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Abstract

In mammals, the white adipocyte is a cell type that is specialized for storage of energy, in the form of triacylglycerols, and for energy mobilization, as fatty acids. White adipocyte metabolism confers an essential role to adipose tissue in whole-body homeostasis. Dysfunction of white adipocyte metabolism is a cardinal event in the development of insulin resistance and associated disorders. This Review focuses on our current understanding of lipid and glucose metabolic pathways in the white adipocyte. We survey recent advances in humans on the importance of adipocyte hypertrophy and on in vivo turnover of adipocytes and stored lipids. At the molecular level, identification of novel regulators and interplay between metabolic pathways explains the fine-tuning between anabolic and catabolic fates of fatty acids and glucose in different physiological states. We also examine the metabolic alterations involved in the genesis of obesity-associated metabolic disorders, lipodystrophic states, cancers and cancer-associated cachexia. New challenges include defining the heterogeneity of white adipocytes in different anatomical locations throughout the lifespan and investigating the importance of rhythmic processes. Targeting white fat metabolism offers opportunities for improved patient stratification and a wide, yet not exploited, range of therapeutic opportunities.

Introduction

White adipose tissue (WAT) was long considered an inactive tissue that primarily served a thermal insulation purpose[1]. In the mid-20th century, it became increasingly apparent that WAT is important for energy homeostasis, as it is able to utilize glucose as well as to store and release energy-rich fatty acids (FIG. 1). Lipids are stored mostly as triacylglycerol (TAG), in a single lipid droplet in mature white adipocytes or in multiple lipid droplets in most other cell types, including brown adipocytes[2]. In 1964, a major breakthrough was the development of collagenase digestion, which enabled the isolation of fairly pure preparations of adipocytes[3]. This breakthrough paved the way for studies of TAG metabolism, including uptake, synthesis and hydrolysis, a process known as lipolysis. Defects of glucose metabolism in hypertrophic adipocytes were identified in 1976[4]. In 1980, insulin was shown to stimulate the translocation of the glucose transport machinery to the plasma membrane in adipocytes[5,6]. The discovery, in the early 1990s, that WAT is an endocrine and inflammatory organ, notably with the identification of the hormones leptin and adiponectin, added new dimensions to research in this field[7-11]. In parallel, knowledge was progressing on WAT being a major metabolic regulator. Historical aspects of adipocyte biology have been comprehensively reviewed elsewhere[12].

Among the many cell types in WAT (BOX 1), the adipocyte is the one that is specialized in energy metabolism. Metabolic alterations drive changes from healthy to dysfunctional adipocytes, with systemic consequences. This Review focuses on the current understanding of glucose and lipid metabolic pathways in white adipocytes and dysfunctions reported in situations of excess WAT (for example, obesity and the related condition type 2 diabetes mellitus (T2DM)), or of WAT paucity (such as lipodystrophy and cachexia). We also address therapeutic perspectives in targeting white fat metabolism and some of the outstanding questions in this field of research. Other aspects of adipose biology, such as the role of brown and beige fat and the endocrine function of WAT, have been reviewed elsewhere[13-17].

Adipocyte size and turnover

Cell size and turnover are major determinants of white adipocyte metabolism and fat mass, the alterations of which are associated with pathological conditions (FIG. 2a, b). Since the development of methods to determine the size of adipocytes in the late 1960s and 1970s, it became clear that adipocyte size varies considerably within fat depots of the same person and between individuals, and that the average adipocyte size increases during body weight gain and decreases after weight loss[18]. From a clinical point of view, the most important aspect of adipocyte size is its relation to cardiometabolic status (FIG. 2b). Numerous studies have shown a strong association between large adipocytes and cardiometabolic disorders[19-21], including risk of developing T2DM, as well as associations with insulin resistance, dyslipidaemia and hypertension (BOX 2). Adipose mass can develop in two ways, by adipose tissue hypertrophy or adipose tissue hyperplasia, which respectively define the WAT morphologies termed hypertrophic WAT and hyperplastic WAT (FIG. 2b). Hypertrophic WAT is characterized by large adipocytes, which can be formed through two processes during build-up of fat mass: formation of few large-sized adipocytes, or storage of more lipids in pre-existing fat cells. Hyperplastic WAT shows a greater number of adipocytes of a smaller diameter than in normal or hypertrophic WAT. When fat mass develops, there is an increase in the number of smaller adipocytes through differentiation of progenitor cells. In humans, the two morphologies are found irrespective of body weight status, although obesity is usually characterized by a combination of WAT hypertrophy and hyperplasia[22]. The hypertrophic morphology is associated with adverse cardiometabolic profile[23,24]. Advances in understanding of the origin of the new adipocytes formed during adipogenesis have been reviewed elsewhere[16,17,25].

De novo adipocyte formation and differentiation are complex processes that are subject to regulation by multiple signalling pathways, including, amongst others, signalling by the nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ) and its co-activator PGC1α, as well as by WNT and NOTCH signalling pathways [26-28]. Studies in mice have shed new light on the control of adipogenesis. The process is inhibited by low steady-state oxidative stress, which alters mitochondrial function in adipocyte precursors[29]. Increased adipogenesis in obese mice is mediated, at least in part, by the mechanosensitive cationic channel Piezo1 through the FGF1 signalling pathway[30]. The adipocyte insulin receptor also seems to be important in the turnover of adipocytes, as demonstrated with conditional knock-out experiments[31]. Finally, mammary adipocyte turnover may be governed by site-specific regulation. These adipocytes dedifferentiate during pregnancy and remain dedifferentiated during lactation. Upon weaning, dedifferentiated cells proliferate and redifferentiate into adipocytes[32]. Multiple origins of precursor cells have now been identified in mice[33]and in humans[34]. One source of adipocyte precursors in humans is stem cells from the bone marrow[35,36]. On average, bone marrow precursors contribute 10% to the total adipocyte pool, a figure that is doubled in obesity (FIG. 2a).

The anatomical location of the fat depot also influences adipose tissue morphology. Subcutaneous WAT comprises more than 80% of total body fat, whereas visceral fat comprises up to 10 or 20% of total body fat in women or men, respectively[37]. The small visceral depot is often considered to be more pernicious than the larger subcutaneous depot. Visceral WAT hypertrophy has been associated with insulin resistance and cardiometabolic disorders[23]. Nevertheless, the pathophysiological consequences of regional adipose tissue morphology are complex. Two independent studies demonstrated that visceral adipocyte hypertrophy is predominantly associated with dyslipidaemia whereas subcutaneous adipocyte hypertrophy is mainly associated with insulin resistance in humans[38,39]. Moreover, a reduction in adipocyte size in subcutaneous WAT improves insulin sensitivity in individuals with obesity [18]. In visceral but not in subcutaneous WAT, the association between adipocyte hypertrophy and M1-like macrophage-mediated and/or B-cell-mediated inflammation may be involved in insulin resistance[40]. It should be emphasized that, in these human studies, the associations between adipocyte size and clinical phenotypes are not evidence of a causal link. An exception might be a possible role of adipocyte size in T2DM, as prospective studies reveal that enlarged subcutaneous adipocytes confer increased risk of developing T2DM[41,42].

At the whole-body level, WAT mass is determined by the dynamics of adipocyte and lipid turnover[43]. A breakthrough in investigating cell turnover in vivo came with methods to study incorporation of atmospheric ^{14}C into DNA of free-living individuals[44]. The method has been used to determine the age and turnover of human subcutaneous adipocytes[45]. On average, 10% of these cells are renewed each year. In obesity, adipocyte turnover at the whole-body level increases about two-fold, owing to an acceleration of adipogenesis. Importantly, hypertrophic WAT is associated with low generation rate of new adipocytes, irrespective of body fat mass[46].

Lipid turnover in white adipocytes

The ^{14}C method has been further used to determine the age and turnover parameters for lipids within human adipocytes (FIG. 2c). The lipid content of a human adipocyte is renewed six times on average during its ~10-year life span[47], a turnover rate that has been confirmed using multi-isotope imaging mass spectrometry[48]. Lipid age data can be modelled to determine parameters reflecting the adipocyte capacity for storage (that is, lipid input; K_{in}) and removal (that is, lipid output; K_{out}) [36,47-49]. Cross-sectional studies show that weight gain is associated with increased lipid age (reflecting decreased turnover) in the subcutaneous region, which already appears in the overweight state, owing to a combination of increased K_{in} and decreased K_{out}[36,47]. In the visceral region, lipid turnover is decreased only among very obese individuals[49]. This regional difference may explain why lipid mobilization is usually more rapid in the visceral compared to subcutaneous WAT among overweight and obese individuals[50,51]. It could also partly explain why visceral fat is more pernicious than subcutaneous fat because a high output of fatty acids from visceral fat to the liver via the portal vein has direct effects on liver metabolism. Longitudinal studies of subcutaneous WAT show that lipid turnover decreases (that is, lipid age increases) over time irrespective of variations in body weight[52]. If the decrease in K_{out} is not counterbalanced by a decrease in K_{in}, then body fat will accumulate over time (FIG. 2c). In those individuals with obesity whose body weight decreases markedly following bariatric surgery, adipocyte lipid turnover increases and the initial weight reduction is maintained. Conversely, those individuals who do not show an increase in lipid turnover experience long-term weight regain. Moreover, adipocyte lipid turnover is decreased in insulin-resistant individuals and in patients with familial or common dyslipidaemic conditions[47,52]. These data highlight the physiological and pathophysiological importance of adipocyte and lipid turnover[36,45-49,52], although the short-term regulation of these two processes in physiological and pathological states remains largely unknown[43].

Fat storage

Most of the fatty acid stored in adipocytes originates from circulating TAG that is carried by lipoproteins, such as very-low-density lipoproteins and chylomicrons (FIG. 3). Following hydrolysis by lipoprotein lipase, fatty acids rapidly enter the adipocyte, both passively by diffusion and actively by protein-mediated processes involving fatty acid transporters[53,54]. The fatty acid translocase CD36, which is localized in plasma membrane lipid microdomains, acts in concert with fatty acid-binding proteins in the plasma membrane to promote uptake of long-chain fatty acids. Fatty acid transport proteins and long-chain acyl-CoA synthetases are responsible for uptake and conversion of fatty acids into acyl-CoA derivatives that can be esterified on the glycerol-3-phosphate backbone to be stored as TAG in the lipid droplet. The various steps leading to storage of fat as TAG are stimulated by insulin (FIG. 3). In the fed state, glycerol-3-phosphate is produced from glucose during glycolysis. The esterification process is performed by the sequential action of glycerol-3-phosphate acyltransferases, 1-acyl-glycerol-3-phosphate-acyltransferases (such as AGPAT2), phosphatidic acid phosphatases (also known as lipins) and diacylglycerol acyltransferases (DGATs)[55]. There is emerging evidence that large protein assemblies ensure compartmentalization of enzyme pathways and high local concentrations of substrates and intermediates[56]. The protein complexes allowing proper channelling of fatty acids and acyl-CoAs into specific pathways of the white adipocyte have not yet been characterized. DGATs catalyse the formation of TAG from diacylglycerol (DAG) and are important regulators of this pathway. Mice with adipocyte-specific ablation of either *Dgat1* or *Dgat2* fed a chow diet display normal adipose tissue development, indicating that either isoform is sufficient for TAG production and storage[57]. However, in mice fed a high-fat diet, adipocyte-specific ablation of *Dgat1*, but not *Dgat2*, leads to a slight decrease in WAT mass, ectopic lipid storage in liver and skeletal muscle, and insulin resistance[57]. DGAT1 may be protective against insulin resistance by preventing fatty acid-induced endoplasmic reticulum stress and inflammation in adipocytes, which is achieved by promoting fatty acid re-esterification during increased lipolysis[57,58].

In addition to exogenous lipid sources, fatty acids stored in adipocytes can also originate from endogenous synthesis from glucose, a pathway termed de novo lipogenesis (DNL) [59,60] (FIG. 3). After entering the adipocyte through insulin-sensitive (GLUT4) and non-insulin-sensitive (GLUT1) glucose transporters, glucose is metabolized through glycolysis and the tricarboxylic acid (TCA) cycle to produce citrate molecules that are required for DNL. ATP citrate lyase (ACLY) and acetyl-CoA carboxylase (ACC1) respectively produce acetyl-CoA and malonyl-CoA, which are used by fatty acid synthase (FASN) to generate palmitic acid. Another source of acetyl-CoA in white adipocytes comes from the conversion of acetate by the acyl-CoA synthetase ACSS2[61]. The relative contribution of ACLY and ACSS2 to the acetyl-CoA pool in various pathophysiological conditions is unclear at present. Fatty acid elongases and desaturases subsequently modify the length and the degree of unsaturation of newly synthesized palmitic acid [62]. In vivo, the assessment of adipose tissue DNL is complicated by the contribution of hepatic DNL, as fatty acids newly synthesized in the liver are exported to adipose tissue and stored as TAG. During chronic glucose infusion, de novo production of fatty acids in human adipose tissue has been demonstrated[63,64]. In habitual dietary conditions, the contribution of adipose DNL to fatty acids stored in human adipose tissue seems limited[65].

Fat mobilization

The mobilization of WAT lipids after hydrolysis of TAG is maximal during periods of energy demands, such as fasting or physical exercise. Neuroendocrine control of lipolysis and the associated signalling pathways have been extensively reviewed eslewhere[66,67]. In human adipocytes, catecholamines, natriuretic peptides and insulin are the main hormonal regulators of lipolysis (FIG. 4). In addition, many autocrine and paracrine factors act through activation of anti-lipolytic G-protein-coupled receptors. Furthermore, locally produced inflammatory mediators, in particular tumour necrosis factor, act through specific signal transduction pathways to regulate basal lipolysis[68].

In adipocytes, three neutral lipases are involved in TAG breakdown. Adipose triglyceride lipase (ATGL; encoded by *PNPLA2*) is the main enzyme responsible for TAG hydrolysis to DAG. Whole-body[69] as well as adipocyte-specific *Pnpla2*-knockout mice show drastically reduced basal and stimulated lipolysis[70,71]. *PNPLA2* knockdown in human adipocytes also reduces basal and stimulated lipolysis[72]. Accordingly, human mutations leading to inactive ATGL are associated with decreased rate of glycerol and fatty acids formation in response to lipolytic agents as well as with neutral lipid storage disease with myopathy[73,74]. An unexpected aspect of the phenotype in this storage disease is the lack of marked alteration of fat mass in carriers of these mutations. The second enzyme, hormone-sensitive lipase (HSL; encoded by *LIPE*), hydrolyses DAG, although it also displays TAG hydrolysis activity. Whole-body HSL-deficiency leads to DAG accumulation within adipose tissue and decreased stimulated lipolysis in both mice[75] and humans[72,76]. The third enzyme, monoglyceride lipase, catalyses the hydrolysis of monoacylglycerol to glycerol and a fatty acid. Studies of monoglyceride lipase-deficient mice show that HSL also participates in WAT monoacylglycerol hydrolysis[77].

The activity of lipases depends on their intracellular localization and interactions with cofactors (FIG. 4). ATGL is located on lipid droplets and different lipid droplet-associated proteins regulate its activity. For example, CGI-58 (encoded by *ABHD5*) is essential for full ATGL activation in stimulated lipolytic states. Mutations in *ABHD5* lead to TAG accumulation in adipose tissue in mice and humans[78,79]. Conversely, ATGL activity is inhibited by G0S2 and CIDEC (also known as FSP27) by their direct interaction with ATGL[80-83]. Perilipin 1 (PLIN1) is a major protein of the adipocyte lipid droplet and inhibits ATGL function by sequestrating CGI-58 in basal conditions[84]. When lipolysis is stimulated, phosphorylation of PLIN1 promotes the release of CGI-58 from PLIN1, allowing it to interact with ATGL. PLIN1 also increases HSL activity by binding directly to HSL[85]. The fatty acid-binding protein FABP4 also binds to the phosphorylated HSL and translocates to the lipid droplet to regulate HSL lipolytic activity[86,87]. PTRF (encoded by *CAVIN1*) interacts with caveolin 1 (encoded by *CAV1*) to stabilize caveolae, which are small invaginations of the plasma membrane that control lipid trafficking; PTRF promotes lipolysis by recruiting HSL to caveolae[88,89]. Human adipocytes express another member of the CIDE family of proteins, CIDEA, at higher levels than mouse white adipocytes[90,91]. CIDEA is localized to lipid droplets, where it controls basal lipolysis, but also to the nucleus, where it acts as a transcription cofactor[92-94]. In white adipocytes, shuttling of proteins between lipid droplets and the nucleus is a novel and potentially important level of regulation connecting transcriptional control and metabolic pathways. Proteomic studies have identified other lipid droplet-associated proteins that are involved in lipid droplet maturation and fatty acid storage as well as proteins with unknown roles, which require further study to determine their function[95].

In addition to the classic lipolysis pathway involving neutral lipases, other lipolytic pathways have been described. In vitro experiments suggest that lipophagy contributes to β-adrenergic-receptor-stimulated lipolysis[96]. Mice with adipocyte-specific knockout of *Atg7*, a crucial macroautophagy gene, had decreased WAT mass with appearance of brown fat-like adipocytes [97,98], a phenotype that might result from an impairment of adipocyte differentiation rather than an inhibition of lipolysis in mature adipocytes. In addition, a lipase-independent pathway of lipid mobilization through release of lipid droplet-derived exosome-like vesicles has been described [99]. In mice, WAT releases ~1–2% of its lipid content each day via exosomes. Overall, several new lipid degradation pathways that are independent of neutral lipases have been described in the last few years. However, their importance in lipid droplet TAG hydrolysis and regulation in pathophysiological conditions remains unclear.

