitochondrial electron transport chain produced reactive oxygen products represent precursors for hydrogen peroxide, which in turn regulates endothelium-independent anticontractile effect and thus, the physiological anticontractile activity of PVAT [164,165].

PVAT exhibits remarkable heterogeneity at the levels of progenitor cell lineages and cellular components [166-169]. Although abdominal PVAT primarily consists of white adipocytes, thoracic PVAT comprises white and brown adipocytes, the dominance of either phenotypes being highly dependent on the metabolic context [170]. Thoracic PVAT generally comprises multilocular adipocytes with abundant mitochondria and is thought to have a lower susceptibility to macrophage infiltration in murine models of DIO in comparison to *bona fide* white depots [171]. Nevertheless, this has been contested as PVAT inflammation was shown to occur in a prediabetic rat model with no detectable hypoxic or inflammatory alterations taking place in *bona fide* WAT and BAT despite marked adipocyte hypertrophy [17]. Indeed, this was attributed to HFD-induced bioenergetic and mitochondrial dynamics alterations in PVAT evidenced by increased mitochondrial fission and UCP1 expression, which, in combination with adipocyte hypertrophy leads to AT inflammation [17,172]. Interestingly, reducing PVAT UCP1 activity and expression in these rats through the supplementation of inorganic phosphorus was shown to halt PVAT inflammation [172]. Nevertheless, it was also suggested that PVAT whitening in aging and obesity, which is characterized by the suppression of UCP1 expression and enhanced inflammation, leads to PVAT-dysfunction associated cardiovascular deterioration [173,174]. Moreover, it was recently demonstrated that inhibiting PVAT browning, through the genetically silencing the expression of PRDM16 in a mouse model of endovascular injury, exacerbates inflammation and vascular remodeling [175]. These dichotomous outcomes of PVAT browning likely stem from the use of different models of vascular injury which might or might not coincide with PVAT adipocyte hypertrophy, and thus suggest that the role PVAT browning may play, whether detrimental or beneficial, is highly dependent on the overall environmental context.

Mitochondrial dysfunction and lipid droplet disruption were also suggested to drive PVAT-mediated obesity-associated cardiovascular complications. Indeed, perilipin $1^{-/-}$ spontaneous hypertensive mice develop PVAT dysfunction characterized by reduced anti-contractile activity, increased lipolysis, angiotensin II secretion, macrophage infiltration, and oxidative stress [176]. Moreover, PVAT adipocytes of genetically induced obese mice exhibit mitochondrial dysfunction characterized by increased ROS production and mitochondrial uncoupling, which is associated with adipocyte senescence, decreased Sirt1 and Sirt3 levels, and the loss of PVAT-mediated anticontractile effect [177]. Indeed, PVAT immune cells infiltration, particularly macrophages and T cells and their differential activation states contribute to PVAT dysfunction-associated hypertension [178]. Particularly, it was shown that myeloid-specific $Sirt3^{-/-}$ mice treated with angiotensin II develop PVAT inflammation and fibrosis, which is accompanied by NLRP3 inflammasome activation, enhanced IL-1β secretion, and importantly PVAT adipocyte mitochondrial dysfunction [179]. Sirt3 deletion metabolically rewires macrophage metabolism from OXPHOS to glycolysis, which is consistent with macrophage pro-inflammatory polarization [179]. Moreover, it was shown that angiotensin II treatment induces PVAT T cell miR-214 expression in mice, while $miR\text{-}214^{-/-}$ mice exhibited no periaortic fibrosis and hydroxyproline accumulation and were protected from angiotensin II-induced hypertension, endothelial dysfunction, and oxidative stress [180]. Fig. 1 summarizes some

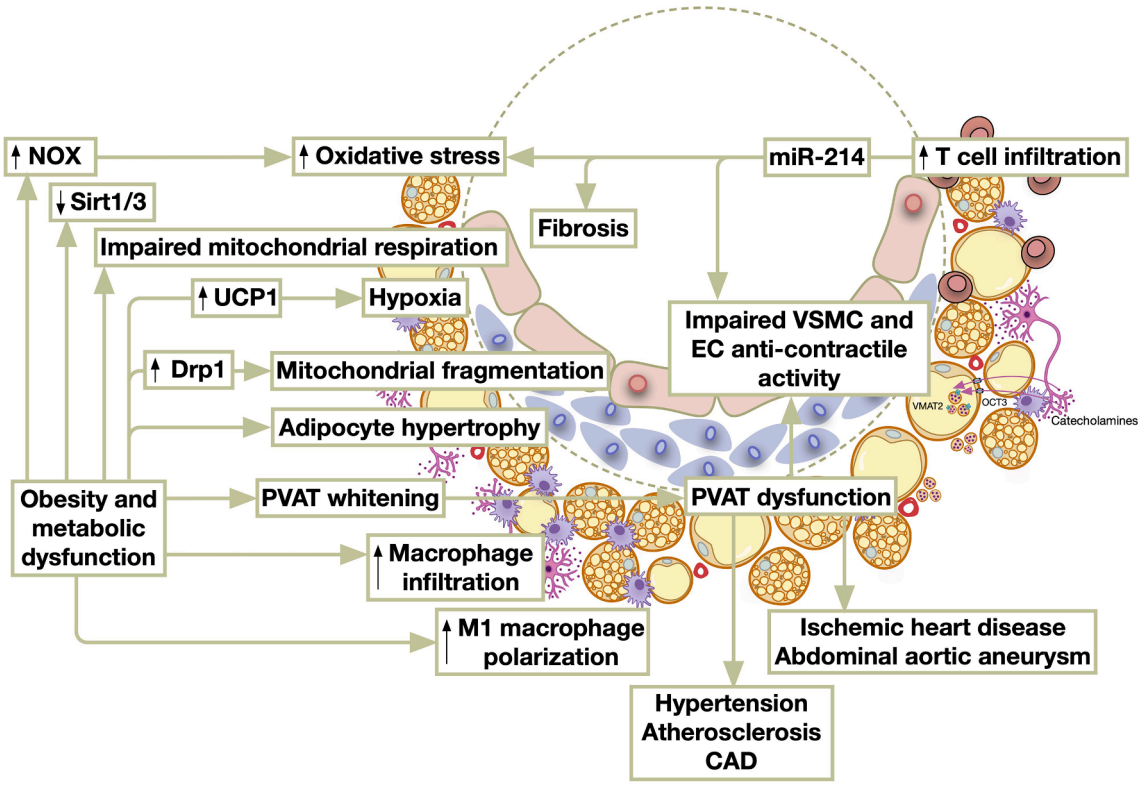

Fig. 1. The suggested pathways for the contribution of mitochondrial alteration in PVAT to the adipose dysfunction and the ensuing vascular impairment. Metabolic dysfunction evokes several molecular pathways culminating in impaired mitochondrial microbial homeostasis with an impact on hypoxia and oxidative stress. Such changes are observed in an overall inflammatory PVAT milieu that is characteristic of many vascular disorders. CAD, Coronary artery disease; Drp1, Dynamin-related protein 1; NOX; NADPH oxidase; UCP1, Uncoupling protein 1.

of the changes in mitochondrial function occurring in metabolic disease together with their consequences on vascular function.

4.2. *Pericardial adipose tissue*

Pericardial AT (PeriCAT) comprises both paracardial and epicardial adipose depots. Paracardial AT (ParaCAT) surrounds the external surfaces of the pericardium, while EpiCAT localizes to the atrioventricular and interventricular heart grooves between the myocardium and the visceral pericardial layer and is considered a major regulator of FFA homeostasis in the myocardium. EpiCAT also surrounds the adventitia of coronary arteries and plays protective roles during mechanical and metabolic perturbations [21]. EpiCAT and pericoronary AT thickness are predictors for the development of essential hypertension and cardiovascular morbidity in asymptomatic patients and in patients with one or more cardiovascular risk factors [181-183]. Moreover, EpiCAT expansion in T2D patients is associated with worsened cardiopulmonary performance and subclinical cardiac systolic dysfunction [184]. EpiCAT expansion in hypertensive patients is associated with the occurrence of metabolic syndrome independent of obesity and waist circumference and the measurement of EpiCAT thickness is a predictor of the severity of hypertension and arterial stiffness [185-187]. CAD patients also exhibit increased EpiCAT volume, which is associated with coronary atherosclerosis, coronary artery stenosis, myocardial ischemia, and major adverse cardiovascular events [188-191].