Glucose metabolism

It has now been repeatedly shown that adipose tissue expression of lipogenic enzymes and cognate transcription factors, notably carbohydrate-responsive element-binding protein (ChREBP), is strongly and positively correlated with insulin sensitivity, suggesting that DNL plays a part in adipocyte and whole-body metabolism that extends beyond the simple production of fatty acids for storage[100-103]. There is evidence that DNL serves as a regulator of adipocyte membrane fluidity and insulin signalling[103,104]. As described below, DNL may also interact with other metabolic pathways and modulate the production of lipid species that control systemic insulin sensitivity. Furthermore, adipocyte-specific *Fasn*-deficiency in mice suggests that products of DNL are involved in sympathetic neuronal signalling, conversion of white adipocytes into beige adipocytes and in the promotion of thermogenic activity in brown adipose tissue (BAT) [105,106].

Somewhat surprisingly, the important early steps of glucose metabolism have not been thoroughly studied in adipocytes; notably, the role of adipocyte glycolysis is poorly documented. During fasting and starvation, induction of aerobic glycolysis is mediated by the forkhead transcription factors FOXK1 and FOXK2[107]. This reprogramming of cellular metabolism results in enhanced production of lactate (FIG. 3). Three decades ago, white adipocytes were shown to be important producers of lactate [108], which was later confirmed in humans and has been recently reassessed using tracer labelling[109,110]. In vivo, the impairment of lactate production by the *Drosophila* fat body, which has features of mammalian WAT and liver, results in enhanced whole-body glucose utilization[110]. Lactate production by WAT therefore seems to contribute to whole-body lactate turnover. Lactate is a metabolic intermediate that can feed into the TCA cycle in most tissues, including the liver, for gluconeogenesis [111]. Lactate production enables the uncoupling of glycolysis and the TCA cycle, notably in the fasted state[112]. This uncoupling may reduce whole-body glucose utilization and be part of a complex regulation of glucose carbon fate in the adipocyte that includes lactate production, glycerol-3-phosphate synthesis, DNL and glucose oxidation. The investigation of functional heterogeneity among white adipocytes identified a population with enhanced glycolytic metabolism whereas another population showed increased DNL[113,114]. These populations co-exist within a single fat depot but their relative proportions differ from one depot to another. WAT heterogeneity has been reviewed elsewhere [115,116], however, the physiological and pathophysiological importance of this heterogeneity remains to be established.

Energy dissipation

Mammalian cells rely on several mechanisms to dissipate energy. Mitochondrial oxidative respiration can be a major contributor to heat production. Substrate cycles, sometimes improperly referred to as futile cycles, may also contribute to energy dissipation and are viewed as essential for metabolic control[117]. Brown and beige adipocytes have the unique capacity to oxidize fatty acids at very high rates. Compared with white adipocytes, thermogenic adipocytes are uniquely equipped to dissipate energy as heat instead of storing energy in chemical forms. Strong evidence exists to support *de novo* differentiation of thermogenic adipocytes from progenitor cells[118]. Early studies suggesting direct conversion of white adipocytes into beige adipocytes during cold exposure or treatments with β_3-adrenergic and PPAR agonists have been confirmed[119-122]. In this Review, we focus on the interconversion of unilocular white adipocytes into beige adipocytes.

The prototypical adaptive thermogenesis pathway in beige adipocytes involves uncoupling protein 1 (UCP1)[14]. UCP1 is located in the mitochondrial inner membrane, where it dissipates the proton electrochemical gradient across the lipid bilayer, which is then no longer available to be used for ATP synthesis (FIG. 5a). UCP1 is one among many components that constitute a cellular machinery that allows energy dissipation as heat. During white-to-beige conversion of human adipocytes, mitochondrial fragmentation from sustained fission results in enhanced UCP1-dependent uncoupling of respiration[123]. Moreover, the interconversion provokes a major metabolic reprogramming with induction of fatty acid anabolic and catabolic pathways in the cytosol and the mitochondria[124]. Inhibition of the pyruvate dehydrogenase complex through its phosphorylation by pyruvate dehydrogenase kinase 4 redirects glucose from oxidation towards TAG synthesis and favours the use of fatty acids as an energy source by uncoupled mitochondria. Independently of the control of UCP1 expression and activity by the adrenergic signalling pathway, succinate, an intermediate in the TCA cycle, participates in activation of UCP1-mediated thermogenesis by stimulating the production of reactive oxygen species in brown and beige fat[125]. Moreover, extracellular succinate is readily taken up by brown adipocytes to be oxidized. The response of human beige adipocytes to extracellular succinate has not been established. Whether succinate activates thermogenesis during conditions that are known to induce its release, such as physical exercise and ischaemia, is not known[125,126].

Conversely, brown-to-white adipocyte conversion is observed during adaptation to thermoneutral environments in mice and during ageing in both mice and humans. Whitened brown adipocytes show a unilocular lipid droplet that is typical of white adipocytes but their mitochondria, with low UCP1 content, retain brown-adipocyte-like features. As in hypertrophic and dysfunctional white adipocytes, whitened brown adipocytes show inflammasome activation that may favour pyroptotic cell death [127]. During warming, beige but not brown adipocytes display chromatin remodelling towards that of the white state[128]. However, beige adipocytes retain an epigenomic memory that allows reactivation of a thermogenic programme following re-exposure to cold. These data support a full bidirectional interconversion between white and beige adipocytes, whereas unilocular white-like adipocytes in BAT may constitute hidden brown adipocytes. Specific chromatin-remodelling enzymes modulate this interconversion. Histone methylation is chemically stable and thus may act as a long-term cell memory mechanism. Several enzymes that regulate methylation of histone lysine residues, notably members of the lysine (K)-specific demethylase (KDM) family, are involved in the control of beige adipocyte metabolism[129]. The most studied family member is KDM1A, which activates a beiging programme while repressing WAT-specific genes by interacting with the thermogenic transcription factors ZFP516 and PRDM16[130-132]. Collectively, data on the various enzymes point to an essential role of demethylation of histone H3 lysine residues in the maintenance of a beige phenotype.

In recent years, several UCP1-independent thermogenic processes in beige and white adipocyte metabolism have been characterized [14] (FIG. 5b). The TAG–fatty acid cycle is a long-recognized substrate cycle in adipocytes. During lipolysis, breakdown of TAG by lipases releases fatty acids and glycerol, which are either exported from the adipocyte or oxidized. The phosphorylation of glycerol by glycerol kinase and activation of fatty acids to form acyl-CoAs allow re-esterification to TAG. The expression and activity of glycerol kinase is much lower in human white adipocytes than in brown or beige adipocytes[124]. However, glycerol kinase can be induced in white adipocytes following adrenergic activation and PPAR agonist treatments, allowing the fine-tuning of fatty acid fate between release, oxidation and esterification[133,134]. As such, the energy cost of the TAG–fatty acid cycle is low. However, when other pathways such as DNL and fatty acid oxidation are integrated, prototypical white fat may significantly contribute to energy dissipation and a lean phenotype in mice[135]. In malignant hyperthermia, an uncontrolled release of intracellular Ca^{2+} from skeletal muscle sarcoplasmic reticulum results in hypermetabolism and heat production. Similarly, cold-induced thermogenesis may occur in beige fat when ATP-dependent Ca^{2+} cycling by sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase and the ryanodine receptor is enhanced[136]. The functional importance of the ATP-dependent Ca^{2+} cycling was shown in beige adipocytes in pigs (*Sus scrofa domesticus*) lacking functional UCP1[136]. In addition, evidence exists for a mitochondrial substrate cycle that is regulated by creatine to drive thermogenic respiration when ADP is limiting in beige fat[137,138]. Irrespective of the occurrence or not of UCP1-dependent thermogenic proton leak, beige adipocytes exhibit this futile creatine cycling, which contributes to the basal metabolic rate of cells rather than being a response to acute adrenergic stimulation[139]. The selective reduction of creatine transport in adipocytes results in impaired adrenergic thermogenesis[140]. The expression of the creatine transporter in human subcutaneous adipocytes is negatively correlated with obesity and insulin resistance[140]. These data therefore suggest a role for extracellular creatine in the control of beige-fat-mediated energy expenditure. An additional example of UCP1-independent thermogenesis in subcutaneous WAT is provided by mice with genetic activation of AMP kinase that show increased energy expenditure[141], although the molecular pathway involved has yet to be identified.

From a metabolic standpoint, the colour of an adipocyte can therefore be considered to be defined by the metabolic machinery that enables the use of different substrates.

Crosstalk between metabolic pathways

Lipolysis and lipogenesis in WAT are typically viewed as independent pathways with opposite outcomes. However, chronic adrenergic activation promotes not only TAG hydrolysis but also DNL and lipid turnover in mouse WAT[142]. Interestingly, ablation of *Pnpla2* diminishes lipolysis, as expected, but also leads to a decrease in lipid turnover owing to downregulation of DNL enzymes (FIG. 6). The exact molecular mechanism underlying the ATGL-mediated and/or lipolysis-mediated induction of DNL following adrenergic activation and its relevance in human WAT are not known. Another example of crosstalk is provided by studies of another neutral lipase highly expressed in adipocytes, HSL. Partial deficiency in HSL improves whole-body insulin sensitivity in obese mice without changes in plasma fatty acid levels, suggesting that mechanisms other than lipolysis are involved[143]. The genetic inhibition of HSL in human adipocytes and mouse WAT also results in enhanced insulin sensitivity and induction of DNL. The fatty acid elongase of very-long chain fatty acid 6 (ELOVL6) shows the highest upregulation among DNL enzymes[103]. ELOVL6, together with stearoyl desaturase, promotes an increase in phospholipid oleic acid content, which increases plasma membrane fluidity and enhances insulin signalling[103]. In adipocytes, ELOVL6 is the main transcriptional target of the glucose-responsive transcription factor ChREBP (encoded by *MLXIPL*). Mechanistically, HSL physically interacts with ChREBPα, thereby impairing ChREBPα translocation to the nucleus and blocking ChREBPα-mediated induction of the transcriptionally highly active isoform ChREBPβ (which is produced from an alternative transcription start site in *MLXIPL*)[103]. The expression of ChREBPβ in WAT is strongly associated with whole-body insulin sensitivity[101-103]. Glucose metabolism is also linked to the metabolism of the branched-chain amino acids (BCAA) leucine, isoleucine and valine. In contrast to the beneficial effects of BCAAs on protein synthesis in conditions such as ageing or cachexia, elevated blood levels of BCAAs are associated with obesity, insulin resistance, T2DM and cardiovascular diseases in humans[144,145]. Mendelian randomization analysis in a large number of individuals is consistent with a causal role of BCAA metabolism in the aetiology of T2DM[146].The increased circulating BCAA levels are related in part to decreased oxidation in WAT owing to suppressed expression of catabolic enzymes[147,148]. Protein catabolism may provide BCAAs to support mitochondrial metabolism and DNL. *In vitro*, catabolized BCAAs can account for up to one third of the lipogenic acetyl-CoA pool in mouse and human white adipocytes[149]. Moreover, an unexpected link between mitochondrial BCAA catabolism and DNL has been identified.

In adipose tissue, enzyme promiscuity of fatty acid synthase and carnitine acetyltransferase supports the synthesis of monomethyl branched-chain fatty acids from BCAAs, which are incorporated into TAG[150]. The physiological conditions in which this pathway is important have not yet been established. Branched-chain are mobilized during fasting and their turnover is decreased with a high-fat diet, although their role and importance in these conditions is unknown. Conversely, mice with enhanced glucose transport in adipocytes show decreased expression of BCAA-metabolizing enzymes in WAT[151]. How glucose metabolism regulates BCAA enzyme expression has not yet been described. These studies describe a few examples of the interplay between glucose, fatty acid and amino acid metabolism in the adipocyte. Advanced systems-biology approaches aimed at building genome-scale metabolic models of the adipocyte may help us to better understand the crosstalk between metabolic pathways[152,153].

Adipocyte metabolic dysfunction

Adipocyte lipid droplet disorders

An excess or a lack of WAT may cause similar pathological conditions. In both situations, inadequate storage in subcutaneous WAT favours lipid spill-over to other depots and organs, such as visceral fat, liver, skeletal muscle and pancreatic β-cells[154,155]. The resulting lipid toxicity leads to altered metabolic function in these organs and subsequently causes an adverse cardiometabolic phenotype. In this respect, inherited lipodystrophies are valuable models of impaired adipocyte metabolism with clinical relevance. Disease-associated variants in *AGPAT2* and *CAVIN1* cause forms of congenital generalized lipodystrophies, which are rare autosomal recessive disorders characterized by a near complete lack of adipose tissue[156,157] (FIG. 3 and 4).

Mutations in the genes encoding the three lipid-droplet-associated proteins PLIN1, HSL and CIDEC cause forms of familial partial lipodystrophies, which are autosomal recessive or autosomal dominant disorders characterized by varying degrees of body-fat loss in different fat depots[76,158,159]. Broadly speaking, the extent of fat loss governs the severity of complications, such as insulin resistance, dyslipidaemia, hepatic steatosis and polycystic ovary syndrome. In the general population, there is genetic evidence that a limited capacity of peripheral WAT to store surplus energy is implicated in human insulin resistance[160] (BOX 2), suggesting that common genetic variation influences cardiometabolic disease risk through lipodystrophy-like mechanisms. Of note, the inability to form or expand fat depots may occur despite an increase in adipocyte size. Collectively, studies in humans and transgenic mouse models reveal that the metabolic dysfunction in lipodystrophies and obesity are similar[24,155].

Hepatic glucose production

Compelling evidence exists that dysfunction of fatty acid metabolism in adipocytes has a systemic impact. The basal rate of lipolysis is positively associated with insulin resistance, independently of body mass index and age[143]. In prospective cohorts, high basal and low stimulated lipolysis at baseline predict later development of insulin resistance[161]. Evidence for the contribution of adipocyte lipolysis to insulin resistance also comes from lipase-deficient mouse models and patients with *PLIN1*-deficiency[70,71,143,158]. An impaired insulin-mediated suppression of hepatic glucose production is a prominent feature of insulin resistance (FIG. 7). Acute suppression of hepatic glucose production by insulin involves insulin-induced inhibition of WAT lipolysis. A reduction in fatty acid flux to the liver lowers hepatic acetyl-CoA concentrations and glucose production through decreased pyruvate carboxylase activity[162]. The antilipolytic action of insulin is impaired in rodents with insulin resistance induced by a high-fat diet, thereby promoting hepatic glucose production. However, several studies in rodents and dogs suggest that the direct effects of insulin on hepatocytes are dominant over the contributions of extrahepatic tissues (such as adipose tissue) in the control of hepatic glucose production[163,164]. Whether the direct or the indirect (that is, anti-lipolytic) effects of insulin are more important in the regulation of hepatic glucose production seems to depend on the experimental context. Despite a wealth of studies, several questions remain unanswered. Lipolysis-derived fatty acids in hepatocytes have several fates when entering the liver. The relative contributions of fatty acids to different metabolic pathways, notably TAG synthesis and fatty acid oxidation, which vary according to physiological and pathological states, will modulate the impact of insulin in control of hepatic glucose metabolism. The importance of chronic delivery of lipolysis-derived fatty acids in obesity-associated insulin resistance is not firmly established in humans. A systematic review of the literature revealed that circulating levels of non-esterified fatty acids (NEFAs) in fasting conditions are poorly correlated with body fat and insulin sensitivity in humans[165,166]. The kinetics of when insulin resistance occurs in the liver and WAT are also not well-characterized in humans. The onset of insulin resistance in the two tissues may differ among obese individuals.

Tumour aggressiveness and cachexia

In addition to their role in diabetes and cardiovascular risk, adipocyte lipolysis and white fat metabolism play a role in the development of some cancers and in cancer-associated cachexia[167]. In breast cancer, the secretory activity of tumour cells promotes depletion of lipids in surrounding adipocytes, which results in a massive release of fatty acids[168]. The uptake of these fatty acids by breast cancer cells induces a profound metabolic remodelling leading to enhanced tumour aggressiveness[168]. Cancer-associated cachexia is a life-threatening condition in which loss of fat mass may precede the loss of lean mass[169,170]. Increased stimulated lipolysis and increased circulating NEFA and glycerol levels are observed in some patients and animal models with cancer-associated cachexia[169,171,172]. A reduced loss of body weight and skeletal muscle mass has been reported in tumour-bearing ATGL-deficient mice[171]. The inhibition of lipolysis and DNL in white adipocytes by blocking the interaction between CIDEA and the cellular energy homeostasis regulator AMP kinase partially protects against loss of fat mass and prolongs the resistance of tumour-bearing mice to cachexia[172]. One can hypothesize that increased production of fatty acids favours the accumulation of lipids and lipotoxic species in skeletal muscle, which participate in the development of muscular atrophy[173,174].

Effects of fatty acids on macrophages

White adipocyte-derived fatty acids have emerged as important modulators of macrophage metabolism. In conditions of chronic activation of lipolysis, fatty acids released from adipocytes are taken up by macrophages, leading to lipid accumulation in these immune cells[175,176]. This fatty acid-scavenging role is reminiscent of foam cell accumulation of cholesteryl esters in atherosclerotic plaques. In mouse models, obesity is associated with an accumulation of lipid droplets in macrophages and activation of lysosome biogenesis, resulting in TAG catabolism[177]. Alternatively, as mentioned above, these lipids in adipose tissue macrophages may originate from lipid-droplet-derived exosome-like vesicles released by adipocytes[99]. Therefore, the net release of fatty acids from WAT could be controlled concomitantly by adipocyte lipid mobilization and adipose tissue macrophage lysosomal activity. The importance of adipocytes and macrophages in WAT fatty acid release in humans is currently unknown. Whether these buffering mechanisms substantially affect the circulating levels of fatty acids that are available for storage as ectopic lipids in other organs, and thus mitigate the detrimental effect of exacerbated WAT lipolysis, remains to be determined.

Earlier studies suggested that fatty acids released from adipocytes may have an impact on other adipose cell types and thereby have an indirect systemic effect. The crosstalk between adipocytes and other cell types in WAT contributes to modulation of the immune response and fibrosis[178] (BOX1, FIG. 7). This tissue remodelling alters the secretory profile of stromavascular cells, which produce molecules that may have endocrine actions[15]. Hypertrophic adipocytes under severe metabolic stress are prone to pyroptosis, a pro-inflammatory form of programmed cell death[179]. The increased number of dying adipocytes in obese WAT provokes recruitment of macrophages, forming crown-like structures[180,181]. The recruited macrophages show a pro-inflammatory M1-like phenotype and produce an array of cytokines and chemokines. The pathogenetic role of so-called low-grade inflammation in adipose tissue in the development of obesity and insulin resistance is well-documented[182]. However, the relative importance of the pro-inflammatory M1-like phenotype and lipid trafficking in WAT macrophages during obesity and fasting in humans and mice is unclear and may vary according to the anatomical location of fat depots. Notwithstanding these features of adipose tissue macrophages, the studies summarized here indicate that adipocyte metabolism may be the main driver of the immune response in WAT. Accordingly, transcriptomic analysis of WAT from women with different degrees of obesity and metabolic impairment showed a tight inverse correlation between the expression of adipocyte genes involved in lipid and glucose metabolism and of macrophage genes involved in the immune response, both in subcutaneous and in visceral fat depots[147]. Of note, the induction of insulin resistance in mouse white adipocytes induces a macrophage pro-inflammatory response[183]. Adipose tissue inflammation may therefore be considered a local adaptation to primary dysfunction in adipocyte metabolism. Different metabolic impairments in the adipocyte may be envisaged to have different local consequences. This viewpoint may help to reconcile apparently contradictory findings, such as the possible occurrence of insulin resistance in the absence of WAT inflammation, as observed in *Cidec*-null mice fed a high-fat diet[184].

Bioactive lipid and lipocalin secretion

In addition to the production of fatty acids, adipocytes can modulate systemic insulin sensitivity through the secretion of other bioactive lipid products (FIG. 7). The monounsaturated fatty acid (MUFA) palmitoleate (C16:1n-7) is the second most abundant MUFA in human blood and adipose tissue[185]. Palmitoleate was identified as an adipocyte-specific, DNL-derived fatty acid with insulin-sensitizing properties in mice[186]. However, the positive association between circulating levels of palmitoleate and insulin sensitivity in humans is debated[187]. Differences in synthesis between the main sites of production of circulating palmitoleate, WAT and liver, as well as differences in DNL between rodents and humans may explain some of the discrepancies[59]. Nevertheless, a recent longitudinal study of a large cohort of non-diabetic individuals showed, after adjustment for potential confounders, notably NEFA, that circulating palmitoleate is an independent determinant of insulin sensitivity[188]. Large-scale intervention studies are now warranted to establish the causal role of palmitoleate in preserving insulin sensitivity. A new class of fatty acids, fatty acid-hydroxyl-fatty acids (FAHFAs), has been identified in WAT and serum of mice overexpressing GLUT4 in adipocytes[189]. FAHFAs can be stored in adipocyte TAGs and mobilized through lipolysis[190]. In humans, levels of FAHFAs composed of palmitic and stearic acids have been reported to be lower in serum and adipocytes of insulin-resistant individuals[189,191]. FAHFAs exert a beneficial effect on insulin sensitivity, through the promotion of insulin secretion, an increase in adipocyte glucose uptake and the inhibition of WAT inflammation and hepatic glucose production[189,192,193]. The pharmacological administration of FAHFAs in mice has yielded conflicting data on insulin sensitivity[189,192,194]. There are methodological issues in studying this class of lipids that require cross-validation between laboratories[194,195]. In WAT, FAHFA levels are under the control of ChREBP[196]. The threonine hydrolases AIG1 and ATRP have been shown to participate in the degradation of FAHFAs but the enzymes responsible for their synthesis are still unknown[197]. The combined deficiency of these two threonine hydrolases resulted in increased FAHFA levels in WAT but not in plasma and does not restore insulin sensitivity in mice fed a high fat diet. An inhibitor of the threonine hydrolases that can be administered in vivo has been synthesized[197]. Whether chronic treatment with this inhibitor would improve insulin sensitivity in rodent models of insulin resistance needs to be assessed. In brown and beige fat, an oxidized metabolite of linoleic acid, 12,13-diHOME, is produced during cold exposure and promotes thermogenesis by increasing fatty acid uptake in adipocytes[198]. Plasma levels of 12,13-diHOME are negatively associated with body mass index and insulin resistance in different cohorts of individuals with various degrees of fat mass and glucose tolerance[198,199]. In addition to a paracrine effect on BAT, increased secretion of 12,13-diHOME in response to exercise promotes fatty acid uptake in skeletal muscle[198,200]. Ceramides are potential lipid mediators of insulin resistance[201]. In adipocytes, inhibiting the synthesis or activating the degradation of ceramide leads to systemic improvement in metabolic parameters, notably by reducing adipose tissue inflammation and liver steatosis[201-203]. Of note, the modulation of ceramide metabolism has similar effects in the liver and there is efficient exchange of these lipid species between WAT and liver to maintain metabolic homeostasis.

Adipocytes also secrete a wide range of lipocalins, which transport fatty acids and other lipid species. A prototypical example is the fatty acid-binding protein FABP4[15], which plays a part in intracellular lipolysis but is also secreted through a non-classical pathway when lipolysis is stimulated[204]. Circulating FABP4 activates gluconeogenesis and stimulates hepatic glucose production, favouring the development of diabetes in obese mice[205]. The retinol-binding protein RBP4 is another example of a lipocalin that deleteriously affects insulin sensitivity[15,206]. The expression of RBP4 is elevated in mice with defective adipose tissue glucose transport[207]. RBP4 contributes to the development of insulin resistance through both metabolic and inflammatory effects[207,208].

Therapeutic targeting of WAT metabolism

Drugs that act on WAT metabolism can be effective at treating T2DM, even in the absence of body weight lowering (FIG. 7). Thiazolidinediones (TZDs) provide a proof of principle: this class of drug, which comprises rosiglitazone and pioglitazone, acts on PPARγ, a nuclear factor that is essential for adipogenesis. Whereas high-affinity synthetic agonists such as TZDs are potent adipogenesis activators, the identity of endogenous PPARγ ligands is an old yet unresolved question in the field. Based on the nature of the ligands in this class of nuclear receptors, PPARγ ligands are predicted to be lipids or their derivatives, with eicosanoids and fatty acid metabolites proposed as natural ligands[209]. TZDs promote lipid storage in WAT, improve the secretory profile of adipocytes and decrease WAT inflammation, resulting overall in a robust insulin sensitization[210]. Despite a safety profile that precludes the widespread use of TZDs, there is substantial evidence for the beneficial effects of TZDs beyond plasma glucose lowering and insulin sensitization, notably on atherosclerosis, cardiovascular events and nonalcoholic steatohepatitis[211,212]. Together, these studies show that drugs acting on WAT have the potential to treat diabetes and to decrease the risk of cardiometabolic diseases.

Controlling fatty acid release from WAT is an attractive avenue to achieve insulin sensitization. In mice, the chronic inhibition of lipolysis using selective inhibitors of HSL or ATGL results in improvement in insulin sensitivity[143,213]. Agonists of anti-lipolytic G_i-coupled receptors are postulated to have similar effects. One such drug is nicotinic acid, which acts through HCAR2 (also known as GPR109A), resulting in acute reduction in NEFA levels [66] (FIG. 4). However, HCAR2-independent mechanisms also contribute to the chronic lipid-lowering effects observed with nicotinic acid treatment[214,215]. The worsening, rather than expected improvement, of glycaemic control observed during chronic nicotinic acid treatment may be due to the development of tolerance that occurs with prolonged nicotinic acid treatment and/or to a major rebound in NEFA levels observed during rapid nicotinic acid washout[216]. An intermittent dosing strategy is successful in retaining the ability of nicotinic acid to lower NEFA levels and improves insulin sensitivity[217,218]. A well-defined nicotinic acid exposure, timed to feeding periods, profoundly improves metabolic profile in obese Zucker rats. Inhibiting lipolysis via other receptors may be able to circumvent the problems of tolerance and NEFA rebound observed with HCAR2 agonists.

HCAR1 (also known as GPR81) is, like HCAR2, an anti-lipolytic G_i-coupled receptor[66]. Chronic dosing with HCAR1 agonists in obese and insulin-resistant mice leads to robust insulin-sensitizing and antidiabetic effects in the absence of body weight changes[219]. However, an unexpected hypertensive effect is observed owing to activation of HCAR1 in the microvasculature of the kidney, which precluded further testing in humans[219]. Nevertheless, these results show that the inhibition of lipolysis holds promise for improving insulin sensitivity. The inhibition of adipocyte lipolysis could also counteract the development of cancer-associated cachexia, as convincingly shown in mice[169].

Conversely, activating lipolysis coupled to fatty acid utilization is another strategy to modulate blood glucose levels and insulin sensitivity. The mobilization of fatty acids from WAT is crucial in providing substrates to promote energy expenditure. Such a link is probably altered during ageing, which is associated with a decline in various components of energy expenditure[220]. A recent longitudinal study in women revealed an age-related decrease in catecholamine-induced lipolysis in subcutaneous WAT[221]. The stimulation of adipocyte lipolysis may be considered as a therapeutic approach only if fatty acid utilization is not rate-limiting as, otherwise, fatty acids are likely to be deposited in non-adipose tissues and contribute to a worsening of insulin resistance. In this regard, caution should be exercised when comparing the effects of lipolysis activation in humans and rodents, as mice and rats have larger amounts of active BAT and a higher capacity to oxidize lipids[222]. Combined with the interspecific differences in tissue distribution of the β_3 adrenoceptor among fat depots, these differences explain the much greater beneficial effects of β_3 adrenergic agonists in rodents than in humans.

Targeting adipose tissue also has the potential to achieve a safe increase in energy expenditure by increasing thermogenesis through either browning of WAT or acting on substrate cycles and UCP1-independent thermogenic processes in WAT [223]

(FIG. 5). However, a negative energy balance seems to be a prerequisite for weight reduction; increasing fatty acid oxidation alone has little impact on overall adiposity and body weight[224]. Moreover, the relative contribution of different targetable thermogenic pathways in various fat depots to increased energy expenditure is still not firmly established in adult humans. Other recently identified pathways in white adipocytes may be of interest. For example, activating white adipocyte DNL may be beneficial given the strong positive association between this pathway and insulin sensitivity in humans[100,102]. However, activating DNL in the liver is generally considered to be detrimental, as hepatic DNL is increased during the development of fatty liver disease[59]. As HSL is expressed at very low levels in the liver, disrupting the interaction between HSL and ChREBP may constitute an adipocyte-specific mechanism to enhance DNL and insulin signalling[103].

As illustrated with the use of TZDs and HCAR2 and HCAR1 agonists, safety concerns can derail clinical development of molecules targeting WAT metabolism. The development of more targeted drugs or restricting the action of a drug to an intended tissue or cell type may avoid off-target effects in the future. Genes with tissue-specific expression are enriched among targets of marketed non-oncology drugs[225] but such an enrichment is not found among drugs in early-phase clinical trials. For novel therapeutic targets under consideration, priority should therefore be given to those drugs that target genes that are highly or exclusively expressed in adipocytes.

Conclusions and future perspectives

An outstanding issue in adipose research is WAT heterogeneity, which may comprise a minimum of four levels. First, WAT is distributed among many different fat depots that differ in their anatomical location and function[226,227]. Subcutaneous and visceral adipose depots are generally considered to have opposite roles in the development of insulin resistance and diabetes. However, a full parallel metabolic characterization of adipocytes in these two depots is still lacking in humans. The contribution of adipocytes in smaller depots, such as bone marrow, perivascular, mammary, epicardial, joint, dermal, retro-orbital and plantar WAT, to overall metabolism and organ function is not yet resolved. Second, sex differences in WAT exist, and dynamic changes occur in WAT over a lifetime [228-230]. Ageing-related and sex-specific physiological states, such as pregnancy, lactation and menopause, are accompanied by changes in adipocyte metabolism, which are not well characterized. Regarding these two layers of heterogeneity, differences between mice and humans require that extrapolating insights from mouse studies to humans must be done with extreme caution.

Each fat depot contains many different cell types in the stroma-vascular fraction, conferring a third layer of heterogeneity (BOX 1). The extent of immune cell infiltration, vascularization and innervation differs greatly between the depots[226,227]. Adipocytes themselves come in different colours, that is, white, brown and beige, which are associated with different intrinsic properties; the recently recognized diversity among each category of adipocytes within a fat depot represents a fourth layer of heterogeneity. Several populations of white adipocytes with unique metabolic properties and differential responses to exogenous stimuli have been characterized[113,114]. A subset of human adipocytes lacking the lipolytic β_2-adrenoceptor has recently been shown to be enriched in subcutaneous WAT of metabolically impaired individuals with obesity[231]. Similarly, not all beige adipocytes share similar metabolic features. A population with high glucose uptake and oxidation capacity has been identified in mice lacking β-adrenergic signalling[232]. Whether this specific population exists in substantial amounts in human fat depots is unknown. Single-nucleus RNA sequencing brought new information on adipocyte heterogeneity in mouse and human WAT. A subpopulation of acetate-producing adipocytes decreases the thermogenic capacity of neighbouring adipocytes [233]. As this subpopulation is more represented in human than in mouse adipose tissue, it may contribute to the lower energy dissipation capacity of human adipose tissue.

Recognition of the importance of rhythmic processes and metabolic flexibility is increasing. Besides oscillations in hormones, temperature and feeding behaviour, endogenous circadian clocks found in metabolic tissues ensure proper rhythmicity of metabolism[234]. WAT itself is subject to large variations in gene expression that follow circadian patterns, both in mice and humans. Disruptions in these rhythms, which cause physiological processes to be out of alignment with internal clocks, contribute to insulin resistance[235]. Furthermore, obesity and insulin resistance are associated with a state of metabolic inflexibility, that is, the inability to switch between carbohydrate and lipid utilization during the fed and fasted states, respectively[236]. However, chronically forcing the utilization of a particular energy substrate is contrary to normal physiological processes. Drug and food administration to restricted and specific time periods may avoid some of the deleterious consequences observed with the constant chronic therapeutic manipulation of metabolic pathways[217,237].

Pharmacotherapy is rarely equally effective in all treated patients. This is the case for TZDs, where a substantial fraction of patients with T2DM do not show improvement in insulin sensitivity with treatment[238]. T2DM is a highly heterogeneous disease: cluster analysis based on six simple variables identified five subgroups of patients with T2DM that differed in disease progression and risk of diabetic complications[239,240]. Recent studies indicate the importance of WAT function for the development of whole-body insulin resistance and diabetes in obese individuals. Characterizing the extent of alterations in adipocyte metabolism may allow refined patient stratification and help in identifying individuals who could benefit the most from existing and future drugs in both metabolic diseases and cancer[161,241].

White adipocytes are definitely much more than inanimate fat-laden entities. We believe that targeting WAT holds promise for the treatment of cardiometabolic diseases and other conditions with dysregulation of adipocyte metabolism. Future novel adipocyte-based strategies for the treatment of metabolic diseases may include the conversion of energy-storing white adipocytes into energy-consuming brown-like adipocytes, exploiting both UCP1-dependent and UCP1-independent mechanisms to increase energy expenditure, promoting adipocyte lipid storage and oxidation, and time-dependent activation of glucose and lipid utilization to restore metabolic flexibility. Combinatorial approaches with other pharmacological agents that reduce food intake or increase energy expenditure may be required to promote a catabolic state and fully harness the potential of adipocyte-based therapies.

References

1 Pond, C. M. An evolutionary and functional view of mammalian adipose tissue. *Proc Nutr Soc* **51**, 367-377 (1992).

2 Thiam, A. R. & Beller, M. The why, when and how of lipid droplet diversity. *J Cell Sci* **130**, 315-324 (2017).

3 Rodbell, M. Metabolism of Isolated Fat Cells. I. Effects of Hormones on Glucose Metabolism and Lipolysis. *J Biol Chem* **239**, 375-380 (1964).

4 Czech, M. P. Cellular basis of insulin insensitivity in large rat adipocytes. *J Clin Invest* **57**, 1523-1532 (1976).

5 Cushman, S. W. & Wardzala, L. J. Potential mechanism of insulin action on glucose transport in the isolated rat adipose cell. Apparent translocation of intracellular transport systems to the plasma membrane. *J Biol Chem* **255**, 4758-4762 (1980).

6 Suzuki, K. & Kono, T. Evidence that insulin causes translocation of glucose transport activity to the plasma membrane from an intracellular storage site. *Proc Natl Acad Sci U S A* **77**, 2542-2545 (1980).

7 Hotamisligil, G. S., Shargill, N. S. & Spiegelman, B. M. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* **259**, 87-91 (1993).

8 Hu, E., Liang, P. & Spiegelman, B. M. AdipoQ is a novel adipose-specific gene dysregulated in obesity. *J Biol Chem* **271**, 10697-10703 (1996).

9 Maeda, K. *et al.* cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). *Biochem Biophys Res Commun* **221**, 286-289 (1996).

10 Scherer, P. E., Williams, S., Fogliano, M., Baldini, G. & Lodish, H. F. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* **270**, 26746-26749 (1995).

11 Zhang, Y. *et al.* Positional cloning of the mouse obese gene and its human homologue. *Nature* **372**, 425-432 (1994).