EpiCAT exhibits impaired mitochondrial OXPHOS in patients with CAD that correlates with the severity of coronary artery stenosis [192]. Moreover, EpiCAT mitochondrial dysfunction correlates with reduced adiponectin expression. Consistently, several reports indicated that EpiCAT adiponectin expression is reduced while that of pro-inflammatory adipokines and cytokines increased in obese, hypertensive, and CAD patients [193-195]. Particularly, EpiCAT-derived adiponectin, downstream of PPARγ-induced ADIPOQ expression, was shown to regulate the myocardial redox state in a paracrine or endocrine manner through the reduction of myocardial nicotinamide adenine dinucleotide phosphate oxidase activity through the inhibition of AMPK-mediated membrane translocation of Rac1 and p47(phox) [196].

Although it was demonstrated that patients with CAD exhibit increased EpiCAT macrophage infiltration and pro-inflammatory cytokines levels [18], recent evidence suggests that cardiometabolic conditions, specifically obesity and diabetes rather than underlying CAD or hypertension enhance the proinflammatory activity of EpiCAT infiltrating adaptive immune cells evidenced by higher levels of the proinflammatory mediators IL-1, IL-6, TNF-α, and IFN-γ [20]. Indeed, HFD-fed obese minipigs exhibit cardiac energy deficit and left ventricular fibrosis, which is associated with increased IL-6 and malondialdehyde expression in the PeriCAT [197]. Importantly, obese pig PeriCAT conditioned media inhibited H9C2 cells basal mitochondrial respiration and ATP production, and suppressed the expression of Mfn2, Opa1, Drp1, Fis1, and Parkin, while enhancing the expression of LC3II. This indicates that PeriCAT secretome impairs mitochondrial dynamics and function in cardiomyocytes in a paracrine manner. Consistently, EpiCAT expansion correlated with cardiac fibrosis in a rat model of myocardial infarction [198]. Mechanistically, EpiCAT conditioned media upregulated the expression of miR-134-5p in cultured cardiomyocytes, which suppressed the expression of lysine acetyl transferase 7 expression and the acetylation of manganese superoxide and catalase, thereby enhancing cellular ROS levels.

Adult human epicardial adipocytes abundantly express PGC-1α, PRDM16, and UCP1 and show molecular features characteristic of bright adipocytes [199-201]. Adrenergic stimulation enhances EpiCAT thermogenic capacity, which is negatively associated with oxidative stress-related genes [202]. Indeed, high EpiCAT UCP1 expression is associated with differential gene expression that functionally corresponds

with downregulation of ROS production and immune responses [203]. EpiCAT in CAD patients exhibit decreased expression of mitochondrial respiratory chain genes in comparison to patients with no CAD [204], indicating impaired oxidative capacity. EpiCAT and PeriCAT thermogenic activities are impaired in patients with atrial fibrillation, acute coronary syndrome, CAD, and heart failure with reduced ejection fraction due to bright fat involution and the emergence of white-like adipocytes with reduced UCP1, PGC-1α, and PRDM16 expression [205-207]. PeriCAT of CAD patients also exhibits reduced expression of metabolic enzymes involved in glycolysis, TCA cycle, and fatty acid metabolism [207]. Moreover, in a mammalian model of atherosclerosis, EpiCAT exhibit enlarged adipocytes, reduced UCP1 and PPARγ expression, impaired mitochondrial cristae remodeling, indicating conversion to white-like adipocytes [208]. PPARγ agonism in obese Zucker rats enhanced EpiCAT expression of PGC-1α, NADH dehydrogenase 1, PRDM16, and UCP1, as well as lipid turnover [209]. Importantly, diabetes exacerbates the reduction of PGC-1α and UCP1 in EpiCAT of patients with CAD [210]. It was recently shown that the size and function of ParaCAT are controlled by alcohol dehydrogenase 1 (ADH1), an enzyme that oxidizes retinol into retinaldehyde [211]. Obese individuals exhibit reduced ParaCAT expression of ADH1 and the genetic deletion of ADH1 in mice promoted ParaCAT expansion and dysfunction probably through altering fatty acid biosynthesis. Indeed, the ADH1/retinaldehyde pathway drives PGC-1α nuclear translocation, promoting mitochondrial fusion and biogenesis in ParaCAT [211]. Although the induction of EpiCAT browning seems beneficial, exploiting EpiCAT browning for the treatment of CVDs remains controversial [21]. A summary of the above details is depicted in Fig. 2.

4.3. Perirenal adipose tissue

PRAT represents a richly vascularized and innervated retroperitoneal adipose depot surrounding the kidneys [212]. Human embryonic PRAT exhibits abundant UCP1 and PRDM16 expression, as well as mitochondrion copy number and oxygen consumption rate comparable to that of brown adipocytes [213,214]. PRAT brown adipocytes undergo age-dependent involution such that adult PRAT appears predominantly white with dispersed pockets of multilocular adipocytes [212]. As such, adult PRAT comprises spatially distinct populations of thermogenically-dormant unilocular and multilocular UCP1-expressing adipocytes [215-217]. While multilocular UCP1-expressing adipocytes accumulate around the adrenal gland, an area with abundant sympathetic nerve endings, unilocular UCP1-expressing adipocytes are evenly distributed within PRAT [215]. Indeed, systemic catecholamine excess in patients with pheochromocytoma and paraganglioma induces PRAT browning [218,219]. Periadrenal AT from pheochromocytoma patients exhibit a robustly increased number of *peri*-droplet mitochondria in comparison with control subjects [220]. Peri-droplet mitochondria showed major bioenergetic alterations associated with browning such as increased ATP-linked respiration, maximal respiratory capacity, and complex IV content and activity, in comparison to cytoplasmic mitochondria. Moreover, the consumption of high fat, high carbohydrate, and low protein diets induce PRAT browning evidenced by the upregulation of UCP1, PRDM16, and β_3-adrenergic receptors expression [16,221]. Although studies investigating PRAT thermogenic potential are scarce, available evidence points towards reduced and increased PRAT adipocyte UCP1 expression in disease states such as hypertension and renal cell carcinoma, respectively [222,223]. Moreover, PRAT dysfunction is thought to drive renovascular diseases by virtue of the spatial proximity between PRAT and the kidney, in addition to their common innervation and vascularization networks [224].

An augmentation of central obesity in overweight and obese individuals is associated with PRAT expansion, which independently associates with IR and cardiovascular risk factors [225,226]. Increased PRAT thickness positively correlates with blood pressure levels in overweight and obese individuals, and is considered a risk factor for the development of arterial hypertension and chronic kidney disease in obese individuals [227,228]. Indeed, the expansion of PRAT was demonstrated to compromise renal function in hypertensive patients regardless of their body mass index [229], and was associated with reduced glomerular filtration rates in diabetic individuals [230]. Moreover, PRAT thickness was recently associated with the risk for development of chronic kidney disease in diabetic patients [231]. Moreover, PRAT expansion is associated with IR and dysregulated glucose homeostasis in CKD patients [225]. Indeed, PRAT expansion and inflammation has been shown to compromise cardiovascular and renovascular function through distinct molecular pathways that has been recently reviewed elsewhere [212]. Noteworthy, recent evidence implicates localized PRAT expansion, increased oxidative stress, and inflammation in the pathogenesis of renal dysfunction in non-hypertensive, non-obese, prediabetic rats, secondary to UCP1 upregulation-mediated exacerbation of hypoxia in the hypertrophied tissue [16].