12 Lafontan, M. Historical perspectives in fat cell biology: the fat cell as a model for the investigation of hormonal and metabolic pathways. *Am J Physiol Cell Physiol* **302**, C327-359 (2012).

13 Guilherme, A., Henriques, F., Bedard, A. H. & Czech, M. P. Molecular pathways linking adipose innervation to insulin action in obesity and diabetes mellitus. *Nat Rev Endocrinol* **15**, 207-225 (2019).

14 Chouchani, E. T. & Kajimura, S. Metabolic adaptation and maladaptation in adipose tissue. *Nat. Metab.* **1**, 189–200 (2019).

15 Scheja, L. & Heeren, J. The endocrine function of adipose tissues in health and cardiometabolic disease. *Nat Rev Endocrinol* **15**, 507-524 (2019).

16 Vishvanath, L. & Gupta, R. K. Contribution of adipogenesis to healthy adipose tissue expansion in obesity. *J Clin Invest* **129**, 4022-4031 (2019).

17 Ghaben, A. L. & Scherer, P. E. Adipogenesis and metabolic health. *Nat Rev Mol Cell Biol* **20**, 242-258 (2019).

18 Stenkula, K. G. & Erlanson-Albertsson, C. Adipose cell size: importance in health and disease. *Am J Physiol Regul Integr Comp Physiol* **315**, R284-R295 (2018).

19 Engfeldt, P. & Arner, P. Lipolysis in human adipocytes, effects of cell size, age and of regional differences. *Horm Metab Res Suppl* **19**, 26-29 (1988).

20 Laforest, S., Labrecque, J., Michaud, A., Cianflone, K. & Tchernof, A. Adipocyte size as a determinant of metabolic disease and adipose tissue dysfunction. *Crit Rev Clin Lab Sci* **52**, 301-313 (2015).

21 Pausova, Z. From big fat cells to high blood pressure: a pathway to obesity-associated hypertension. *Curr Opin Nephrol Hypertens* **15**, 173-178 (2006).

22 Arner, P. & Spalding, K. L. Fat cell turnover in humans. *Biochem Biophys Res Commun* **396**, 101-104 (2010).

23 Tandon, P., Wafer, R. & Minchin, J. E. N. Adipose morphology and metabolic disease. *J Exp Biol* **221** (2018).

24 Rutkowski, J. M., Stern, J. H. & Scherer, P. E. The cell biology of fat expansion. *J Cell Biol* **208**, 501-512 (2015).

25 Berry, R., Jeffery, E. & Rodeheffer, M. S. Weighing in on adipocyte precursors. *Cell Metab* **19**, 8-20 (2014).

26 Christodoulides, C., Lagathu, C., Sethi, J. K. & Vidal-Puig, A. Adipogenesis and WNT signalling. *Trends Endocrinol Metab* **20**, 16-24 (2009).

27 Ma, X., Wang, D., Zhao, W. & Xu, L. Deciphering the Roles of PPARgamma in Adipocytes via Dynamic Change of Transcription Complex. *Front Endocrinol (Lausanne)* **9**, 473 (2018).

28 Shan, T., Liu, J., Wu, W., Xu, Z. & Wang, Y. Roles of Notch Signaling in Adipocyte Progenitor Cells and Mature Adipocytes. *J Cell Physiol* **232**, 1258-1261 (2017).

29 Fernando, R. *et al.* Low steady-state oxidative stress inhibits adipogenesis by altering mitochondrial dynamics and decreasing cellular respiration. *Redox Biol* **32**, 101507 (2020).

30 Wang, S. *et al.* Adipocyte Piezo1 mediates obesogenic adipogenesis through the FGF1/FGFR1 signaling pathway in mice. *Nat Commun* **11**, 2303 (2020).

31 Sakaguchi, M. *et al.* Adipocyte Dynamics and Reversible Metabolic Syndrome in Mice with an Inducible Adipocyte-Specific Deletion of the Insulin Receptor. *Cell Metab* **25**, 448-462 (2017).

32 Wang, Q. A. *et al.* Reversible De-differentiation of Mature White Adipocytes into Preadipocyte-like Precursors during Lactation. *Cell Metab* **28**, 282-288 e283 (2018).

33 Sebo, Z. L. & Rodeheffer, M. S. Assembling the adipose organ: adipocyte lineage segregation and adipogenesis in vivo. *Development* **146** (2019).

34 Raajendiran, A. *et al.* Identification of Metabolically Distinct Adipocyte Progenitor Cells in Human Adipose Tissues. *Cell Rep* **27**, 1528-1540 e1527 (2019).

35 Gavin, K. M. *et al.* De novo generation of adipocytes from circulating progenitor cells in mouse and human adipose tissue. *FASEB J* **30**, 1096-1108 (2016).

36 Ryden, M., Andersson, D. P., Bernard, S., Spalding, K. & Arner, P. Adipocyte triglyceride turnover and lipolysis in lean and overweight subjects. *J Lipid Res* **54**, 2909-2913 (2013).

37 Walker, G. E., Marzullo, P., Ricotti, R., Bona, G. & Prodam, F. The pathophysiology of abdominal adipose tissue depots in health and disease. *Horm Mol Biol Clin Investig* **19**, 57-74 (2014).

38 Hoffstedt, J. *et al.* Regional impact of adipose tissue morphology on the metabolic profile in morbid obesity. *Diabetologia* **53**, 2496-2503 (2010).

39 Veilleux, A., Caron-Jobin, M., Noel, S., Laberge, P. Y. & Tchernof, A. Visceral adipocyte hypertrophy is associated with dyslipidemia independent of body composition and fat distribution in women. *Diabetes* **60**, 1504-1511 (2011).

40 Verboven, K. *et al.* Abdominal subcutaneous and visceral adipocyte size, lipolysis and inflammation relate to insulin resistance in male obese humans. *Sci Rep* **8**, 4677 (2018).

41 Lonn, M., Mehlig, K., Bengtsson, C. & Lissner, L. Adipocyte size predicts incidence of type 2 diabetes in women. *FASEB J* **24**, 326-331 (2010).

42 Weyer, C., Foley, J. E., Bogardus, C., Tataranni, P. A. & Pratley, R. E. Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. *Diabetologia* **43**, 1498-1506 (2000).

43 White, U. & Ravussin, E. Dynamics of adipose tissue turnover in human metabolic health and disease. *Diabetologia* **62**, 17-23 (2019).

44 Spalding, K. L., Bhardwaj, R. D., Buchholz, B. A., Druid, H. & Frisen, J. Retrospective birth dating of cells in humans. *Cell* **122**, 133-143 (2005).

45 Spalding, K. L. *et al.* Dynamics of fat cell turnover in humans. *Nature* **453**, 783-787 (2008).

46 Arner, E. *et al.* Adipocyte turnover: relevance to human adipose tissue morphology. *Diabetes* **59**, 105-109 (2010).

47 Arner, P. *et al.* Dynamics of human adipose lipid turnover in health and metabolic disease. *Nature* **478**, 110-113 (2011).

48 Guillermier, C. *et al.* Imaging mass spectrometry demonstrates age-related decline in human adipose plasticity. *JCI Insight* **2**, e90349 (2017).

49 Spalding, K. L. *et al.* Impact of fat mass and distribution on lipid turnover in human adipose tissue. *Nat Commun* **8**, 15253 (2017).

50 Ibrahim, M. M. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev* **11**, 11-18 (2010).

51 Lee, M. J., Wu, Y. & Fried, S. K. Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications. *Mol Aspects Med* **34**, 1-11 (2013).

52 Arner, P. *et al.* Adipose lipid turnover and long-term changes in body weight. *Nat Med* **25**, 1385-1389 (2019).

53 Kersten, S. Physiological regulation of lipoprotein lipase. *Biochim Biophys Acta* **1841**, 919-933 (2014).

54 Thompson, B. R., Lobo, S. & Bernlohr, D. A. Fatty acid flux in adipocytes: the in's and out's of fat cell lipid trafficking. *Mol Cell Endocrinol* **318**, 24-33 (2010).

55 Coleman, R. A. & Mashek, D. G. Mammalian triacylglycerol metabolism: synthesis, lipolysis, and signaling. *Chem Rev* **111**, 6359-6386 (2011).

56 Coleman, R. A. It takes a village: channeling fatty acid metabolism and triacylglycerol formation via protein interactomes. *J Lipid Res* **60**, 490-497 (2019).

57 Chitraju, C., Walther, T. C. & Farese, R. V., Jr. The triglyceride synthesis enzymes DGAT1 and DGAT2 have distinct and overlapping functions in adipocytes. *J Lipid Res* **60**, 1112-1120 (2019).

58 Chitraju, C. *et al.* Triglyceride Synthesis by DGAT1 Protects Adipocytes from Lipid-Induced ER Stress during Lipolysis. *Cell Metab* **26**, 407-418 e403 (2017).

59 Solinas, G., Boren, J. & Dulloo, A. G. De novo lipogenesis in metabolic homeostasis: More friend than foe? *Mol Metab* **4**, 367-377 (2015).

60 Wallace, M. & Metallo, C. M. Tracing insights into de novo lipogenesis in liver and adipose tissues. *Semin Cell Dev Biol* (2020).

61 Zhao, S. *et al.* ATP-Citrate Lyase Controls a Glucose-to-Acetate Metabolic Switch. *Cell Rep* **17**, 1037-1052 (2016).

62 Guillou, H., Zadravec, D., Martin, P. G. & Jacobsson, A. The key roles of elongases and desaturases in mammalian fatty acid metabolism: Insights from transgenic mice. *Prog Lipid Res* **49**, 186-199 (2010).

63 Aarsland, A., Chinkes, D. & Wolfe, R. R. Hepatic and whole-body fat synthesis in humans during carbohydrate overfeeding. *Am J Clin Nutr* **65**, 1774-1782 (1997).

64 Diraison, F. *et al.* Differences in the regulation of adipose tissue and liver lipogenesis by carbohydrates in humans. *J Lipid Res* **44**, 846-853 (2003).

65 Smith, G. I. *et al.* Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease. *J Clin Invest* (2019).

66 Lafontan, M. & Langin, D. Lipolysis and lipid mobilization in human adipose tissue. *Prog Lipid Res* **48**, 275-297 (2009).

67 Morigny, P., Houssier, M., Mouisel, E. & Langin, D. Adipocyte lipolysis and insulin resistance. *Biochimie* **125**, 259-266 (2016).

68 Langin, D. & Arner, P. Importance of TNFalpha and neutral lipases in human adipose tissue lipolysis. *Trends Endocrinol Metab* **17**, 314-320 (2006).

69 Haemmerle, G. *et al.* Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. *Science* **312**, 734-737 (2006).

70 Ahmadian, M. *et al.* Desnutrin/ATGL is regulated by AMPK and is required for a brown adipose phenotype. *Cell Metab* **13**, 739-748 (2011).

71 Schoiswohl, G. *et al.* Impact of Reduced ATGL-Mediated Adipocyte Lipolysis on Obesity-Associated Insulin Resistance and Inflammation in Male Mice. *Endocrinology* **156**, 3610-3624 (2015).

72 Bezaire, V. *et al.* Contribution of adipose triglyceride lipase and hormone-sensitive lipase to lipolysis in hMADS adipocytes. *J Biol Chem* **284**, 18282-18291 (2009).

73 Fischer, J. *et al.* The gene encoding adipose triglyceride lipase (PNPLA2) is mutated in neutral lipid storage disease with myopathy. *Nat Genet* **39**, 28-30 (2007).

74 Natali, A. *et al.* Metabolic consequences of adipose triglyceride lipase deficiency in humans: an in vivo study in patients with neutral lipid storage disease with myopathy. *J Clin Endocrinol Metab* **98**, E1540-1548 (2013).

75 Haemmerle, G. *et al.* Hormone-sensitive lipase deficiency in mice causes diglyceride accumulation in adipose tissue, muscle, and testis. *J Biol Chem* **277**, 4806-4815 (2002).

76 Albert, J. S. *et al.* Null mutation in hormone-sensitive lipase gene and risk of type 2 diabetes. *N Engl J Med* **370**, 2307-2315 (2014).

77 Taschler, U. *et al.* Monoglyceride lipase deficiency in mice impairs lipolysis and attenuates diet-induced insulin resistance. *J Biol Chem* **286**, 17467-17477 (2011).

78 Lass, A. *et al.* Adipose triglyceride lipase-mediated lipolysis of cellular fat stores is activated by CGI-58 and defective in Chanarin-Dorfman Syndrome. *Cell Metab* **3**, 309-319 (2006).

79 Radner, F. P. *et al.* Growth retardation, impaired triacylglycerol catabolism, hepatic steatosis, and lethal skin barrier defect in mice lacking comparative gene identification-58 (CGI-58). *J Biol Chem* **285**, 7300-7311 (2010).

80 El-Assaad, W. *et al.* Deletion of the gene encoding G0/G 1 switch protein 2 (G0s2) alleviates high-fat-diet-induced weight gain and insulin resistance, and

promotes browning of white adipose tissue in mice. *Diabetologia* **58**, 149-157 (2015).

81 Yang, X. *et al.* The G(0)/G(1) switch gene 2 regulates adipose lipolysis through association with adipose triglyceride lipase. *Cell Metab* **11**, 194-205 (2010).

82 Grahn, T. H. *et al.* Fat-specific protein 27 (FSP27) interacts with adipose triglyceride lipase (ATGL) to regulate lipolysis and insulin sensitivity in human adipocytes. *J Biol Chem* **289**, 12029-12039 (2014).

83 Nishino, N. *et al.* FSP27 contributes to efficient energy storage in murine white adipocytes by promoting the formation of unilocular lipid droplets. *J Clin Invest* **118**, 2808-2821 (2008).

84 Granneman, J. G., Moore, H. P., Krishnamoorthy, R. & Rathod, M. Perilipin controls lipolysis by regulating the interactions of AB-hydrolase containing 5 (Abhd5) and adipose triglyceride lipase (Atgl). *J Biol Chem* **284**, 34538-34544 (2009).

85 Wang, H. *et al.* Activation of hormone-sensitive lipase requires two steps, protein phosphorylation and binding to the PAT-1 domain of lipid droplet coat proteins. *J Biol Chem* **284**, 32116-32125 (2009).

86 Shen, W. J. *et al.* Characterization of the functional interaction of adipocyte lipid-binding protein with hormone-sensitive lipase. *J Biol Chem* **276**, 49443-49448 (2001).

87 Smith, A. J. *et al.* Physical association between the adipocyte fatty acid-binding protein and hormone-sensitive lipase: a fluorescence resonance energy transfer analysis. *J Biol Chem* **279**, 52399-52405 (2004).

88 Aboulaich, N., Ortegren, U., Vener, A. V. & Stralfors, P. Association and insulin regulated translocation of hormone-sensitive lipase with PTRF. *Biochem Biophys Res Commun* **350**, 657-661 (2006).

89 Zhou, S. R. *et al.* Acetylation of Cavin-1 Promotes Lipolysis in White Adipose Tissue. *Mol Cell Biol* **37** (2017).

90 Nordstrom, E. A. *et al.* A human-specific role of cell death-inducing DFFA (DNA fragmentation factor-alpha)-like effector A (CIDEA) in adipocyte lipolysis and obesity. *Diabetes* **54**, 1726-1734 (2005).

91 Puri, V. *et al.* Cidea is associated with lipid droplets and insulin sensitivity in humans. *Proc Natl Acad Sci U S A* **105**, 7833-7838 (2008).

92 Jash, S., Banerjee, S., Lee, M. J., Farmer, S. R. & Puri, V. CIDEA Transcriptionally Regulates UCP1 for Britening and Thermogenesis in Human Fat Cells. *iScience* **20**, 73-89 (2019).

93 Kulyte, A. *et al.* CIDEA interacts with liver X receptors in white fat cells. *FEBS Lett* **585**, 744-748 (2011).

94 Wang, W. *et al.* Cidea is an essential transcriptional coactivator regulating mammary gland secretion of milk lipids. *Nat Med* **18**, 235-243 (2012).

95 Zhang, C. & Liu, P. The New Face of the Lipid Droplet: Lipid Droplet Proteins. *Proteomics* **19**, e1700223 (2019).

96 Lizaso, A., Tan, K. T. & Lee, Y. H. beta-adrenergic receptor-stimulated lipolysis requires the RAB7-mediated autolysosomal lipid degradation. *Autophagy* **9**, 1228-1243 (2013).

97 Singh, R. *et al.* Autophagy regulates adipose mass and differentiation in mice. *J Clin Invest* **119**, 3329-3339 (2009).

98 Zhang, Y. *et al.* Adipose-specific deletion of autophagy-related gene 7 (atg7) in mice reveals a role in adipogenesis. *Proc Natl Acad Sci U S A* **106**, 19860-19865 (2009).

99 Flaherty, S. E., 3rd *et al.* A lipase-independent pathway of lipid release and immune modulation by adipocytes. *Science* **363**, 989-993 (2019).

100 Eissing, L. *et al.* De novo lipogenesis in human fat and liver is linked to ChREBP-beta and metabolic health. *Nat Commun* **4**, 1528 (2013).

101 Herman, M. A. *et al.* A novel ChREBP isoform in adipose tissue regulates systemic glucose metabolism. *Nature* **484**, 333-338 (2012).

102 Kursawe, R. *et al.* Decreased transcription of ChREBP-alpha/beta isoforms in abdominal subcutaneous adipose tissue of obese adolescents with prediabetes or early type 2 diabetes: associations with insulin resistance and hyperglycemia. *Diabetes* **62**, 837-844 (2013).