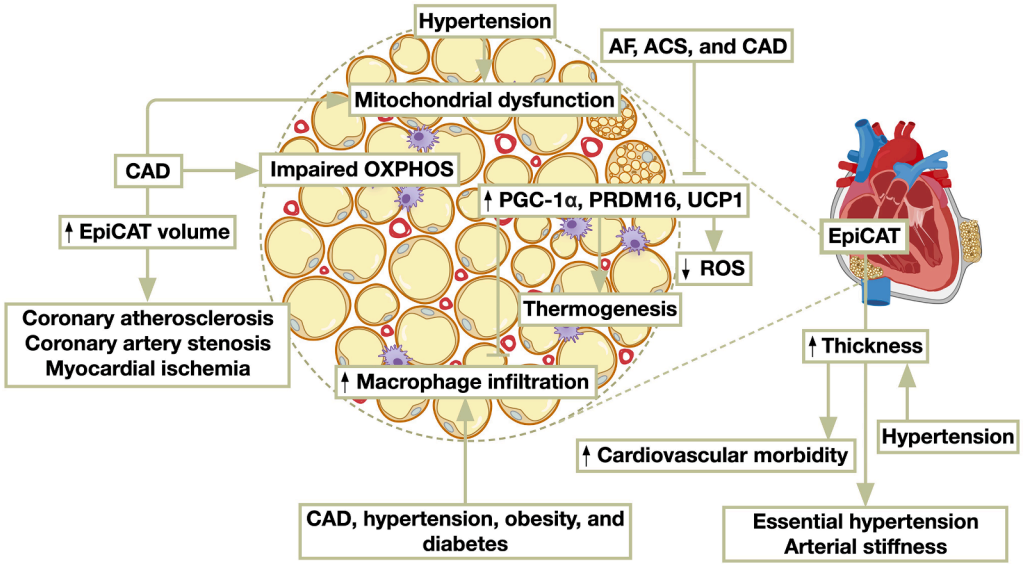

Fig. 2. Potential pathways for the contribution of mitochondrial alteration in EpiCAT to the adipose dysfunction and the ensuing cardiac disorders. Metabolic dysfunction evokes adipocyte hypertrophy and tissue thickness that is associated with impaired mitochondrial respiration and altered oxidative phosphorylation and UCP1-dependent thermogenesis. These are associated with hypoxia, increased reactive oxygen species, decreased mitochondrial biogenesis, and increased fragmentation. These changes occur in an inflammatory context characterized by increased immune cell infiltration with consequential cardiac tissue damage similar to that seen in many cardiac disorders. AF, Atrial fibrillation; ACS, Acute coronary syndromes; CAD, Coronary artery disease; PGC-1, Peroxisome proliferator-activated receptor gamma coactivator 1; PRDM16, PR domain containing 16; UCP1, Uncoupling protein 1.

5. Targeting adipose tissue mitochondria: Pharmacological and dietary interventions

Despite growing evidence of its involvement in cardiometabolic disease pathogenesis, there has been no direct interventions with a definitive indication for modulation of adipose tissue inflammation. However, data describing the potential beneficial effect of molecules from disparate drug classes on the detrimental adipose tissue remodeling in cardiometabolic disease and its association with positive cardiovascular outcomes has been accumulating. Such effects were often ascribed to a "pleiotropic" anti-inflammatory effect that these molecules or interventions could exert on adipose tissue. Below, we report the known effects of some of these interventions on adipose tissue inflammation, which could potentially be mediated by a parallel effect on the mitochondria.

5.1. Pharmacological interventions: antidiabetic and antihypertensive drugs

5.1.1. Thiazolidinediones

Thiazolidinediones are FDA-approved PPARγ agonists with potent insulin-sensitizing effects. Thiazolidinediones have been shown to produce pleiotropic effects that extend well beyond their normoglycemic activity. For example, pioglitazone was shown to significantly improve endothelial and AT dysfunction in non-diabetic patients with essential hypertension, prediabetic patients with CAD, and obese diabetic patients [232-235]. Rosiglitazone treatment was also shown to improve insulin sensitivity and to lower blood pressure in nondiabetic hypertensive patients and in patients with metabolic syndrome [236,237]. However, molecular mechanisms underpinning these ameliorative effects of PPARγ agonism are poorly described and seem to be, at least in part, dependent on PPARγ agonism-associated adipocyte mitochondrial remodeling. PPARγ agonism drives mitochondrial biogenesis and remodeling during white and brown adipogenesis and reduced adipocyte PPARγ activity in obesity results in the failure of adipocytes to maintain their cellular identity [32,39,238,239]. Pioglitazone enhances mitochondrial biogenesis through upregulating PGC-1α and TFAM expression in the SAT of diabetic patients [41]. As such, rosiglitazone-treated ob/ob and db/db mice exhibit ameliorated obesity-associated mitochondrial dysfunction [39,240]. PPARγ agonism induces white adipocyte multilocularity, increases mitochondrial content, and enhances mitochondrial biogenesis and respiratory capacity in obese mice and cultured adipocytes [241-243]. Rosiglitazone enhanced human SAT and VAT adipocyte browning, evidenced by increased expression of PGC-1α and PRDM16, as well as triglyceride synthesis and lipolysis [242]. However, pioglitazone was shown not to synergize with mirabegron in increasing WAT browning or further improving glucose metabolism in obese insulin-resistant individuals [244].

Pioglitazone has been shown to bind and stabilize MitoNEET (also referred to as CDGSH iron sulfur domain 1 (CISD1)), a dimeric outer mitochondrial membrane FeS protein implicated in the regulation of redox homeostasis, mitochondrial oxidative capacity, and mitochondrial homeostasis [245-247]. CISD1 expression positively correlates with insulin sensitivity in morbidly obese patients and obese individuals exhibit reduced VAT and SAT expression of MitoNEET [248]. Importantly, CISD1 gene expression is associated with the expression of Sirt1, PGC-1α, TFAM, PRDM16, and UCP1 in both adipose depots [248]. In response to mitoNEET overexpression in mice, SAT exhibits an upregulated browning signature that delays AT expansion in response to HFD feeding and preserves insulin sensitivity [249,250]. Conversely, the reduction of mitoNEET expression enhances oxidative stress and leads to glucose intolerance. Mice deficient in PGC-1α and PGC-1β show reduced PVAT expression of mitoNEET in comparison to wildtype mice, in which PVAT mitoNEET expression increases in response to cold exposure [251]. PVAT mitoNEET overexpression is associated with increased thermogenesis and ApoE$^{-/-}$ mice overexpressing mitoNEET exhibit reduced atherosclerosis development secondary to HFD consumption. Moreover, pioglitazone induced PVAT mitoNEET was demonstrated to prevent PVAT inflammation and arterial stiffness [252]. The proposed effects of thiazolidinediones are summarized in Fig. 3.

5.1.2. Metformin

Metformin is a biguanide antidiabetic that is heavily used clinically, and acts through AMPK-dependent and AMPK-independent pathways to modulate glucose metabolism and AT biology [253]. Although metformin ameliorates metabolic CVD risk factors, it seems not to significantly affect blood pressure in nondiabetic, obese nondiabetic, and diabetic hypertensive patients [254-256]. Emerging studies implicate a direct effect of metformin-mediated AMPK activation on mitochondrial bioenergetics, mitochondrial turnover, and mitochondrial dynamics [257-260]. For example, metformin was shown to inhibit high glucose-treated adipocyte ROS-associated mitochondrial fission through enhancing Drp1 Ser637 phosphorylation in an AMPK-dependent manner [261]. Biguanides were also shown to non-specifically inhibit mitochondrial dehydrogenases activities at supraphysiological concentrations, which is associated with a burst in ROS production, precluding generalized inhibition of the mitochondrial respiratory chain as a beneficial effect of biguanides [262]. Emerging evidence suggests that metformin improves obesity-associated AT inflammation through direct and indirect effects on tissue-resident and infiltrating immune cells likely through AMPK activation [253,263,264]. Moreover, metformin inhibits excessive ECM deposition in WAT of diet-induced and genetically induced models of obesity through the activation of AMPK and the inhibition of TGF-β1/Smad3 signaling [265]. Consistently, diabetic patients treated with metformin exhibit reduced VAT expression of MCP-1, NF-κB, and NLRP3 [266].

Metformin treatment in mice results in BAT activation, which is associated with increased expression and activity of AMPKα1, and increased expression of HSL and mitochondrial content [267]. Indeed, AMPK is a major determinant of the thermogenic potency and development of brown adipocytes and metformin treatment of fructose rich diet-fed mice enhances BAT thermogenesis through the upregulation of UCP1 and PGC-1α, mitochondrial biogenesis through the upregulation of NRF1 and TFAM, and lipolysis and FA uptake through the upregulation of perilipin, HSL, ATL, LPL, CD36, and aP2 [268-270]. Mice with inducible deletion of the two AMPK β subunits in adipocytes were cold intolerant and resistant to β-AR-mediated BAT activation and WAT browning [271]. Moreover, AMPK β subunits-deficient adipocytes show altered mitochondrial structure, decreased mitochondrial respiration, and disrupted mitophagy. The effects of metformin are summarized in Fig. 4.

5.1.3. Glucagon-like peptide 1 receptor (GLP-1R) agonists

This is a class of drugs that include molecules that are widely clinically-used including liraglutide and exenatide. GLP-1R agonism is known to reduce body weight, subcutaneous and visceral adiposity, and AT insulin resistance and is therefore thought to modulate obesity-associated AT dysfunction [272-274]. Consistently, liraglutide-induced weight loss is thought to occur secondary to reduced energy intake rather than increased energy expenditure [275]. Liraglutide was shown to reduce the adipogenic and inflammatory markers in the AT of T2D obese subjects [276]. GLP-1 downregulates the lipogenic gene expression in *in vitro* differentiated human adipocytes from morbidly obese patients and the adipogenic genes in AT explants and mature adipocytes, while increasing lipolytic markers [276]. Consistently, liraglutide treatment activates AMPK, suppresses Akt and reduces the lipogenic processes in VAT of db/db mice [277]. Exenatide treatment of DIO mice reduces AT hypoxia, inflammation, and macrophage infiltration, in addition to enhancing AT pro-angiogenic factors including VEGF and AT capillary density [278].