103 Morigny, P. *et al.* Interaction between Hormone-Sensitive Lipase and ChREBP in Fat Cells Controls Insulin Sensitivity. *Nature Metabolism* **1**, 133-146 (2019).

104 Collins, J. M., Neville, M. J., Hoppa, M. B. & Frayn, K. N. De novo lipogenesis and stearoyl-CoA desaturase are coordinately regulated in the human adipocyte and protect against palmitate-induced cell injury. *J Biol Chem* **285**, 6044-6052 (2010).

105 Guilherme, A. *et al.* Adipocyte lipid synthesis coupled to neuronal control of thermogenic programming. *Mol Metab* **6**, 781-796 (2017).

106 Guilherme, A. *et al.* Neuronal modulation of brown adipose activity through perturbation of white adipocyte lipogenesis. *Mol Metab* **16**, 116-125 (2018).

107 Sukonina, V. *et al.* FOXK1 and FOXK2 regulate aerobic glycolysis. *Nature* **566**, 279-283 (2019).

108 DiGirolamo, M., Newby, F. D. & Lovejoy, J. Lactate production in adipose tissue: a regulated function with extra-adipose implications. *FASEB J* **6**, 2405-2412 (1992).

109 Jansson, P. A., Larsson, A., Smith, U. & Lonnroth, P. Lactate release from the subcutaneous tissue in lean and obese men. *J Clin Invest* **93**, 240-246 (1994).

110 Krycer, J. R. *et al.* Lactate production is a prioritized feature of adipocyte metabolism. *J Biol Chem* **295**, 83-98 (2020).

111 Hui, S. *et al.* Glucose feeds the TCA cycle via circulating lactate. *Nature* **551**, 115-118 (2017).

112 Rabinowitz, J. D. & Enerbäck, S. Lactate: the ugly duckling of energy metabolism. *Nature Metab* **in press** (2020).

113 Lee, K. Y. *et al.* Developmental and functional heterogeneity of white adipocytes within a single fat depot. *EMBO J* **38** (2019).

114 Lee, K. Y. *et al.* Tbx15 Defines a Glycolytic Subpopulation and White Adipocyte Heterogeneity. *Diabetes* **66**, 2822-2829 (2017).

115 Luong, Q., Huang, J. & Lee, K. Y. Deciphering White Adipose Tissue Heterogeneity. *Biology (Basel)* **8** (2019).

116 Lynes, M. D. & Tseng, Y. H. Deciphering adipose tissue heterogeneity. *Ann N Y Acad Sci* **1411**, 5-20 (2018).

117 Newsholme, E. A. & Crabtree, B. Substrate cycles in metabolic regulation and in heat generation. *Biochem Soc Symp*, 61-109 (1976).

118 Sanchez-Gurmaches, J., Hung, C. M. & Guertin, D. A. Emerging Complexities in Adipocyte Origins and Identity. *Trends Cell Biol* **26**, 313-326 (2016).

119 Harms, M. J. *et al.* Mature Human White Adipocytes Cultured under Membranes Maintain Identity, Function, and Can Transdifferentiate into Brown-like Adipocytes. *Cell Rep* **27**, 213-225 e215 (2019).

120 Kroon, T. *et al.* PPARgamma and PPARalpha synergize to induce robust browning of white fat in vivo. *Mol. Metab.* **36**, 100964 (2020).

121 Tiraby, C. *et al.* Acquirement of brown fat cell features by human white adipocytes. *J Biol Chem* **278**, 33370-33376 (2003).

122 Wang, W. & Seale, P. Control of brown and beige fat development. *Nat Rev Mol Cell Biol* **17**, 691-702 (2016).

123 Pisani, D. F. *et al.* Mitochondrial fission is associated with UCP1 activity in human brite/beige adipocytes. *Mol Metab* **7**, 35-44 (2018).

124 Barquissau, V. *et al.* White-to-brite conversion in human adipocytes promotes metabolic reprogramming towards fatty acid anabolic and catabolic pathways. *Mol Metab* **5**, 352-365 (2016).

125 Mills, E. L. *et al.* Accumulation of succinate controls activation of adipose tissue thermogenesis. *Nature* **560**, 102-106 (2018).

126 Murphy, M. P. & O'Neill, L. A. J. Krebs Cycle Reimagined: The Emerging Roles of Succinate and Itaconate as Signal Transducers. *Cell* **174**, 780-784 (2018).

127 Kotzbeck, P. *et al.* Brown adipose tissue whitening leads to brown adipocyte death and adipose tissue inflammation. *J Lipid Res* **59**, 784-794 (2018).

128 Roh, H. C. *et al.* Warming Induces Significant Reprogramming of Beige, but Not Brown, Adipocyte Cellular Identity. *Cell Metab* **27**, 1121-1137 e1125 (2018).

129 Inagaki, T. Histone demethylases regulate adipocyte thermogenesis. *Diabetol Int* **9**, 215-223 (2018).

130 Duteil, D. *et al.* LSD1 promotes oxidative metabolism of white adipose tissue. *Nat Commun* **5**, 4093 (2014).

131 Sambeat, A. *et al.* LSD1 Interacts with Zfp516 to Promote UCP1 Transcription and Brown Fat Program. *Cell Rep* **15**, 2536-2549 (2016).

132 Zeng, X. *et al.* Lysine-specific demethylase 1 promotes brown adipose tissue thermogenesis via repressing glucocorticoid activation. *Genes Dev* **30**, 1822-1836 (2016).

133 Guan, H. P. *et al.* A futile metabolic cycle activated in adipocytes by antidiabetic agents. *Nat Med* **8**, 1122-1128 (2002).

134 Mazzucotelli, A. *et al.* The transcriptional coactivator peroxisome proliferator activated receptor (PPAR)gamma coactivator-1 alpha and the nuclear receptor PPAR alpha control the expression of glycerol kinase and metabolism genes independently of PPAR gamma activation in human white adipocytes. *Diabetes* **56**, 2467-2475 (2007).

135 Flachs, P. *et al.* Induction of lipogenesis in white fat during cold exposure in mice: link to lean phenotype. *Int J Obes (Lond)* **41**, 372-380 (2017).

136 Ikeda, K. *et al.* UCP1-independent signaling involving SERCA2b-mediated calcium cycling regulates beige fat thermogenesis and systemic glucose homeostasis. *Nat Med* **23**, 1454-1465 (2017).

137 Chouchani, E. T., Kazak, L. & Spiegelman, B. M. New Advances in Adaptive Thermogenesis: UCP1 and Beyond. *Cell Metab* **29**, 27-37 (2019).

138 Kazak, L. *et al.* A creatine-driven substrate cycle enhances energy expenditure and thermogenesis in beige fat. *Cell* **163**, 643-655 (2015).

139 Bertholet, A. M. *et al.* Mitochondrial Patch Clamp of Beige Adipocytes Reveals UCP1-Positive and UCP1-Negative Cells Both Exhibiting Futile Creatine Cycling. *Cell Metab* **25**, 811-822 e814 (2017).

140 Kazak, L. *et al.* Ablation of adipocyte creatine transport impairs thermogenesis and causes diet-induced obesity. *Nat Metab* **1**, 360-370 (2019).

141 Pollard, A. E. *et al.* AMPK activation protects against diet induced obesity through Ucp1-independent thermogenesis in subcutaneous white adipose tissue. *Nat Metab* **1**, 340-349 (2019).

142 Mottillo, E. P. *et al.* Coupling of lipolysis and de novo lipogenesis in brown, beige, and white adipose tissues during chronic beta3-adrenergic receptor activation. *J Lipid Res* **55**, 2276-2286 (2014).

143 Girousse, A. *et al.* Partial inhibition of adipose tissue lipolysis improves glucose metabolism and insulin sensitivity without alteration of fat mass. *PLoS Biol* **11**, e1001485 (2013).

144 Newgard, C. B. *et al.* A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab* **9**, 311-326 (2009).

145 White, P. J. & Newgard, C. B. Branched-chain amino acids in disease. *Science* **363**, 582-583 (2019).

146 Lotta, L. A. *et al.* Genetic Predisposition to an Impaired Metabolism of the Branched-Chain Amino Acids and Risk of Type 2 Diabetes: A Mendelian Randomisation Analysis. *PLoS Med* **13**, e1002179 (2016).

147 Klimcakova, E. *et al.* Worsening of obesity and metabolic status yields similar molecular adaptations in human subcutaneous and visceral adipose tissue:

decreased metabolism and increased immune response. *J Clin Endocrinol Metab* **96**, E73-82 (2011).

148 Pietilainen, K. H. *et al.* Global transcript profiles of fat in monozygotic twins discordant for BMI: pathways behind acquired obesity. *PLoS Med* **5**, e51 (2008).

149 Green, C. R. *et al.* Branched-chain amino acid catabolism fuels adipocyte differentiation and lipogenesis. *Nat Chem Biol* **12**, 15-21 (2016).

150 Wallace, M. *et al.* Enzyme promiscuity drives branched-chain fatty acid synthesis in adipose tissues. *Nat Chem Biol* **14**, 1021-1031 (2018).

151 Herman, M. A., She, P., Peroni, O. D., Lynch, C. J. & Kahn, B. B. Adipose tissue branched chain amino acid (BCAA) metabolism modulates circulating BCAA levels. *J Biol Chem* **285**, 11348-11356 (2010).

152 Mardinoglu, A. *et al.* Integration of clinical data with a genome-scale metabolic model of the human adipocyte. *Mol Syst Biol* **9**, 649 (2013).

153 Ramirez, A. K. *et al.* Integrating Extracellular Flux Measurements and Genome-Scale Modeling Reveals Differences between Brown and White Adipocytes. *Cell Rep* **21**, 3040-3048 (2017).

154 Patni, N. & Garg, A. Congenital generalized lipodystrophies--new insights into metabolic dysfunction. *Nat Rev Endocrinol* **11**, 522-534 (2015).

155 Mann, J. P. & Savage, D. B. What lipodystrophies teach us about the metabolic syndrome. *J Clin Invest* **130**, 4009-4021 (2019).

156 Agarwal, A. K. *et al.* AGPAT2 is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. *Nat Genet* **31**, 21-23 (2002).

157 Hayashi, Y. K. *et al.* Human PTRF mutations cause secondary deficiency of caveolins resulting in muscular dystrophy with generalized lipodystrophy. *J Clin Invest* **119**, 2623-2633 (2009).

158 Gandotra, S. *et al.* Perilipin deficiency and autosomal dominant partial lipodystrophy. *N Engl J Med* **364**, 740-748 (2011).

159 Rubio-Cabezas, O. *et al.* Partial lipodystrophy and insulin resistant diabetes in a patient with a homozygous nonsense mutation in CIDEC. *EMBO Mol Med* **1**, 280-287 (2009).

160 Lotta, L. A. *et al.* Integrative genomic analysis implicates limited peripheral adipose storage capacity in the pathogenesis of human insulin resistance. *Nat Genet* **49**, 17-26 (2017).

161 Arner, P., Andersson, D. P., Backdahl, J., Dahlman, I. & Ryden, M. Weight Gain and Impaired Glucose Metabolism in Women Are Predicted by Inefficient Subcutaneous Fat Cell Lipolysis. *Cell Metab* **28**, 45-54 e43 (2018).

162 Perry, R. J. *et al.* Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. *Cell* **160**, 745-758 (2015).

163 Titchenell, P. M., Lazar, M. A. & Birnbaum, M. J. Unraveling the Regulation of Hepatic Metabolism by Insulin. *Trends Endocrinol Metab* **28**, 497-505 (2017).

164 Edgerton, D. S. *et al.* Targeting insulin to the liver corrects defects in glucose metabolism caused by peripheral insulin delivery. *JCI Insight* **5** (2019).

165 Hodson, L. & Karpe, F. Hyperinsulinaemia: does it tip the balance toward intrahepatic fat accumulation? *Endocr Connect* **8**, R157-R168 (2019).

166 Karpe, F., Dickmann, J. R. & Frayn, K. N. Fatty acids, obesity, and insulin resistance: time for a reevaluation. *Diabetes* **60**, 2441-2449 (2011).

167 Rohm, M., Zeigerer, A., Machado, J. & Herzig, S. Energy metabolism in cachexia. *EMBO Rep* **20** (2019).

168 Duong, M. N. *et al.* The fat and the bad: Mature adipocytes, key actors in tumor progression and resistance. *Oncotarget* **8**, 57622-57641 (2017).

169 Agustsson, T. *et al.* Mechanism of increased lipolysis in cancer cachexia. *Cancer Res* **67**, 5531-5537 (2007).

170 Fouladiun, M. *et al.* Body composition and time course changes in regional distribution of fat and lean tissue in unselected cancer patients on palliative care--correlations with food intake, metabolism, exercise capacity, and hormones. *Cancer* **103**, 2189-2198 (2005).

171 Das, S. K. *et al.* Adipose triglyceride lipase contributes to cancer-associated cachexia. *Science* **333**, 233-238 (2011).

172 Rohm, M. *et al.* An AMP-activated protein kinase-stabilizing peptide ameliorates adipose tissue wasting in cancer cachexia in mice. *Nat Med* **22**, 1120-1130 (2016).

173 Lipina, C. & Hundal, H. S. Lipid modulation of skeletal muscle mass and function. *J Cachexia Sarcopenia Muscle* **8**, 190-201 (2017).

174 Stephens, N. A. *et al.* Intramyocellular lipid droplets increase with progression of cachexia in cancer patients. *J Cachexia Sarcopenia Muscle* **2**, 111-117 (2011).

175 Caspar-Bauguil, S. *et al.* Fatty acids from fat cell lipolysis do not activate an inflammatory response but are stored as triacylglycerols in adipose tissue macrophages. *Diabetologia* **58**, 2627-2636 (2015).

176 Kosteli, A. *et al.* Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. *J Clin Invest* **120**, 3466-3479 (2010).

177 Xu, X. *et al.* Obesity activates a program of lysosomal-dependent lipid metabolism in adipose tissue macrophages independently of classic activation. *Cell Metab* **18**, 816-830 (2013).

178 Sun, K., Kusminski, C. M. & Scherer, P. E. Adipose tissue remodeling and obesity. *J Clin Invest* **121**, 2094-2101 (2011).

179 Giordano, A. *et al.* Obese adipocytes show ultrastructural features of stressed cells and die of pyroptosis. *J Lipid Res* **54**, 2423-2436 (2013).

180 Cancello, R. *et al.* Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes* **54**, 2277-2286 (2005).

181 Cinti, S. *et al.* Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J Lipid Res* **46**, 2347-2355 (2005).

182 Zatterale, F. *et al.* Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. *Front Physiol* **10**, 1607 (2019).

183 Shimobayashi, M. *et al.* Insulin resistance causes inflammation in adipose tissue. *J Clin Invest* **128**, 1538-1550 (2018).

184 Zhou, L. *et al.* Insulin resistance and white adipose tissue inflammation are uncoupled in energetically challenged Fsp27-deficient mice. *Nat Commun* **6**, 5949 (2015).

185 Hodson, L., Skeaff, C. M. & Fielding, B. A. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. *Prog Lipid Res* **47**, 348-380 (2008).

186 Cao, H. *et al.* Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. *Cell* **134**, 933-944 (2008).

187 Frigolet, M. E. & Gutierrez-Aguilar, R. The Role of the Novel Lipokine Palmitoleic Acid in Health and Disease. *Adv Nutr* **8**, 173S-181S (2017).

188 Trico, D. *et al.* Circulating palmitoleic acid is an independent determinant of insulin sensitivity, beta cell function and glucose tolerance in non-diabetic individuals: a longitudinal analysis. *Diabetologia* **63**, 206-218 (2020).

189 Yore, M. M. *et al.* Discovery of a class of endogenous mammalian lipids with anti-diabetic and anti-inflammatory effects. *Cell* **159**, 318-332 (2014).

190 Tan, D. *et al.* Discovery of FAHFA-Containing Triacylglycerols and Their Metabolic Regulation. *J Am Chem Soc* **141**, 8798-8806 (2019).

191 Hammarstedt, A. *et al.* Adipose tissue dysfunction is associated with low levels of the novel Palmitic Acid Hydroxystearic Acids. *Sci Rep* **8**, 15757 (2018).

192 Syed, I. *et al.* Palmitic Acid Hydroxystearic Acids Activate GPR40, Which Is Involved in Their Beneficial Effects on Glucose Homeostasis. *Cell Metab* **27**, 419-427 e414 (2018).

193 Zhou, P. *et al.* PAHSAs enhance hepatic and systemic insulin sensitivity through direct and indirect mechanisms. *J Clin Invest* **129**, 4138-4150 (2019).

194 Pflimlin, E. *et al.* Acute and Repeated Treatment with 5-PAHSA or 9-PAHSA Isomers Does Not Improve Glucose Control in Mice. *Cell Metab* **28**, 217-227 e213 (2018).

195 Syed, I. *et al.* Methodological Issues in Studying PAHSA Biology: Masking PAHSA Effects. *Cell Metab* **28**, 543-546 (2018).

196 Vijayakumar, A. *et al.* Absence of Carbohydrate Response Element Binding Protein in Adipocytes Causes Systemic Insulin Resistance and Impairs Glucose Transport. *Cell Rep* **21**, 1021-1035 (2017).

197 Erikci Ertunc, M. *et al.* AIG1 and ADTRP are endogenous hydrolases of fatty acid esters of hydroxy fatty acids (FAHFAs) in mice. *J Biol Chem* **295**, 5891-5905 (2020).

198 Lynes, M. D. *et al.* The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. *Nat Med* **23**, 631-637 (2017).

199 Vasan, S. K. *et al.* The proposed systemic thermogenic metabolites succinate and 12,13-diHOME are inversely associated with adiposity and related metabolic traits: evidence from a large human cross-sectional study. *Diabetologia* (2019).

200 Stanford, K. I. *et al.* 12,13-diHOME: An Exercise-Induced Lipokine that Increases Skeletal Muscle Fatty Acid Uptake. *Cell Metab* **27**, 1111-1120 e1113 (2018).

201 Funcke, J. B. & Scherer, P. E. Beyond adiponectin and leptin: adipose tissue-derived mediators of inter-organ communication. *J Lipid Res* (2019).

202 Xia, J. Y. *et al.* Targeted Induction of Ceramide Degradation Leads to Improved Systemic Metabolism and Reduced Hepatic Steatosis. *Cell Metab* **22**, 266-278 (2015).

203 Chaurasia, B. *et al.* Targeting a ceramide double bond improves insulin resistance and hepatic steatosis. *Science* **365**, 386-392 (2019).

204 Ertunc, M. E. *et al.* Secretion of fatty acid binding protein aP2 from adipocytes through a nonclassical pathway in response to adipocyte lipase activity. *J Lipid Res* **56**, 423-434 (2015).

205 Cao, H. *et al.* Adipocyte lipid chaperone AP2 is a secreted adipokine regulating hepatic glucose production. *Cell Metab* **17**, 768-778 (2013).

206 Oikonomou, E. K. & Antoniades, C. The role of adipose tissue in cardiovascular health and disease. *Nat Rev Cardiol* **16**, 83-99 (2019).

207 Yang, Q. *et al.* Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* **436**, 356-362 (2005).

208 Moraes-Vieira, P. M. *et al.* RBP4 activates antigen-presenting cells, leading to adipose tissue inflammation and systemic insulin resistance. *Cell Metab* **19**, 512-526 (2014).

209 Hallenborg, P. *et al.* The elusive endogenous adipogenic PPARgamma agonists: Lining up the suspects. *Prog Lipid Res* **61**, 149-162 (2016).

210 Soccio, R. E., Chen, E. R. & Lazar, M. A. Thiazolidinediones and the promise of insulin sensitization in type 2 diabetes. *Cell Metab* **20**, 573-591 (2014).

211 Cusi, K. *et al.* Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. *Ann Intern Med* **165**, 305-315 (2016).

212 DeFronzo, R. A., Inzucchi, S., Abdul-Ghani, M. & Nissen, S. E. Pioglitazone: The forgotten, cost-effective cardioprotective drug for type 2 diabetes. *Diab Vasc Dis Res* **16**, 133-143 (2019).

213 Schweiger, M. *et al.* Pharmacological inhibition of adipose triglyceride lipase corrects high-fat diet-induced insulin resistance and hepatosteatosis in mice. *Nat Commun* **8**, 14859 (2017).

214 Lauring, B. *et al.* Niacin lipid efficacy is independent of both the niacin receptor GPR109A and free fatty acid suppression. *Sci Transl Med* **4**, 148ra115 (2012).

215 Romani, M., Hofer, D. C., Katsyuba, E. & Auwerx, J. Niacin: an old lipid drug in a new NAD(+) dress. *J Lipid Res* **60**, 741-746 (2019).

216 Goldie, C. *et al.* Niacin therapy and the risk of new-onset diabetes: a meta-analysis of randomised controlled trials. *Heart* **102**, 198-203 (2016).

217 Kroon, T., Baccega, T., Olsen, A., Gabrielsson, J. & Oakes, N. D. Nicotinic acid timed to feeding reverses tissue lipid accumulation and improves glucose control in obese Zucker rats[S]. *J Lipid Res* **58**, 31-41 (2017).

218 Kroon, T., Kjellstedt, A., Thalen, P., Gabrielsson, J. & Oakes, N. D. Dosing profile profoundly influences nicotinic acid's ability to improve metabolic control in rats. *J Lipid Res* **56**, 1679-1690 (2015).

219 Wallenius, K. *et al.* Involvement of the metabolic sensor GPR81 in cardiovascular control. *JCI Insight* **2**, e92564 (2017).

220 Manini, T. M. Energy expenditure and aging. *Ageing Res Rev* **9**, 1-11 (2010).

221 Ryden, M., Gao, H. & Arner, P. Influence of ageing and menstrual status on subcutaneous fat cell lipolysis. *J. Clin. Endocrinol. Metab.* **105**, dgz245 (2019).

222 Reitman, M. L. Of mice and men - environmental temperature, body temperature, and treatment of obesity. *FEBS Lett* **592**, 2098-2107 (2018).

223 Maurer, S., Harms, M. & Boucher, J. The colorful versatility of adipocytes: white-to-brown transdifferentiation and its therapeutic potential in man. *FEBS J* (2020).

224 Hoehn, K. L. *et al.* Acute or chronic upregulation of mitochondrial fatty acid oxidation has no net effect on whole-body energy expenditure or adiposity. *Cell Metab* **11**, 70-76 (2010).

225 Ryaboshapkina, M. & Hammar, M. Tissue-specific genes as an underutilized resource in drug discovery. *Sci Rep* **9**, 7233 (2019).

226 Schoettl, T., Fischer, I. P. & Ussar, S. Heterogeneity of adipose tissue in development and metabolic function. *J Exp Biol* **221** (2018).

227 Zwick, R. K., Guerrero-Juarez, C. F., Horsley, V. & Plikus, M. V. Anatomical, Physiological, and Functional Diversity of Adipose Tissue. *Cell Metab* **27**, 68-83 (2018).

228 Macotela, Y., Boucher, J., Tran, T. T. & Kahn, C. R. Sex and depot differences in adipocyte insulin sensitivity and glucose metabolism. *Diabetes* **58**, 803-812 (2009).

229 Palmer, B. F. & Clegg, D. J. The sexual dimorphism of obesity. *Mol Cell Endocrinol* **402**, 113-119 (2015).

230 Stout, M. B., Justice, J. N., Nicklas, B. J. & Kirkland, J. L. Physiological Aging: Links Among Adipose Tissue Dysfunction, Diabetes, and Frailty. *Physiology (Bethesda)* **32**, 9-19 (2017).

231 Hagberg, C. E. *et al.* Flow Cytometry of Mouse and Human Adipocytes for the Analysis of Browning and Cellular Heterogeneity. *Cell Rep* **24**, 2746-2756 e2745 (2018).

232 Chen, Y. *et al.* Thermal stress induces glycolytic beige fat formation via a myogenic state. *Nature* **565**, 180-185 (2019).

233 Sun, W. *et al.* snRNA-seq reveals a subpopulation of adipocytes that regulates thermogenesis. *Nature* **587**, 98-102 (2020).

234 Panda, S. Circadian physiology of metabolism. *Science* **354**, 1008-1015 (2016).

235 Stenvers, D. J., Scheer, F., Schrauwen, P., la Fleur, S. E. & Kalsbeek, A. Circadian clocks and insulin resistance. *Nat Rev Endocrinol* **15**, 75-89 (2019).

236 Goodpaster, B. H. & Sparks, L. M. Metabolic Flexibility in Health and Disease. *Cell Metab* **25**, 1027-1036 (2017).

237 Chaix, A., Manoogian, E. N. C., Melkani, G. C. & Panda, S. Time-Restricted Eating to Prevent and Manage Chronic Metabolic Diseases. *Annu Rev Nutr* (2019).

238 Sears, D. D. *et al.* Mechanisms of human insulin resistance and thiazolidinedione-mediated insulin sensitization. *Proc Natl Acad Sci U S A* **106**, 18745-18750 (2009).

239 Ahlqvist, E. *et al.* Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* **6**, 361-369 (2018).

240 Zaharia, O. P. *et al.* Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol* **7**, 684-694 (2019).

241 Cao, Y. Adipocyte and lipid metabolism in cancer drug resistance. *J Clin Invest* **129**, 3006-3017 (2019).

242 Shapiro, B. & Wertheimer, E. The synthesis of fatty acids in adipose tissue in vitro. *J Biol Chem* **173**, 725-728 (1948).

243 Wertheimer, E. & Shapiro, B. The physiology of adipose tissue. *Physiol Rev* **28**, 451-464 (1948).

244 Hausberger, F. X., Milstein, S. W. & Rutman, R. J. The influence of insulin on glucose utilization in adipose and hepatic tissues in vitro. *J Biol Chem* **208**, 431-438 (1954).

245 Korn, E. D. & Quigley, T. W., Jr. Studies on lipoprotein lipase of rat heart and adipose tissue. *Biochim Biophys Acta* **18**, 143-145 (1955).

246 Wadstrom, L. B. Lipolytic effect of the injection of adrenaline on fat depots. *Nature* **179**, 259-260 (1957).

247 Vaughan, M., Berger, J. E. & Steinberg, D. Hormone-Sensitive Lipase and Monoglyceride Lipase Activities in Adipose Tissue. *J Biol Chem* **239**, 401-409 (1964).

248 Fain, J. N., Kovacev, V. P. & Scow, R. O. Antilipolytic effect of insulin in isolated fat cells of the rat. *Endocrinology* **78**, 773-778 (1966).

249 Hirsch, J. & Gallian, E. Methods for the determination of adipose cell size in man and animals. *J Lipid Res* **9**, 110-119 (1968).

250 Fujita, T. *et al.* Reduction of insulin resistance in obese and/or diabetic animals by 5-[4-(1-methylcyclohexylmethoxy)benzyl]-thiazolidine-2,4-dione (ADD-3878, U-63,287, ciglitazone), a new antidiabetic agent. *Diabetes* **32**, 804-810 (1983).

251 Loncar, D. Convertible adipose tissue in mice. *Cell Tissue Res* **266**, 149-161 (1991).

252 Tontonoz, P., Hu, E. & Spiegelman, B. M. Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell* **79**, 1147-1156 (1994).

253 Lehmann, J. M. *et al.* An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* **270**, 12953-12956 (1995).

254 Montague, C. T. *et al.* Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* **387**, 903-908 (1997).

255 Sengenes, C., Berlan, M., De Glisezinski, I., Lafontan, M. & Galitzky, J. Natriuretic peptides: a new lipolytic pathway in human adipocytes. *FASEB J* **14**, 1345-1351 (2000).

256 Abel, E. D. *et al.* Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. *Nature* **409**, 729-733 (2001).

257 Weisberg, S. P. *et al.* Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* **112**, 1796-1808 (2003).

258 Jenkins, C. M. *et al.* Identification, cloning, expression, and purification of three novel human calcium-independent phospholipase A2 family members possessing triacylglycerol lipase and acylglycerol transacylase activities. *J Biol Chem* **279**, 48968-48975 (2004).

259 Villena, J. A., Roy, S., Sarkadi-Nagy, E., Kim, K. H. & Sul, H. S. Desnutrin, an adipocyte gene encoding a novel patatin domain-containing protein, is induced by fasting and glucocorticoids: ectopic expression of desnutrin increases triglyceride hydrolysis. *J Biol Chem* **279**, 47066-47075 (2004).

260 Zimmermann, R. *et al.* Fat mobilization in adipose tissue is promoted by adipose triglyceride lipase. *Science* **306**, 1383-1386 (2004).

261 Wu, J. *et al.* Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell* **150**, 366-376 (2012).

262 Rosenwald, M., Perdikari, A., Rulicke, T. & Wolfrum, C. Bi-directional interconversion of brite and white adipocytes. *Nat Cell Biol* **15**, 659-667 (2013).

263 Thomou, T. *et al.* Adipose-derived circulating miRNAs regulate gene expression in other tissues. *Nature* **542**, 450-455 (2017).

264 Ying, W. *et al.* Adipose Tissue Macrophage-Derived Exosomal miRNAs Can Modulate In Vivo and In Vitro Insulin Sensitivity. *Cell* **171**, 372-384 e312 (2017).

265 Crewe, C. *et al.* An Endothelial-to-Adipocyte Extracellular Vesicle Axis Governed by Metabolic State. *Cell* **175**, 695-708 e613 (2018).

266 Muller, S., Kulenkampff, E. & Wolfrum, C. Adipose Tissue Stem Cells. *Handb Exp Pharmacol* **233**, 251-263 (2016).

267 Caslin, H. L., Bhanot, M., Bolus, W. R. & Hasty, A. H. Adipose tissue macrophages: Unique polarization and bioenergetics in obesity. *Immunol Rev* **295**, 101-113 (2020).

268 Sun, K., Tordjman, J., Clement, K. & Scherer, P. E. Fibrosis and adipose tissue dysfunction. *Cell Metab* **18**, 470-477 (2013).

269 Roden, M. & Shulman, G. I. The integrative biology of type 2 diabetes. *Nature* **576**, 51-60 (2019).

270 Canfora, E. E., Meex, R. C. R., Venema, K. & Blaak, E. E. Gut microbial metabolites in obesity, NAFLD and T2DM. *Nat Rev Endocrinol* **15**, 261-273 (2019).

271 Schlaich, M., Straznicky, N., Lambert, E. & Lambert, G. Metabolic syndrome: a sympathetic disease? *Lancet Diabetes Endocrinol* **3**, 148-157 (2015).

272 Ulrich-Lai, Y. M. & Ryan, K. K. Neuroendocrine circuits governing energy balance and stress regulation: functional overlap and therapeutic implications. *Cell Metab* **19**, 910-925 (2014).

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Author contributions

D.L. conceived the initial version of the article. P.M., J.B., P.A. and D.L. wrote the article. P.M. and P.A. prepared the figures. D.L. integrated contributions and produced the submitted version with input from P.M., J.B. and P.A. All authors approved the final version of the article.

Competing interests

J.B. is an employee of AstraZeneca. The other authors declare no competing interests.

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Key points

- White adipocyte size and turnover are determinants of systemic insulin sensitivity and cardiometabolic phenotype in humans.
- White adipocytes are specialized in fat storage and mobilization; the underlying lipid metabolic pathways are tightly connected with those governing the intracellular fate of glucose.
- In some fat depots, there is a bidirectional switch between white and beige adipocytes, which display an oxidative phenotype with energy dissipation through uncoupling protein 1 (UCP1)-dependent and UCP1-independent pathways.
- White adipocyte metabolic pathways control the secretion of proteins and lipids, with local and systemic effects on inflammation and insulin sensitivity.
- Adipocyte metabolism offers promising targets for the treatment of cardiometabolic diseases and cancer-associated disorders.
- Future research will include the in-depth characterization of adipocyte diversity associated with anatomical location, age, sex and physiological rhythms.

Figure legends

Fig. 1. **Timeline of important advances and promising discoveries in white adipose tissue research**

Main references for each year are listed here: 1948[242,243]; 1954[244]; 1955[245]; 1957[246]; 1964[3,247]; 1966[248]; 1968[249]; 1976[4]; 1980[5,6]; 1983[250]; 1991[251]; 1993[7]; 1994[11,252]; 1996[8-10];1995–1997[253,254]; 2000[255]; 2001[256]; 2003[121,257]; 2004[258-260]; 2008–2011[45,52]; 2012[261]; 2013[262]; 2015[162]; 2017[263,264]; 2015–2019[103,136,138]; 2018–2019[99,265]. The graph depicts the number of publications published each year using the following search query in an August 2020 search of Pubmed: “adipocyte” or "fat cell" or “adipose tissue” [Title/Abstract]. ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase; MGL, monoglyceride lipase; PPAR, peroxisome proliferator-activated receptor; TNF, tumor necrosis factor; TZDs, thiazolidinediones.

Fig. 2. **Turnover of human white adipose tissue.** Schematic overview of the links between adipocyte formation and pathological conditions. **a |**Adipocyte generation and cell death occur constantly. Progenitor cells proliferate in different niches within fat depots. A fraction of these cells originates from bone marrow. In obesity, the generation rate of new large and/or small adipocytes is increased. When the generation rate is decreased, fewer, larger adipocytes form, a process referred to as hypertrophy. **b |** Fat mass can develop in two ways. The formation of a few large adipocytes or the accumulation of lipids in pre-existing cells result in hypertrophy. Alternatively, precursor cells proliferate and differentiate into a large number of small adipocytes, a process termed hyperplasia. Adipocyte hypertrophy is associated with an adverse cardiometabolic phenotype whereas adipocyte hyperplasia at the same fat mass has

benign effects. **c |** Adipocyte lipid turnover decreases with ageing, as reflected by increased lipid age. This reduced turnover decreases the rate of lipid removal (K_{out}) from adipocytes. If a reduced K_{out} is counterbalanced by a decreased rate of lipid storage (K_{in}), fat mass remains unchanged, whereas fat mass expands over time if K_{in} does not decrease (or increases).

Fig. 3. **Fat storage and glucose metabolism in white adipocytes.** GLUT4 and GLUT1 are, respectively, the insulin-sensitive and non-insulin-sensitive glucose transporters in adipocytes. During glycolysis, some glucose is converted into glycerol-3-phosphate (glycerol-3P), which constitutes the backbone of triacylglycerol (TAG). Adipocytes also make a substantial contribution to whole-body lactate turnover. After glycolysis, glucose can be oxidized in the tricarboxylic acid cycle (TCA) to produce energy or be converted into fatty acids by de novo lipogenesis (DNL). This pathway, which is under the control of insulin, involves the sequential action of ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC1) and fatty acid synthase (FASN). Palmitic acid produced by these enzymes can be further elongated and desaturated by elongase of very-long-chain fatty acid 6 (ELOVL6) and stearoyl-CoA desaturase SCD, respectively. DNL-derived fatty acids can be used as components of phospholipids in cellular membranes, serve as extracellular signalling molecules or, to a lesser extent than extracellular fatty acids, be stored as TAG in the lipid droplet. Insulin promotes hydrolysis of fatty-acid-loaded lipoproteins by lipoprotein lipase (LPL) and entry of the released fatty acids through specific fatty acid transporters. Insulin also stimulates fatty acid esterification, which occurs by the sequential action of acetyl-CoA synthetase (ACS), glycerol-3-phosphate-acyltransferase (GPAT), 1-acyl-glycerol-3-phosphate-acyltransferase (AGPAT), phosphatidic acid phosphatase (PAP; also known as lipin)

and diacylglycerol acyltransferase (DGAT) enzymes. ER, endoplasmic reticulum; MCT, monocarboxylate transporters.