Central administration of liraglutide stimulates BAT thermogenesis, adipocyte browning, and energy expenditure through a direct effect on

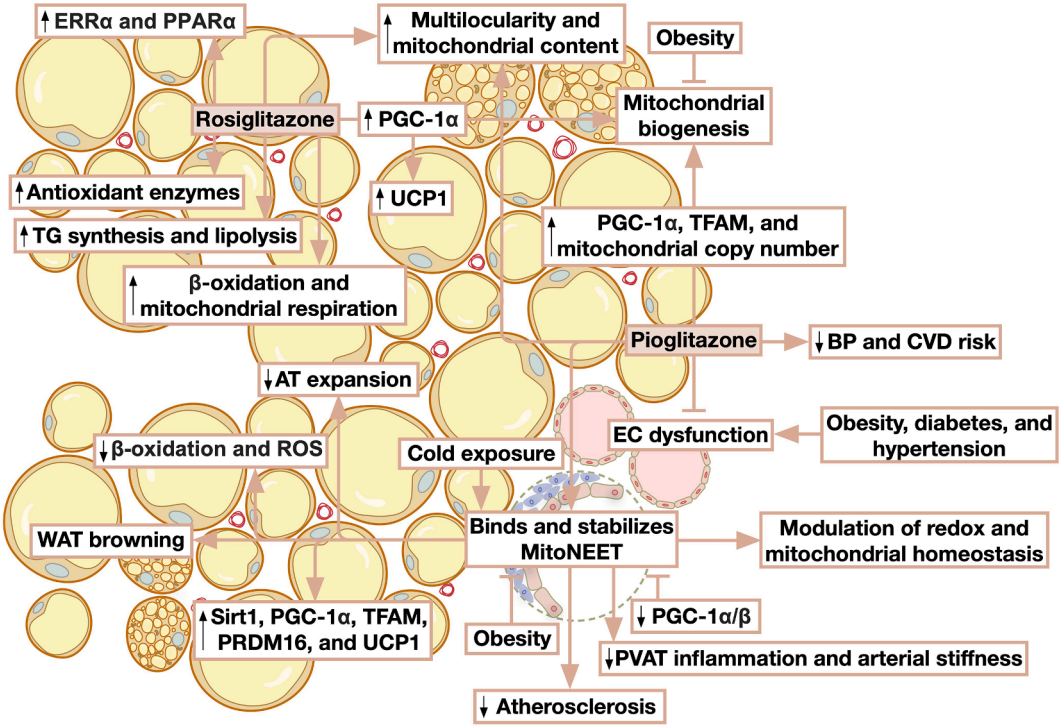

Fig. 3. Thiazolidinediones improve adipose tissue inflammation through several potential pathways leading to increased mitochondrial biogenesis, as well as improved mitochondrial respiration and thermogenesis. The impact of these effects decreases adipose tissue expansion and hypoxia, reactive oxygen species production, immune cell infiltration and inflammation. This counteracts the dysfunctional phenotype triggered by metabolic impairment. ERR, Estrogen-related receptor; PGC-1, Peroxisome proliferator-activated receptor gamma coactivator 1; PPAR, Peroxisome proliferator-activated receptor; PRDM16, PR domain containing 16; TFAM, mitochondrial transcription factor A; UCP1, Uncoupling protein 1.

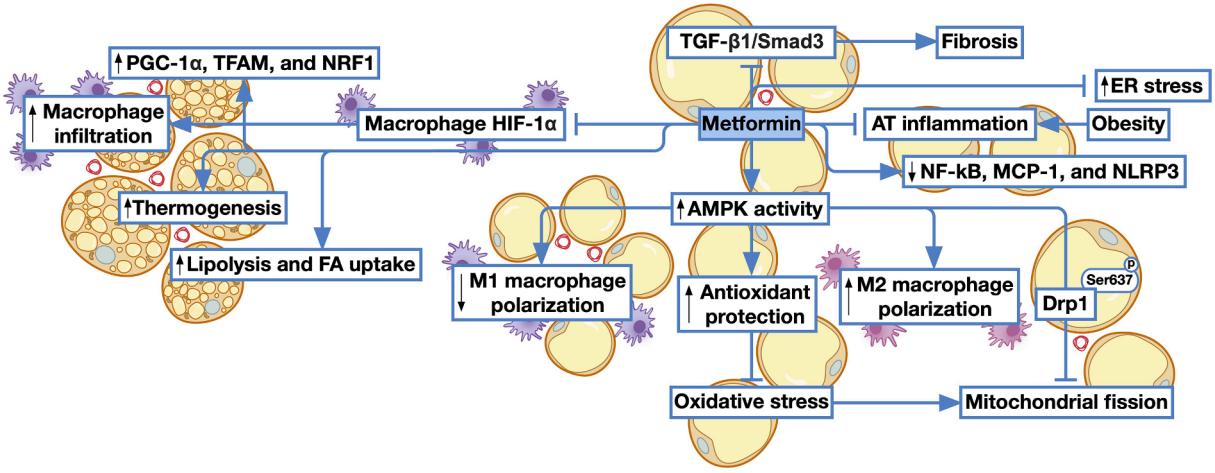

Fig. 4. Metformin decreases adipose tissue inflammation through several pathways involving the activation of AMPK potentially leading to the improvement of different aspects of mitochondrial homeostasis. These effects together with amelioration of adipocyte hypertrophy contribute to mitigating the hypoxic milieu, reducing immune cell infiltration and inflammatory polarization, and correction of the dysfunctional phenotype. AMPK, AMP-activated protein kinase; Drp1, Dynamin-related protein 1; HIF, Hypoxia-inducible factor; NF-κB, Nuclear factor kappa light chain enhancer activated B cells; NLRP3, NLR family pyrin domain containing 3; NRF, Nuclear respiratory factor; PGC-1, Peroxisome proliferator-activated receptor gamma coactivator 1; TFAM, mitochondrial transcription factor A; UCP1, Uncoupling protein 1.

the dorsomedial hypothalamus and hypothalamic ventromedial nucleus, at least in part through AMPK activation [279,280]. Moreover, central administration of exenatide in lean mice increased sympathetic outflow to BAT and WAT, enhancing UCP1 expression and promoting lipolysis [281]. Nevertheless, the effects of centrally administered exenatide on WAT but not on BAT were blunted in DIO mice. It is also suggested that liraglutide exerts an additive effect to those of β3-AR agonism in the stimulation of BAT thermogenic activity [282]. GLP1 receptor agonism promotes the uncoupling of mitochondrial respiration and upregulates the expression of Sirt1 and Sirt3 in cultured adipocytes [283]. Moreover, it was shown that exenatide enhances the lipolytic and oxidative capacities of WAT in wild type but not in Sirt1$^{+/-}$ HFD-fed mice [284]. Exenatide treatment decreases body weight, enhances BAT thermogenesis, and increases energy expenditure in DIO mice [285]. Liraglutide enhances WAT browning in HFD-fed rats through inducing the expression of UCP1, PRDM16, CIDEA, and PGC-1α [286].

Liraglutide treatment reduces adipocyte size and induces WAT browning by enhancing lipolysis and promoting mitochondrial biogenesis through the upregulation of TFAM and PGC-1α expression via a soluble guanylyl cyclase (sGC)/protein kinase G I (PKGI) pathway [287]. It was also suggested that liraglutide-induced WAT browning is partially mediated through AMPK/Sirt1/PGC-1α signaling [288]. Nevertheless, it was suggested that although endogenous GLP-1R signaling contributes to enhanced BAT thermogenesis, liraglutide treatment does not induce BAT thermogenesis in DIO mice [289]. These effects are illustrated in Fig. 5.

5.1.4. Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors, including linagliptin, saxagliptin, sitagliptin, alogliptin, and vildagliptin are clinically-used antidiabetic drugs that inhibit the enzymatic activity of DPP-4 and thus, preserve serum incretin levels. Linagliptin and sitagliptin have been shown to reduce obesity-related insulin resistance and inflammation in DIO mice by modulating WAT macrophage infiltration and polarization and adiponectin production [290-292]. Moreover, vildagliptin was shown to inhibit WAT fibrosis in DIO mice [293]. Indeed, sitagliptin ameliorated hyperinsulinemia and restored glucose homeostasis in DIO mice, partly through decreasing adipocyte hypertrophy, AT macrophage infiltration, and adipocyte proinflammatory cytokines production [294]. Alogliptin was also shown to improve insulin resistance, reduce blood pressure, and modulate macrophage polarization in LDLR$^{-/-}$ mice [295]. Nevertheless, saxagliptin exerted rather modest effects on SAT inflammation in obese non-diabetic individuals, where it neither reduced AT macrophage content nor inhibited inflammatory signaling [296]. As such, the translational potential of studies employing animal models of metabolic dysfunction and investigating the ameliorative effect of DPP-4 inhibitors on AT dysfunction requires further validation. Linagliptin enhances SAT browning in DIO mice, which is evidenced by reduced adipocyte hypertrophy and the emergence of multilocular and thermogenically active adipocytes [297]. Consistently, sitagliptin was also shown to increase glucose uptake in SAT of overweight individuals with prediabetes, while no detectable changes in BAT thermogenic activity was observed [298]. DIO mice treated with experimental des-fluoro-sitagliptin exhibited reduced WAT weight and enhanced BAT PPARα, PGC-1α, and UCP1 expression [299]. The impact of this class of medications is depicted in Fig. 6.

5.1.5. Sodium glucose cotransporter 2 (SGLT2) inhibitors

SGLT2 inhibitors, including canagliflozin, dapagliflozin, and empagliflozin, reduce hyperglycemia through enhancing the urinary excretion of glucose. Although the use of SGLT2 inhibitors has been consistently associated with weight loss and reduced visceral adiposity

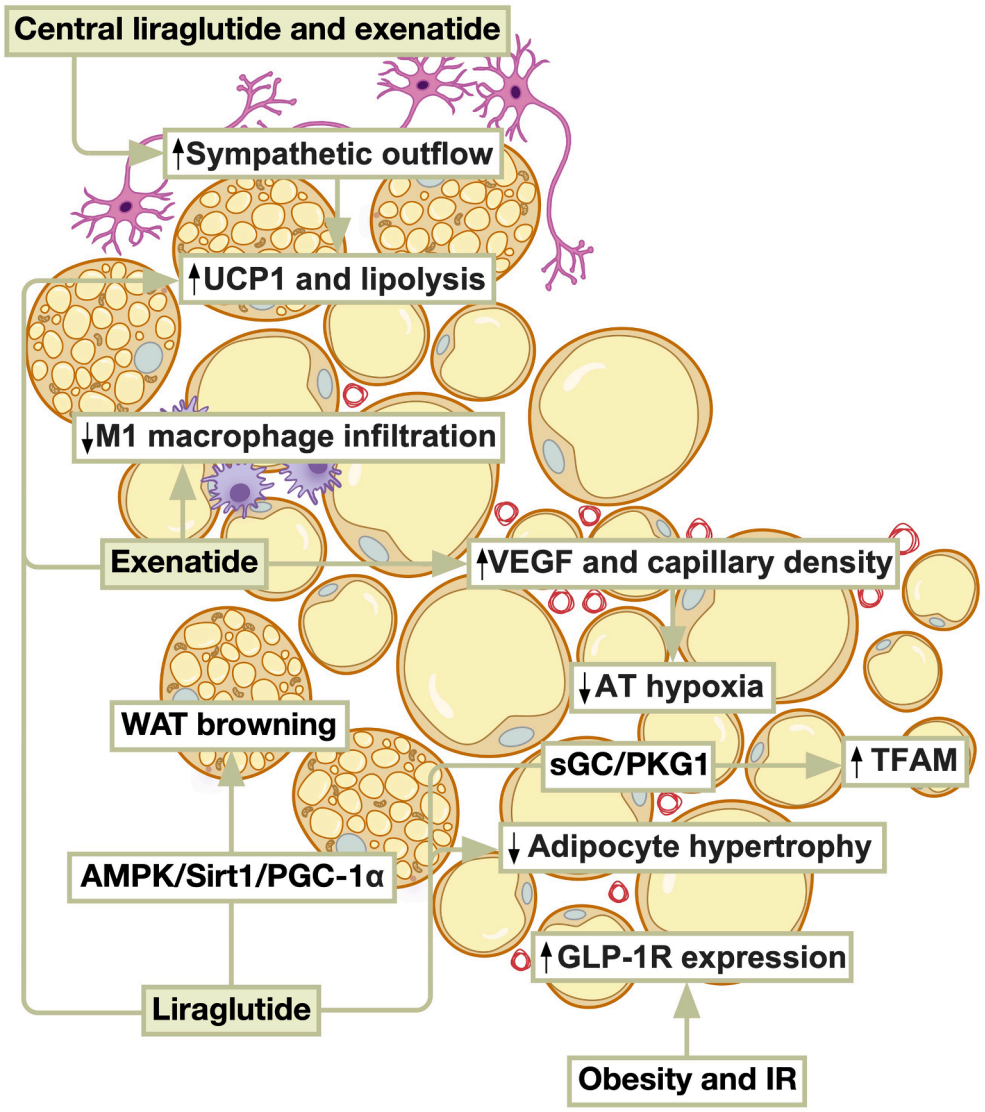

Fig. 5. GLP-1R agonists improve adipose tissue dysfunction by acting through central and peripheral pathways affecting mitochondrial function through modulating adipose tissue thermogenesis, lipolysis, and oxygenation as well as improved mitochondrial respiration and thermogenesis. These effects limit adipose tissue hypoxia, hypertrophy and inflammation. This counteracts the dysfunctional phenotype triggered by metabolic impairment. AMPK, AMP-activated protein kinase; PGC-1, Peroxisome proliferator-activated receptor gamma coactivator 1; TFAM, mitochondrial transcription factor A; UCP1, Uncoupling protein 1.

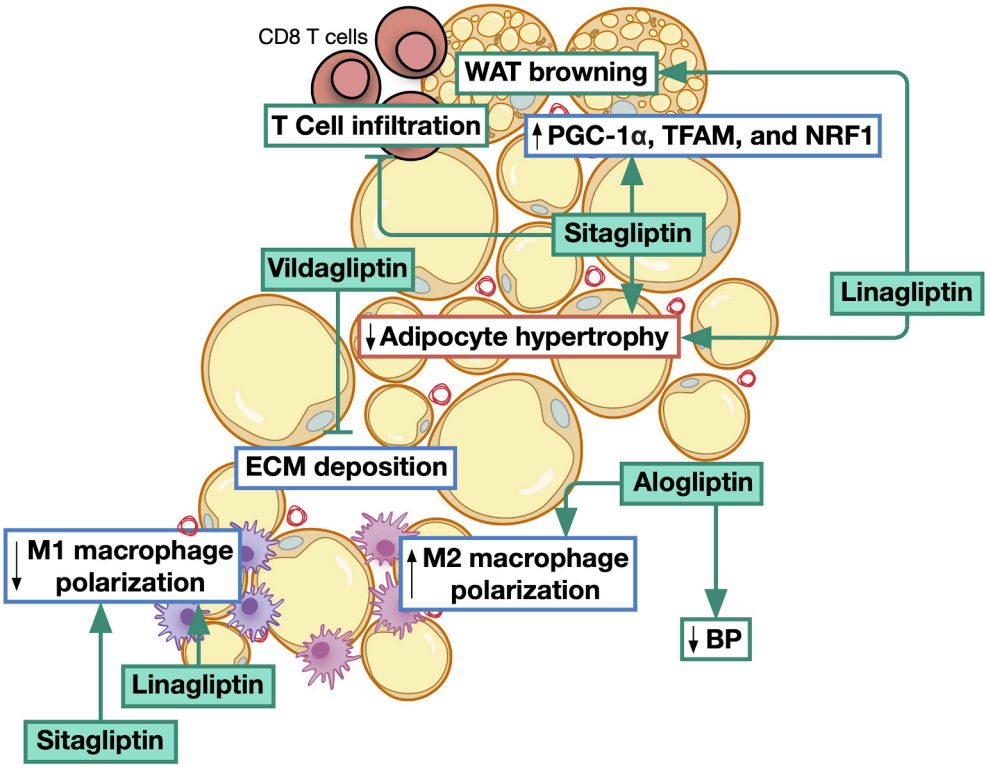

Fig. 6. DPP-4 inhibitors affect adipose tissue remodeling by reducing hypertrophy, inducing browning, decreasing extra-cellular matric deposition, and reducing inflammatory polarization of macrophages. ECM; Extra-cellular matrix; NRF, Nuclear respiratory factor; PGC-1, Peroxisome proliferator-activated receptor gamma coactivator 1; TFAM, mitochondrial transcription factor A.