Fig. 4. **Fat mobilization in white adipocytes**. In basal conditions, insulin inhibits lipolysis through activation of the cAMP-degrading enzyme phosphodiesterase 3B (PDE3B) (part **a**). The inhibition of cAMP synthesis is mediated by activation of anti-lipolytic G-protein coupled receptors (GPCRs) coupled to $G_{\alpha i}$. Through clearance of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) promoted by natriuretic peptide receptor C (NPRC), these natriuretic peptides (NPs) do not exert a lipolytic effect. Adipose triglyceride lipase (ATGL)-mediated triacylglycerol (TAG) hydrolysis is minimal owing to interaction of the ATGL activator CGI58 with the lipid-droplet coating protein perilipin 1 (PLIN1). FSP27 and G0S2 are negative regulators of ATGL activity. Like FSP27, CIDEA is also a member of the CIDE family and controls basal lipolysis. The net action of NPs and catecholamines results from the balance between binding of these molecules to inhibitory receptor complexes (part **a**) and activatory receptor complexes (part **b**). In stimulated conditions, ANP and BNP (through NPRA) and catecholamines (through β-adrenergic receptors coupled to $G_{\alpha s}$) induce an increase in cGMP and cAMP levels, respectively (part **b**). The protein kinases PKG and PKA phosphorylate hormone-sensitive lipase (HSL) and thereby promote its translocation from cytosol to the lipid droplet, where it interacts with PLIN1. HSL is bound to the fatty-acid-binding protein FABP4. Dissociation of CGI58 from phosphorylated PLIN1 allows CGI58 to interact with ATGL. ATGL, HSL and monoglyceride lipase (not shown) catalyse the sequential hydrolysis of TAG into fatty acids and glycerol, which are released from the adipocyte through dedicated transporters or oxidized in the tricarboxylic acid cycle (TCA). PTRF (also known as

cavin 1) is involved in HSL recruitment to the lipid droplet and is a constituent of caveolae (together with caveolin 1 (CAV1)), where it participates in fatty acid trafficking.

Fig. 5. **Energy dissipation in adipocytes. a |** Uncoupling protein 1 (UCP1)-dependent thermogenesis involves β-oxidation of fatty acids and production of reactive oxygen species (ROS) induced by succinate oxidation. In response to thermogenic stimuli, fatty acids, glucose and succinate are imported from the circulation. Fatty acids can be mobilized from intracellular stores of triacylglycerol (TAG). Fatty acid oxidation is favoured over glucose oxidation because of inhibition of the pyruvate dehydrogenase (PDH) complex by phosphorylation of PDH components by pyruvate dehydrogenase kinase 4 (PDK4). **b |** Several UCP1-independent pathways promote energy dissipation. The substrate cycle of TAG synthesis and hydrolysis includes lipolysis and phosphorylation of glycerol into glycerol 3-phosphate (glycerol-3P) to allow re-esterification of fatty acids. Another branch feeding the cycle is the synthesis of fatty acids from glucose (de novo lipogenesis). The contribution of the TAG–fatty acid substrate cycle to heat production is debated. The SERCA2–ryanodine receptor (RyR) pathway in the endoplasmic reticulum (ER) induces Ca^{2+} cycling. In the mitochondria, creatine substrate cycling also results in energy dissipation. The two latter pathways are coupled to ATP synthesis and consumption and generate heat. ETC, electron transport chain; IMS, intermembrane space; RCC, respiratory chain complex; S, F1/F0 ATP synthase; TCA, tricarboxylic acid cycle.

Fig. 6. **Crosstalk between metabolic pathways in the white adipocyte.** The interaction between hormone sensitive lipase (HSL) and the carbohydrate-responsive element-binding protein α (ChREBPα) inhibits ChREBPα translocation into the

nucleus. Disruption of the HSL–ChREBPα interaction promotes ChREBPα transcription activity, involving induction of expression of the highly transcriptionally active isoform ChREBPβ and of lipogenic enzymes, such as ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC1), fatty-acid synthase (FASN), elongase of very-long-chain fatty acid 6 (ELOVL6), and stearoyl-CoA desaturase (SCD). Specific induction of ELOVL6, a preferential target of ChREBP, promotes oleic acid synthesis and incorporation into plasma membrane phospholipids, thereby increasing plasma membrane fluidity and insulin signalling. Conversely, β_3-adrenergic receptor signalling promotes an adipose triglyceride lipase (ATGL)-dependent induction of lipogenic enzyme expression and *de novo* lipogenesis (DNL). Branched-chain amino acids (BCAAs) are another important source of substrate for DNL. BCAAs can be oxidized in the tricarboxylic acid cycle (TCA) and contribute to the lipogenic acetyl-CoA pool. Branched-chain CoA intermediates of BCAA catabolism (BC-CoAs) are produced in mitochondria but can also be exported to the cytosol through carnitine acyl transferase (CrAT). CrAT and FASN promiscuity favours BC-CoA elongation and monomethyl branched-chain fatty acid (mmBCFA) production. mmBCFA can be stored by incorporation in triacylgycerol (TAG) and mobilized during fasting. Glucose metabolism inhibits BCAA metabolism through unknown mechanisms.

Fig. 7. **Systemic impact of adipocyte metabolism and therapeutic perspectives.** In non-pathological conditions, adipocytes exhibit a beneficial metabolism that supports systemic insulin sensitivity (green pathways). This metabolic phenotype promotes healthy lipid storage in the form of triacylglycerol (TAG) in lipid droplets, low basal lipolysis, de novo lipogenesis (DNL) and secretion of beneficial bioactive lipids (such as fatty acid esters of hydroxy fatty acids (FAHFAs) and 12,13-diHOME) and

adipokines (such as leptin and adiponectin). During obesity or lipodystrophy, adipocytes show opposite features, secreting factors (such as fatty acids, ceramides, cytokines and the fatty acid binding protein FABP4 and retinol-binding protein RBP4) that promote chronic inflammation and systemic insulin resistance (red pathways). Multiple aspects of adipocyte metabolism are valuable targets for drug development (blue stars). The inhibition of the interaction between hormone-sensitive lipase and carbohydrate-responsive element-binding protein (ChREBP) results in activation of DNL and enhanced insulin signalling through increased content of monounsaturated fatty acids (MUFA) in plasma membrane phospholipids. Enhanced DNL is associated with the synthesis of beneficial lipid species such as FAHFA, which have systemic insulin-sensitizing effects. The inhibition of ceramide synthesis and/or activation of ceramide degradation protect against systemic insulin resistance. The inhibition of lipolysis using $G_{\alpha i}$-coupled receptor (GPCR) agonists is another promising strategy. Peroxisome proliferator-activated receptor-γ (PPARγ) agonists promote healthy lipid storage and DNL, decrease inflammation and induce a beneficial adipokine profile, which together improve systemic insulin sensitivity. Finally, conversion of white adipocytes into beige adipocytes and stimulation of energy dissipation in beige adipocytes is an attractive strategy to increase energy expenditure. ER, endoplasmic reticulum; GLP-1, glucagon-like peptide 1; glycerol-3P, glycerol-3-phosphate; UCP1, uncoupling protein 1.

Box 1. **Diversity of cell types in white adipose tissue**

White adipose tissue (WAT) contains various cell types that support a diversity of roles and functions. The white adipocyte is the prototypical cell of white fat that imparts its colour to the tissue. This cell type is specialized in metabolism, notably the storage of chemical energy as TAG and its release as fatty acids. Glucose metabolic pathways are associated with lipid metabolism, notably through de novo synthesis of fatty acids and glycerol. Depending on the anatomical location and physiological conditions (for example, cold exposure and season), white fat depots contain various amounts of beige adipocytes, which can derive from differentiation of precursor cells or reversible interconversion of white adipocytes to beige adipocytes [118,124]. Beige adipocytes are enriched in mitochondria and equipped with several pathways that allow energy dissipation as heat. The stromovascular fraction of WAT contains immune and non-immune cells. Non-immune cells in this fraction include progenitor cells and endothelial cells [118,266]. Progenitor cells have the potential to differentiate into white or beige adipocytes and, together with fibroblasts, play an important part in extracellular matrix production and fibrosis. Endothelial cells form the endothelium, which plays a key part as a barrier and exchange area between blood and adipose tissue. A growing number of immune cells have been identified in WAT, with macrophages being the most abundant. The initial binary classification of adipose tissue macrophages as pro-inflammatory or anti-inflammatory cells may be considered obsolete[267]. Some macrophages are specialized in lipid scavenging. Other myeloid cells (such as dendritic cells and neutrophils) and various lymphocyte populations participate in the immune response and tissue remodelling [268]. Adipocytes and some cell types in the stromovascular fraction (notably macrophages), secrete peptides termed adipokines (such as leptin, adiponectin, RBP4, FABP4 and tumor necrosis factor) and lipid molecules termed lipokines (such as FAHFA and 12,13-diHOME)[15]. These factors can act locally on neighbouring cells (paracrine action) or remotely on cells in other organs (endocrine action). Moreover, immune cells and endothelial cells communicate with local nerve fibres[13]. This interplay leads to neurohumoral signalling that regulates whole-body metabolism.

Box 2. **Insulin resistance**

Insulin resistance is a pathophysiological state characterized by an impairment of insulin-mediated control of glucose and fat metabolism. In skeletal muscle and white adipose tissue (WAT), insulin is less efficient in stimulating glucose uptake while, in the liver, the hormone loses its ability to inhibit endogenous glucose production. Insulin resistance also results in uncontrolled release of fatty acids by WAT as the result of diminished anti-lipolytic action of insulin. Insulin resistance can be organ-specific (for example, affecting the liver but not the skeletal muscle and vice versa) or pathway-specific (for example, impairment of insulin action on hepatic gluconeogenesis but not on de novo lipogenesis). This selectivity is explained by molecular defects that affect various levels of insulin signalling pathways. A current view, which proposes adipocyte dysfunction as an early cardinal event in insulin resistance, is that WAT drives metabolic fluxes that impact the liver and skeletal muscle [269]. However, the kinetics of dysfunction in different metabolic organs is not well-characterized in humans. The gut, through microbiota and digestion-related functions, and the brain, through the neuroendocrine control of metabolism, may also have an important role in insulin resistance [270-272]. Insulin resistance results in an increased burden on pancreatic islet β-cells to secrete insulin as a compensatory mechanism for the loss of sensitivity to the hormone. When β-cell function declines, fasting and postprandial blood glucose levels increase, signalling the onset of type 2 diabetes mellitus. Insulin resistance is also found in various pathological conditions, such as polycystic ovary syndrome, lipodystrophies, non-alcoholic fatty liver disease, cardiovascular disease and some cancers.

Glossary terms

Adipose tissue hypertrophy

Adipose tissue expansion through an increase in adipocyte size.

Adipose tissue hyperplasia

Adipose tissue expansion through the generation of new adipocytes.

M1-like macrophages

Subtype of macrophages characterized by the secretion of pro-inflammatory cytokines and chemokines such as IL-6 and TNF.

Lipophagy

Triacylglycerol hydrolysis by lysosomal acid lipases after engulfment of a lipid droplet by an autophagosome, which fuses with lysosomes.

Beige adipocyte

Also known as brown-in-white (brite) adipocytes. A subtype of thermogenic adipocytes located in white fat depots and uniquely equipped to dissipate energy as heat.

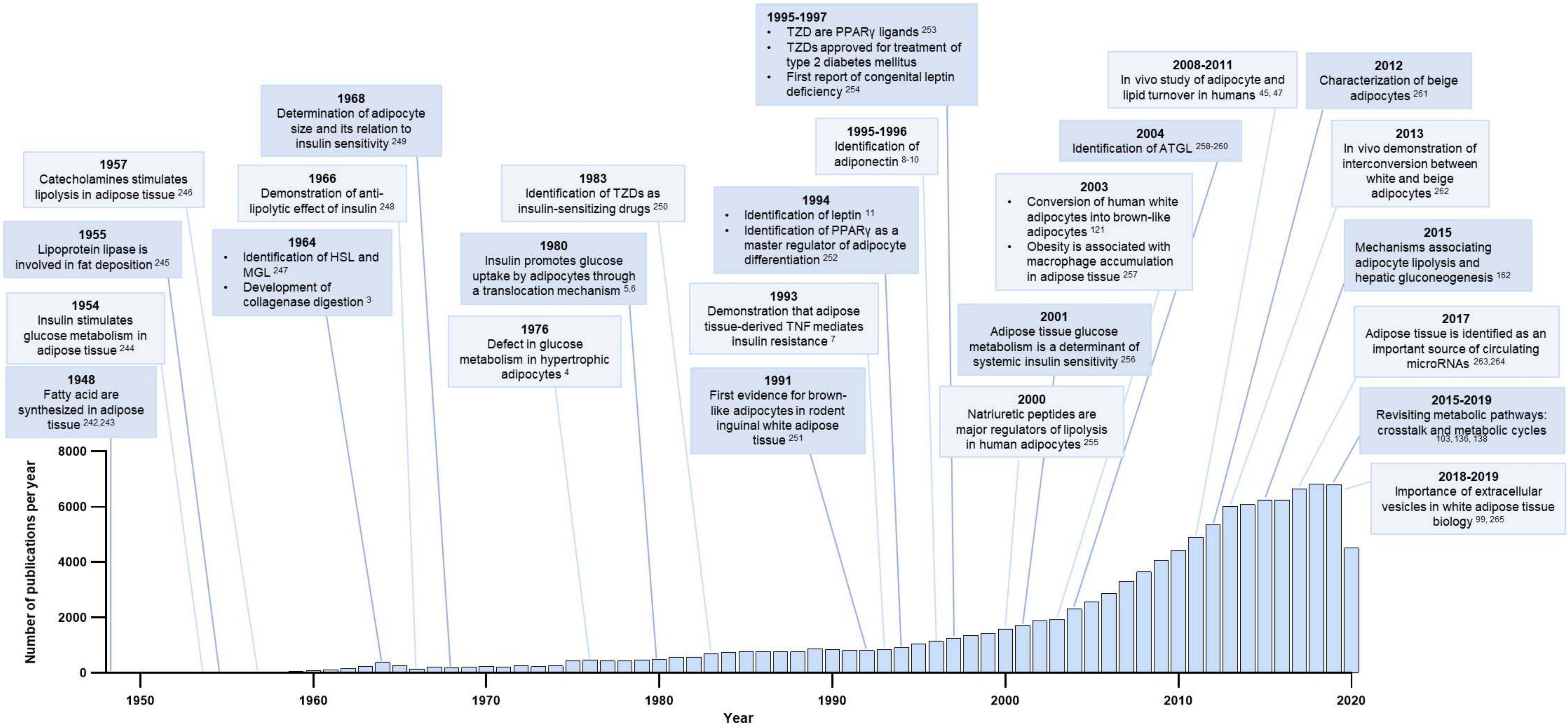
Pyroptotic cell death

Cell death triggered by pro-inflammatory signals and subsequent activation of the NLRP3 inflammasome.

Lipocalins

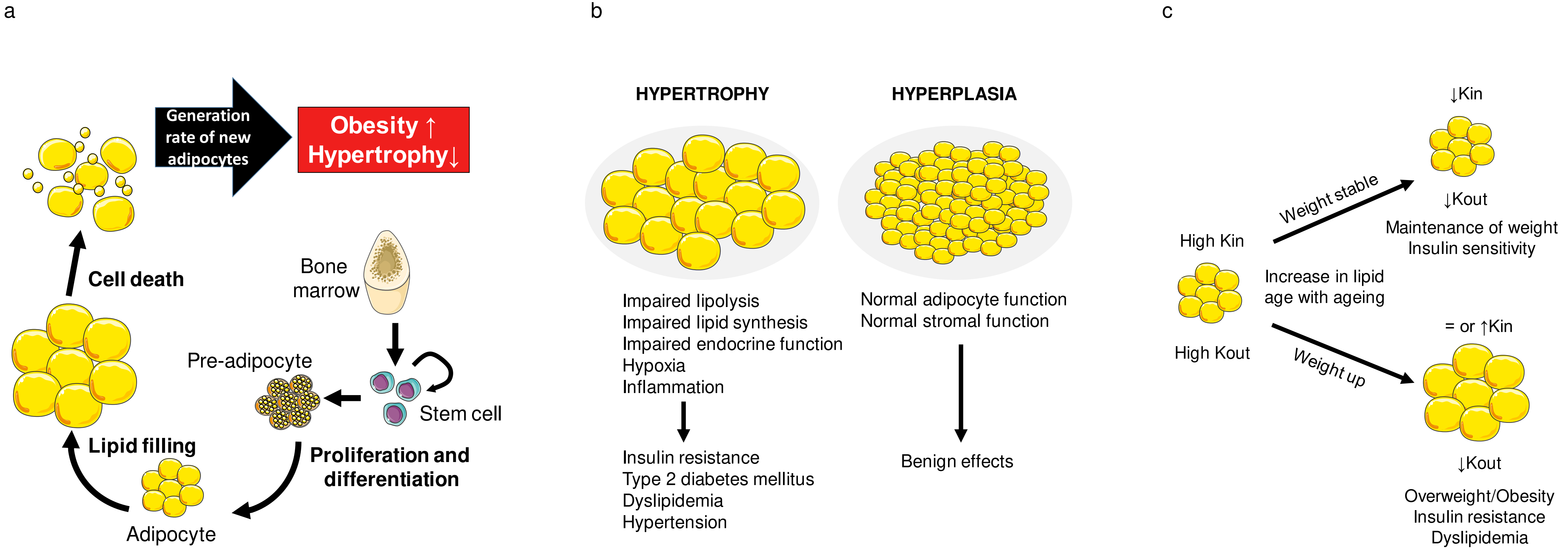
Small extracellular proteins that are responsible for the transport of hydrophobic molecules, such as lipids, steroids and retinoids, in the circulation.