[300-302], the molecular underpinnings of this association are not fully understood. Particularly, direct activities of SGLT2 inhibitors on the AT independent of the inhibition of SGLT2 are recently emerging. Canagliflozin treatment renders HFD-fed mice obesity-resistant through elevating sympathetic innervation and increasing lipolytic and thermogenic activities of the AT [303]. Canagliflozin-treated adipocytes displayed enhanced mitochondrial OXPHOS, mitochondrial FAO, thermogenesis, energy expenditure, and mitochondrial biogenesis secondary to the activation of the AMPK/Sirt1/PGC-1α signaling pathway [304]. Consistently, canagliflozin-supplemented mice exhibited increased AT AMPK phosphorylation and Sirt1 and PGC-1α expression. Importantly, canagliflozin-supplemented HFD-fed obese mice exhibit enhanced white AT FAO and mitochondrial biogenesis evidenced with increased expression of PGC-1α, NRF1, and TFAM in comparison to their control counterparts, which was associated with reduced adipocyte hypertrophy and improved glucose and lipid homeostatic parameters [305]. Likewise, empagliflozin treatment suppresses weight gain and insulin resistance and enhances energy expenditure in HFD-fed mice partly through upregulating UCP1 expression in WAT and BAT and inducing WAT anti-inflammatory macrophage polarization [306,307]. Moreover, empagliflozin treatment enhanced epididymal AT and PRAT browning in KKAy mice through enhancing mitochondrial biogenesis, promoting mitochondrial fusion, and reducing mitochondrial fission secondary to AMPK activation [308]. The effects of SGLT2 inhibitors on AT are illustrated in Fig. 7.

5.1.6. Angiotensin II receptor blockers (ARBs) and angiotensin I converting enzyme inhibitors (ACEIs)

In addition to their antihypertensive activity, ARBs and ACEIs exhibit pleiotropic effects that intersect with metabolic pathways, which in part, highlights their superiority in the treatment of obesity-associated hypertension [309-311]. The overproduction of angiotensinogen in obese mice AT induces adipocyte ER stress, AT inflammation, glucose intolerance, and insulin resistance, pathological manifestations that are reduced in response to ARB treatment [312-314]. Particularly, telmisartan, which also exhibits partial pan-PPAR agonistic activity, modulates human and murine preadipocyte differentiation through the activation of PPARγ and PPARβ/δ [315,316]. Indeed, telmisartan increases energy expenditure and protects mice and hypertensive rats against DIO by reducing VAT accumulation and adipocyte size [316-318]. Telmisartan induces brown adipocyte expression of β3-ARs through the activation of PPARβ/δ, and the expression of UCP1 through PPARα agonism [319]. Moreover, telmisartan inhibits AT inflammation through reducing AT macrophage and T cell infiltration and inducing anti-inflammatory macrophage polarization, thereby improving glucose intolerance and insulin resistance in HFD-fed mice [320,321]. The induction of macrophage M2 polarization by telmisartan through PPARγ and PPARδ activation was shown to drive white adipocyte and WAT browning, evidenced by reduced lipid droplets, increased oxygen consumption rate, and enhanced mitochondrial biogenesis downstream of increased β3-AR signaling [322]. Nevertheless, telmisartan insulin-sensitizing effects are comparable to those of valsartan, an ARB devoid of PPARγ agnostic activity, in KKAy mice, suggesting that the metabolic effects of ARBs extend beyond PPARγ agonism [323]. It was recently shown that telmisartan, but not other sartans, directly binds BCAT2, which converts branched-chain amino acids (BCAAs) to branched-chain keto acids and inhibits its activity [318]. BCAT2-defiecient mice are resistant to HFD-induced obesity due to enhanced WAT thermogenesis and telmisartan protects mice against obesity, glucose intolerance, and insulin resistance by inhibiting BCAT2 [318]. Noteworthy, telmisartan treatment was also associated with reduced vascular inflammation and visceral fat accumulation in hypertensive individuals [324].

Interestingly, a mitochondrial angiotensin system has been described, where functional angiotensin II receptors localize to the inner mitochondrial membrane and colocalize with endogenous angiotensin [325]. The activation of the mitochondrial angiotensin system, which is

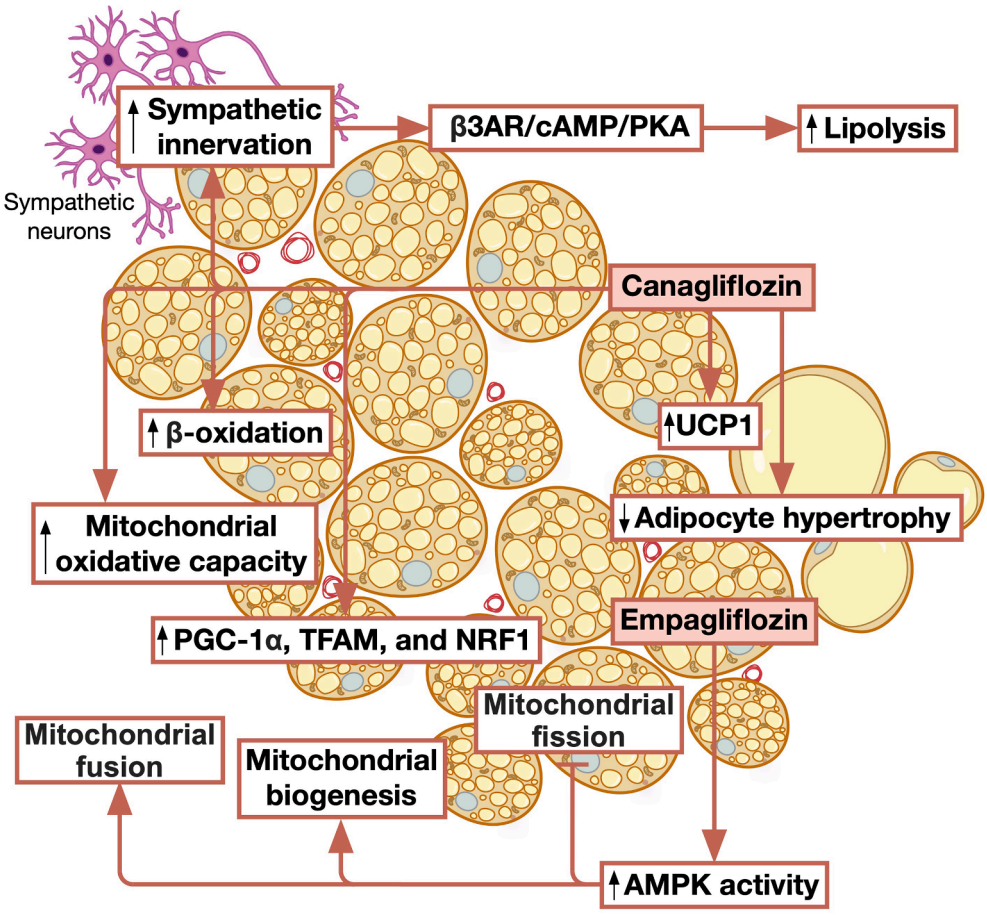

Fig. 7. SGLT2 inhibitors modulate adipose tissue mitochondrial bioenergetics possibly through interference with sympathetic innervation, UCP1 activity, and lipolysis, and mitochondrial homeostasis through activation of AMPK. This has an overall beneficial effect on adipose tissue hypertrophy and inflammation. AMPK, AMP-activated protein kinase; NRF, Nuclear respiratory factor; PGC-1, Peroxisome proliferator-activated receptor gamma coactivator 1; TFAM, mitochondrial transcription factor A; UCP1, Uncoupling protein 1.

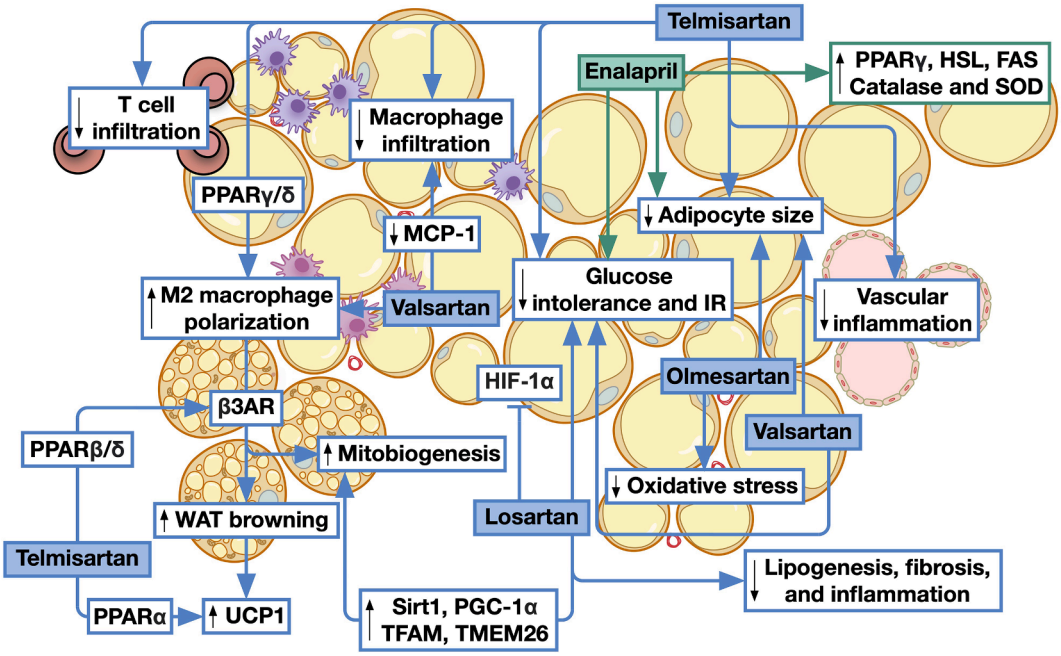

Fig. 8. Pharmacological intervention with renin-angiotensin system modulators reverses the mitochondrial disorders evoked by metabolic impairment increasing mitochondrial respiratory capacity and biogenesis and reducing oxidative stress. Combined, these effects reduce immune cell infiltration and adipose tissue inflammation. HIF, Hypoxia-inducible factor; IR, Insulin resistance; PGC-1, Peroxisome proliferator-activated receptor gamma coactivator 1; PPAR, Peroxisome proliferator-activated receptor; SOD, Superoxide dismutase; TFAM, mitochondrial transcription factor A; TMEM26, Transmembrane protein 26; UCP1, Uncoupling protein 1.

altered during aging and could be modulated by losartan, is coupled to mitochondrial NO production and modulates mitochondrial respiration [325]. Losartan improved glucose intolerance and insulin resistance in ob/ob mice by inhibiting AT expression of HIF-1α, in addition to suppressing, lipogenesis, lipid droplet formation, and inflammatory and fibrotic signaling [326]. Moreover, losartan reduced AT macrophage infiltration and induced anti-inflammatory macrophage polarization in obese mice [326]. Remarkably, losartan treatment induced adipocyte mitochondrial biogenesis by upregulating the expression of SIRT1, PGC-1α, TFAM, and TMEM26, in addition to enhancing browning and thermogenesis through the upregulation of UCP1 expression [326,327]. Similarly, valsartan improved glucose homeostasis and hyperinsulinemia in HFD-fed mice, which was associated with reduced macrophage infiltration and MCP-1 expression [328]. Olmesartan treatment reduced adipocyte hypertrophy and ameliorated AT oxidative stress in genetically and diet-induced obese mice [329,330]. Consistently, valsartan treatment in humans with impaired glucose metabolism improved insulin sensitivity, reduces adipocyte size, and AT macrophage infiltration and inflammation in comparison to placebo-treated subjects [331].

Although angiotensin I converting enzyme inhibitors (ACEI) were also shown to ameliorate obesity-associated AT dysfunction, their modulation of adipocyte mitochondria remains largely uninvestigated. Enalapril treatment of DIO mice reduced visceral adiposity and adipocyte hypertrophy and ameliorated insulin resistance [332]. Enalapril treatment reduced ACE activity and the overactivation of AT Angiotensin II/AT1R signaling in rodent models of metabolic dysfunction and obesity [332,333]. Moreover, enalapril treatment enhanced the expression of PPARγ, hormone sensitive lipase, fatty acid synthase, catalase, and superoxide dismutase in AT [333]. The impact of the renin-angiotensin system modulators is depicted in Fig. 8.

5.2. Caloric restriction and intermittent fasting

Caloric restriction has been extensively linked to the promotion of health and longevity in part through the amelioration of cardiometabolic dysfunction [334-336]. Intermittent fasting and time-restricted feeding regimens involving no reduction of caloric intake were also associated with various metabolic benefits and were shown to extend the lifespan of mice [337-339]. As caloric restriction regimens involve different forms of fasting, it was recently shown that fasting is required for caloric restriction-induced changes in insulin sensitivity and FAO [340]. Caloric restriction regimens have consistently been associated with the reduction of metabolic impairment-associated AT inflammation and the induction of WAT browning and adaptive thermogenesis [335,341,342]. This induction of AT browning is tightly associated with extracellular remodeling in the AT, reduced AT inflammation, and improved metabolic homeostasis [343]. Emerging evidence highlights that caloric restriction-mediated effects are, at least in part, attributed to enhanced mitophagy and mitochondrial homeostasis in several tissues [344]. Indeed, caloric restriction is thought of as a major non-genetic trigger of mitophagy but supporting evidence remains limited and controversial [344]. Although some studies demonstrated that caloric restriction increases the expression of mitophagy-associated markers such as BNIP3 and Parkin, other studies found no significant difference in the mitophagic fluxes of different tissues in mice in both the fasted and the fed states [344]. Nevertheless, following the withdrawal of caloric restriction or β3-adrenergic receptor agonism in mice, beige adipocytes rapidly transition to a white-like phenotype independent of parkin-mediated mitophagy, but through the repression of mitochondrial biogenesis [345]. Importantly, caloric restriction rescues the beige phenotype when applied following the withdrawal of β3-adrenergic receptor agonism, which highlights a key role for mitochondrial biogenesis in caloric restriction-induced WAT browning.

Although it was previously shown that caloric restriction reduces aging-related mitochondrial biogenesis defects by enhancing TFAM expression in BAT [346], recent evidence shows that caloric restriction also promotes mitochondrial biogenesis in WAT and mice deficient in both PGC-1α and PGC-1β specifically in AT exhibit blunted mitochondrial biogenesis in response to caloric restriction [347]. However, the predominant contribution of PGC-1α in caloric restriction-induced mitochondrial biogenesis has been recently contested [348]. Indeed, caloric restriction was shown to enhance mitochondrial biogenesis in WAT evidenced by the upregulation of the expression of PGC-1α, NRF-1, TFAM, and Mnf1/2 secondary to eNOS induction as eNOS-deficient mice displayed blunted mitochondrial response to caloric restriction [349]. Moreover, every-other-day fasting was recently shown to increase SAT and VAT mitochondrial protein content and fatty acid synthesis, while inhibiting VAT adipocyte lipolysis secondary to the downregulation of the expression of β3 adrenergic receptors, which preserves VAT fat stores [350]. Noteworthy, caloric restriction reduces brown adipocyte cytoplasmic lipid droplets and increases mitochondrial cristae formation and fenestration, which is associated with increased mitochondrial cardiolipin levels [351]. As caloric restriction and intermittent fasting are believed to ameliorate metabolic dysfunction-associated PVAT inflammation and the ensuing cardiovascular deterioration [352], systemic investigation into the effect of caloric restriction and intermittent fasting on AT mitophagic flux is warranted. Sirtuin 1 (SIRT1), a nutrient sensitive histone deacetylase, could offer a mechanistic explanation to the remodeling of AT evoked by intermittent fasting and caloric restriction. Intermittent fasting was shown to promote AT macrophage anti-inflammatory polarization through enhancing macrophage SIRT1 activity [353]. Indeed, mice overexpressing Sirt1 were protected against DIO and AT inflammation through the reduction of NF-κB signaling and proinflammatory cytokines production [354]. Mice with adipocyte-specific deletion of Sirt1 fed standard chow exhibit AT inflammation, IR, and glucose intolerance in comparison to their wildtype littermates, and this phenotype was exacerbated by HFD consumption [355]. It is worth noting however that studies in human subjects reported inconsistent results ranging from increased AT Sirt1 expression to no change in response to fasting regimens [354,356]. This could be related to the inconsistency of the employed fasting regimens and warrants further investigation. The effect of calorie restriction is summarized in Fig. 9.

5.3. Exercise

Exercise is regarded as an approach to prevent and treat chronic metabolic disorders and endurance exercise has been consistently linked to the alleviation of obesity-induced reduction in mitochondrial biogenesis [357]. Indeed, acute exercise is associated with favorable metabolic, oxidative, and inflammatory phenotype alterations that are blunted in insulin-resistant subjects [358]. Such an impact is illustrated in Fig. 4. Active individuals exhibit increased PGC-1α expression and mtDNA content but not thermogenic markers in WAT following three weeks of training in comparison to sedentary individuals [359]. Moreover, lifelong physical activity in trained individuals is associated with reduced SAT oxidative stress, enhanced mitochondrial respiratory capacity, and increased mitophagic flux compared to untrained individuals [360]. Indeed, impaired AT and skeletal muscle mitochondrial function is associated with impaired exercise capacity in the absence of altered thermogenesis [361]. A recent clinical trial also demonstrated the lack of BAT activation following 24 weeks of supervised exercise training combining endurance and resistance training in young sedentary adults [362]. The beneficial effects of exercise on metabolic dysfunction partly lie downstream of AMPK activation. Indeed, administration of the pan-AMPK activator O304, an exercise mimetic prevented age-associated hyperinsulinemia and insulin resistance and enhanced exercise capacity in aged mice [360]. Particularly, exercise enhances metabolic dysfunction-associated vascular impairment in DIO mice, which is associated with increased BAT thermogenic genes expression and WAT browning [363].

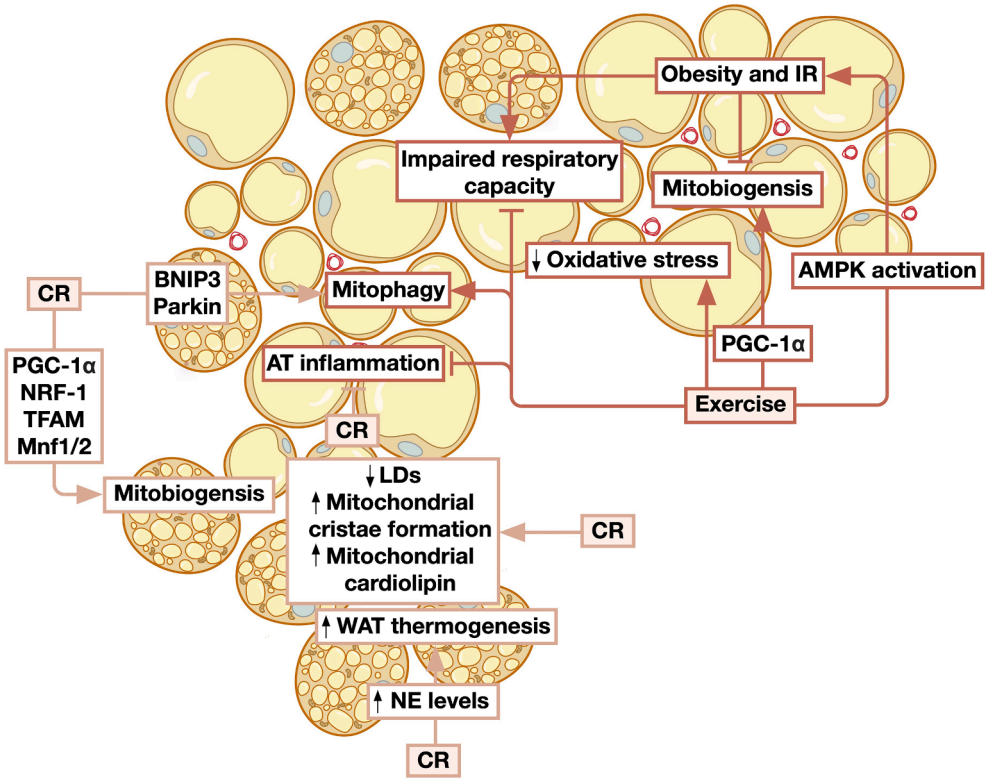

Fig. 9. Non-pharmacological lifestyle changes including calorie restriction and exercise improve adipose tissue dysfunction via several pathways culminating in improved mitochondrial function and homeostasis. AMPK, AMP-activated protein kinase; CR, Calorie restriction; IR, Insulin resistance; NRF, Nuclear respiratory factor; PGC-1, Peroxisome proliferator-activated receptor gamma coactivator 1; TFAM, mitochondrial transcription factor A.

6. Conclusion and future perspectives

As outlined above, mitochondrial function and dynamics represent a fundamental component of AT health. Perturbation in any of these aspects drives diverse forms of AT dysfunction contributing to inflammatory changes and ensuing cardiometabolic impairment. As our understanding of the relevant molecular underpinnings improve, novel therapeutic interventions modulating these processes will become feasible. Indeed, quite a spectrum of the available pharmacologic and non-pharmacologic approaches demonstrates some beneficial modulatory effects. Nevertheless, much work remains needed to refine the pharmacodynamic and therapeutic properties of these tools for such purposes or develop new selective tools. Particularly, approaches geared towards the selection of one mitochondrial pathway over the others might prove valuable, whereby futile creatine cycling might be enhanced in order to bypass the need for an increased UCP1-mediated thermogenesis and hence, possibly reduce PVAT hypoxia and the ensuing cardiovascular dysfunction.

Yet, in spite of our major focus on white and brown adipocyte mitochondrial dysfunction as an instigator of AT inflammation and the ensuing cardiovascular impairment, emerging evidence highlights other components of the AT including adipocyte progenitors, endothelial cells, and immune cells as being critically regulated by mitochondrial activity and mitochondrial dynamics [364]. For example, it was demonstrated that pathological HIF-1α signaling and mitochondrial dysfunction in adipocyte progenitors, being an integral part of the AT stromovascular fraction, drives AT expansion, inflammation, and fibrosis in a mouse model of DIO [9,365]. Indeed, adipocyte progenitors regulate sex-differential and depot-specific adipogenesis and are thus likely to contribute to the sexual dimorphism in cardiometabolic health [366,367]. Further, a reduced oxidative capacity in macrophages, a hallmark of proinflammatory M1-polarized macrophages immunometabolic alterations, results in systemic insulin resistance and AT inflammation [368], and this reduced oxidative capacity in macrophages prevents macrophage repolarization into an anti-inflammatory phenotype [369]. Particularly, AT macrophages show immunometabolic features distinct from classically activated macrophages [1,370]. Indeed, the specific targeting of AT macrophage mitochondria using a near-infrared fluorophore (IR-61) ameliorated DIO and obesity-associated insulin resistance in mice [371]. IR-61 enhances AT macrophage mitochondrial complex levels and OXPHOS capacity through the ROS/Akt/Acly signaling pathway.

Finally, evidence suggests heparan sulfate-mediated intercellular mitochondrial transfer occurring between adipocytes and a transcriptionally-distinct AT macrophage subpopulation [372]. Mitochondrial transfer is decreased in high fat diet fed mice secondary to decreased macrophage heparan sulfate expression. Consistently, the inhibition of heparan sulfate biosynthesis in myeloid cells halts macrophage uptake of mitochondria, decreases energy expenditure, and exacerbates DIO [372]. Moreover, it was recently shown that dietary lipids inhibit adipocyte-macrophage mitochondrial transfer, diverting adipocyte-released mitochondria into the blood for delivery to distant organs supporting their adaptation to metabolic stress [373]. As well, it was demonstrated that thermogenically-stressed adipocytes release extracellular vesicles containing oxidatively damaged mitochondrial parts, that when taken up by parental brown adipocytes, reduce PPARγ signaling and UCP1 expression [374]. The removal of these vesicles by BAT-resident macrophages phagocytic activity preserves BAT thermogenic potential. Indeed, intercellular and inter-organ mitohormesis offers novel avenues in which metabolic disease-triggered AT mitochondrial dysfunction drives AT as well as distant organ beneficial or otherwise deleterious remodeling [364]. This is exemplified by the extensive intercellular vesicle-mediated crosstalk between components of the AT, including activated monocytes, endothelial cells, and adipocytes [375,376]. It was demonstrated that mitochondrially-stressed adipocytes release small extracellular vesicles containing respiration-

competent, but oxidatively-damaged mitochondrial particles, which are taken up by cardiomyocytes to induce a burst of reactive oxygen species and ensuing cardiomyocytic antioxidant signaling consistent with cardiac preconditioning [377]. As such, further research into the potential utility of modulating these processes in achieving a beneficial impact on AT function and cardiometabolic impairment is warranted.

CRediT authorship contribution statement

Ibrahim AlZaim: Conceptualization, Writing – original draft, Visualization. **Ali H. Eid:** Writing – review & editing. **Khaled S. Abd-Elrahman:** Writing – review & editing. **Ahmed F. El-Yazbi:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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