Figure 1



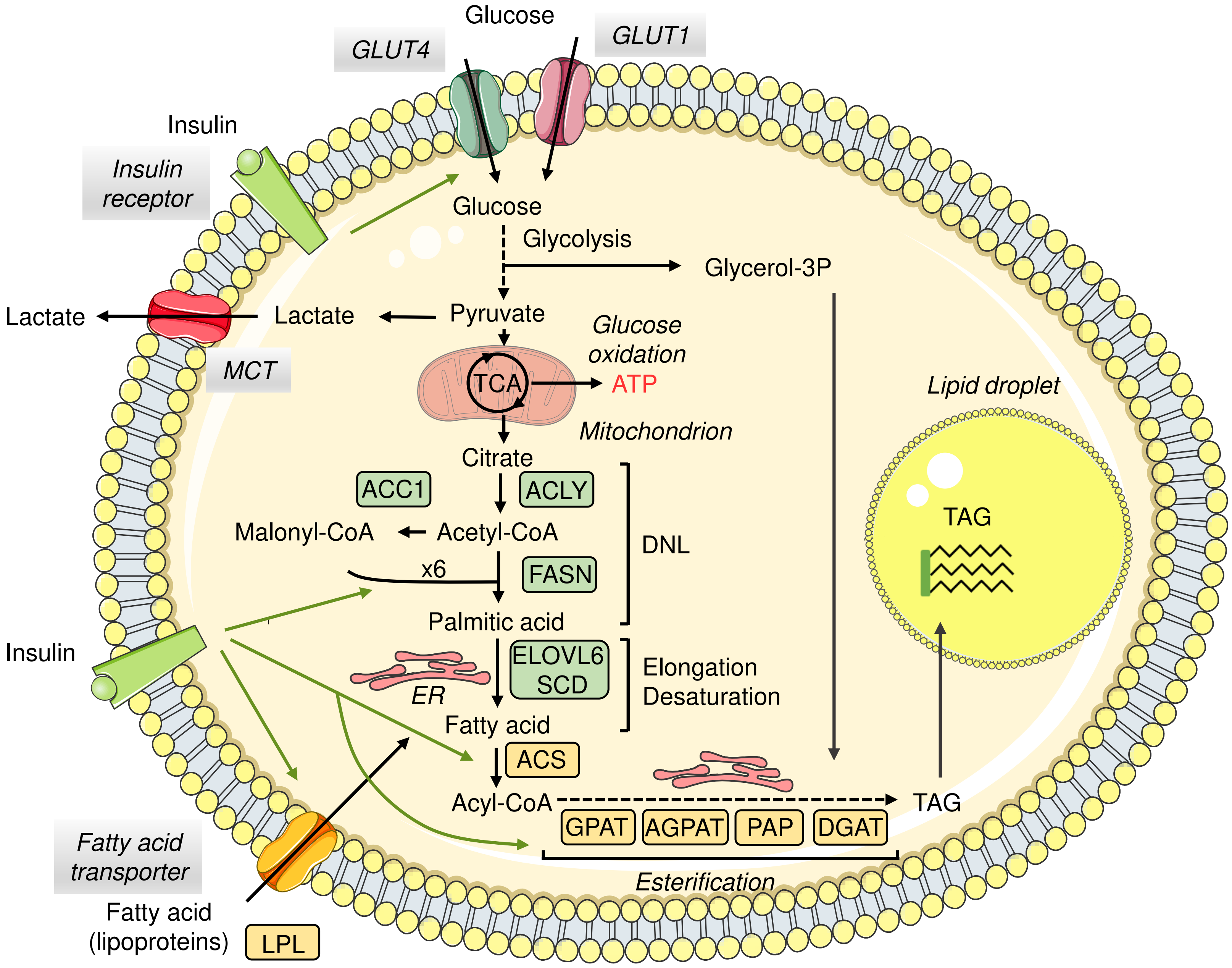
1948
Fatty acid are synthesized in adipose tissue [242,243]
1954
Insulin stimulates glucose metabolism in adipose tissue [244]
1955
Lipoprotein lipase is involved in fat deposition [245]
1957
Catecholamines stimulates lipolysis in adipose tissue [246]
1964
Identification of HSL and MGL [247]
Development of collagenase digestion [3]
1966
Demonstration of anti-lipolytic effect of insulin [248]
1968
Determination of adipocyte size and its relation to insulin sensitivity [249]
1976
Defect in glucose metabolism in hypertrophic adipocytes [4]
1980
Insulin promotes glucose uptake by adipocytes through a translocation mechanism [5,6]
1983
Identification of TZDs as insulin-sensitizing drugs [250]
1991
First evidence for brown-like adipocytes in rodent inguinal white adipose tissue [251]
1993
Demonstration that adipose tissue-derived TNF mediates insulin resistance [7]
1994
Identification of leptin [11]
Identification of PPARγ as a master regulator of adipocyte differentiation [252]
1995-1996
Identification of adiponectin [8-10]
1995-1997
TZD are PPARγ ligands [253]
TZDs approved for treatment of type 2 diabetes mellitus
First report of congenital leptin deficiency [254]
2000
Natriuretic peptides are major regulators of lipolysis in human adipocytes [255]
2001
Adipose tissue glucose metabolism is a determinant of systemic insulin sensitivity [256]
2003
Conversion of human white adipocytes into brown-like adipocytes [121]
Obesity is associated with macrophage accumulation in adipose tissue [257]
2004
Identification of ATGL [258-260]
2008-2011
In vivo study of adipocyte and lipid turnover in humans [45, 47]
2012
Characterization of beige adipocytes [261]
2013
In vivo demonstration of interconversion between white and beige adipocytes [262]
2015
Mechanisms associating adipocyte lipolysis and hepatic gluconeogenesis [162]
2017
Adipose tissue is identified as an important source of circulating microRNAs [263,264]
2015-2019
Revisiting metabolic pathways: crosstalk and metabolic cycles [103, 136, 138]
2018-2019
Importance of extracellular vesicles in white adipose tissue biology [99, 265]
Number of publications per year
8000
6000
4000
2000
0
1950
1960
1970
1980
1990
2000
2010
2020
Year

Figure 2



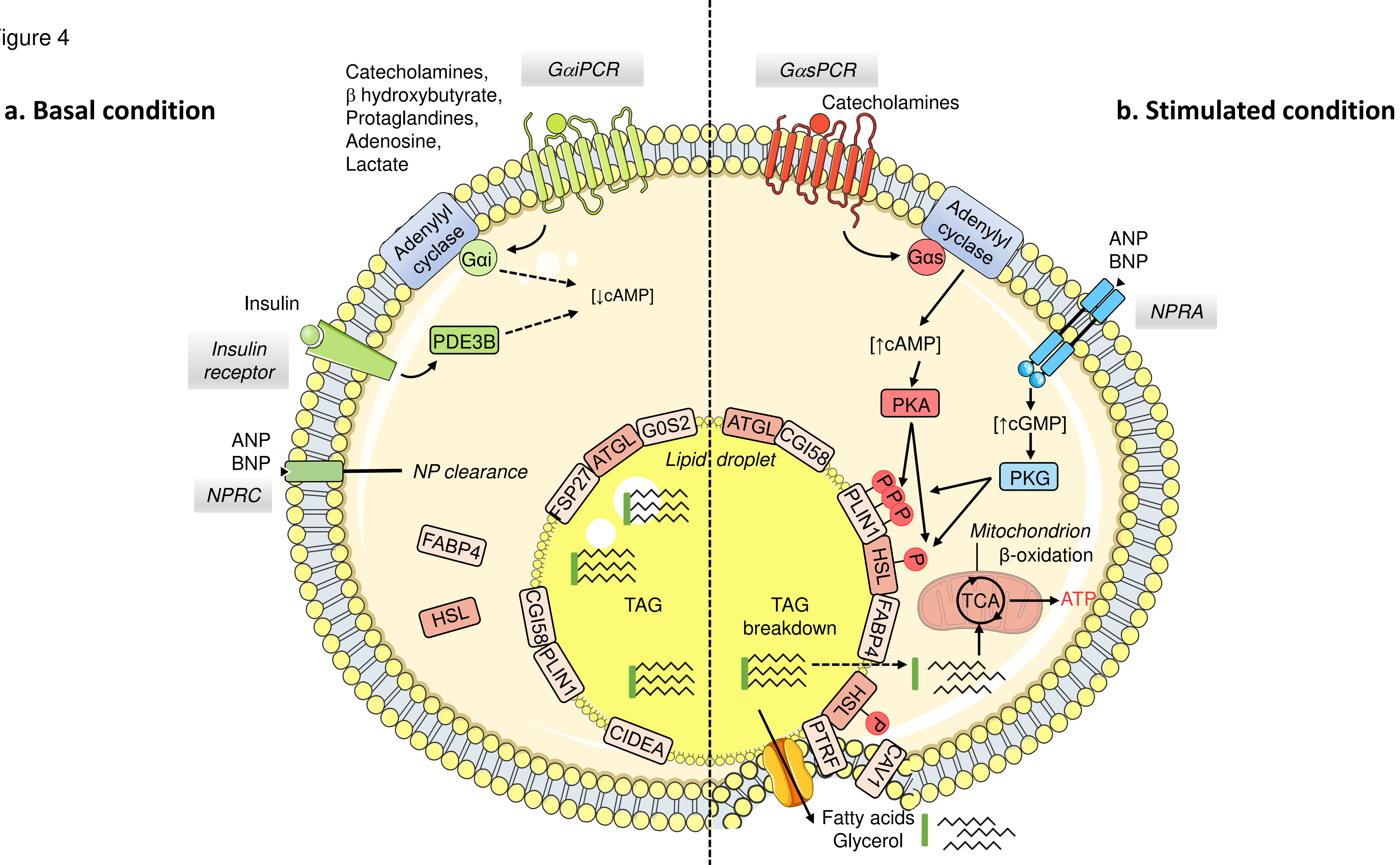
a
Generation rate of new adipocytes
Obesity ↑
Hypertrophy↓
Cell death
Bone marrow
Pre-adipocyte
Stem cell
Lipid filling
Proliferation and differentiation
Adipocyte
b
HYPERTROPHY
HYPERPLASIA
Impaired lipolysis
Impaired lipid synthesis
Impaired endocrine function
Hypoxia
Inflammation
Insulin resistance
Type 2 diabetes mellitus
Dyslipidemia
Hypertension
Normal adipocyte function
Normal stromal function
Benign effects
c
↓Kin
↓Kout
Maintenance of weight
Insulin sensitivity
Weight stable
High Kin
High Kout
Increase in lipid age with ageing
= or ↑Kin
Weight up
↓Kout
Overweight/Obesity
Insulin resistance
Dyslipidemia

Figure 3



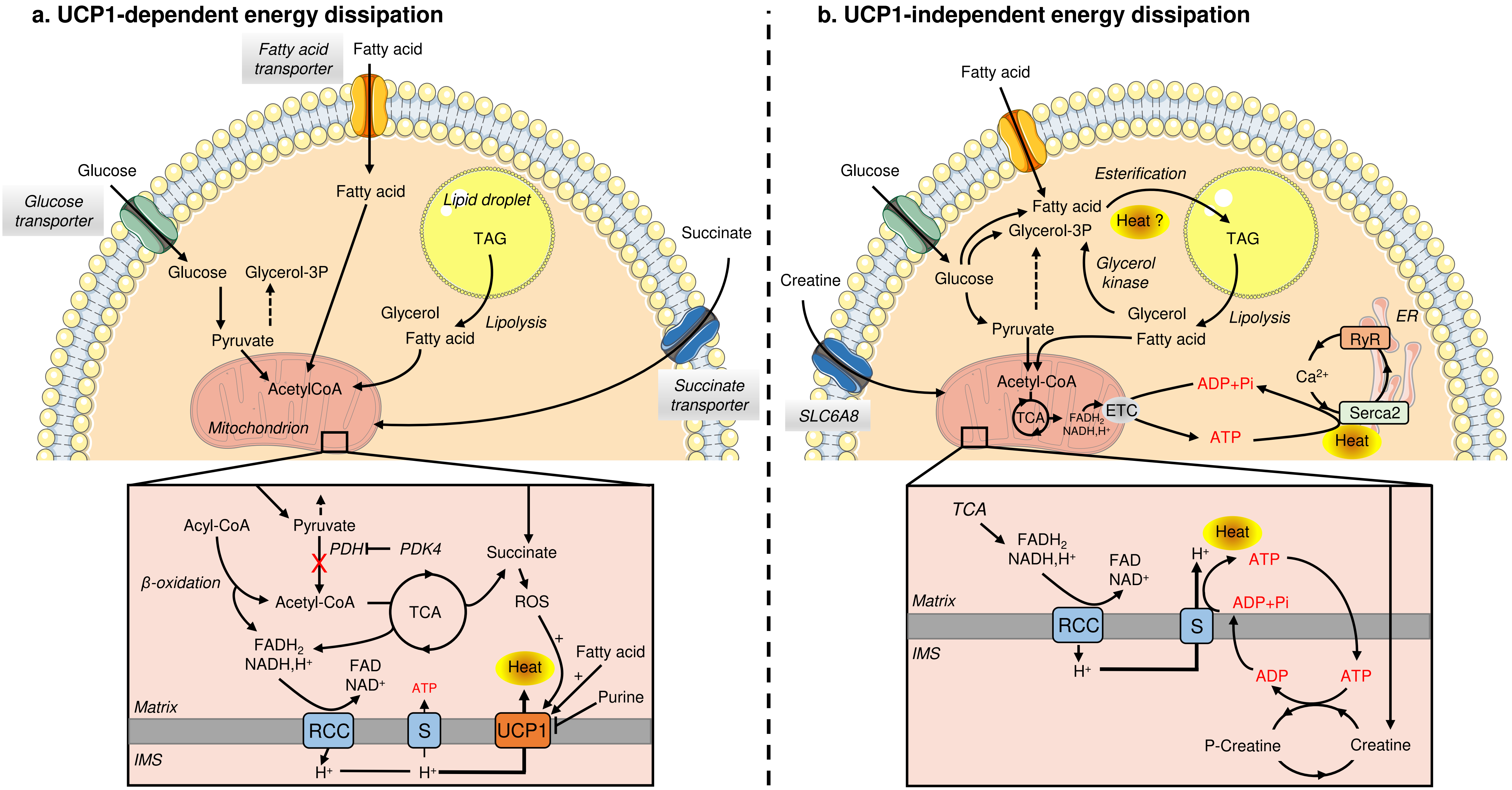
Glucose
GLUT4
GLUT1
Insulin
Insulin receptor
Glucose
Glycolysis
Glycerol-3P
Lactate
Lactate
Pyruvate
MCT
Glucose oxidation
TCA
ATP
Mitochondrion
Lipid droplet
Citrate
ACC1
ACLY
Malonyl-CoA
Acetyl-CoA
DNL
TAG
x6
FASN
Palmitic acid
Insulin
ELOVL6
SCD
Elongation
Desaturation
ER
Fatty acid
ACS
Acyl-CoA
TAG
GPAT
AGPAT
PAP
DGAT
Fatty acid transporter
Esterification
Fatty acid (lipoproteins)
LPL

Figure 4



a. Basal condition
b. Stimulated condition
Catecholamines,
β hydroxybutyrate,
Protaglandines,
Adenosine,
Lactate
GαiPCR
GαsPCR
Catecholamines
Adenylyl cyclase
Gαi
[↓cAMP]
Insulin
Insulin receptor
PDE3B
ANP
BNP
NPRC
NP clearance
FABP4
HSL
G0S2
ATGL
FSP27
CGI58
PLIN1
CIDEA
Lipid droplet
TAG
TAG breakdown
Gαs
Adenylyl cyclase
[↑cAMP]
PKA
ANP
BNP
NPRA
[↑cGMP]
PKG
ATGL
CGI58
P
PLIN1
HSL
FABP4
Mitochondrion
β-oxidation
TCA
ATP
HSL
PTRF
CAV1
Fatty acids
Glycerol

Figure 5



a. UCP1-dependent energy dissipation
Fatty acid transporter
Fatty acid
Glucose
Glucose transporter
Fatty acid
Lipid droplet
TAG
Succinate
Glucose
Glycerol-3P
Glycerol
Lipolysis
Pyruvate
Fatty acid
AcetylCoA
Succinate transporter
Mitochondrion
Acyl-CoA
Pyruvate
PDH
PDK4
Succinate
β-oxidation
Acetyl-CoA
TCA
ROS
FADH2
NADH,H+
FAD
NAD+
ATP
Heat
Fatty acid
Purine
Matrix
RCC
S
UCP1
IMS
H+
H+
b. UCP1-independent energy dissipation
Fatty acid
Glucose
Esterification
Fatty acid
Heat ?
TAG
Glycerol-3P
Creatine
Glucose
Glycerol kinase
Glycerol
Lipolysis
ER
Pyruvate
Fatty acid
RyR
Acetyl-CoA
ADP+Pi
Ca2+
TCA
FADH2
NADH,H+
ETC
Serca2
SLC6A8
ATP
Heat
TCA
FADH2
NADH,H+
Heat
H+
ATP
FAD
NAD+
Matrix
ADP+Pi
RCC
S
IMS
H+
ADP
ATP
P-Creatine
Creatine

Figure 6

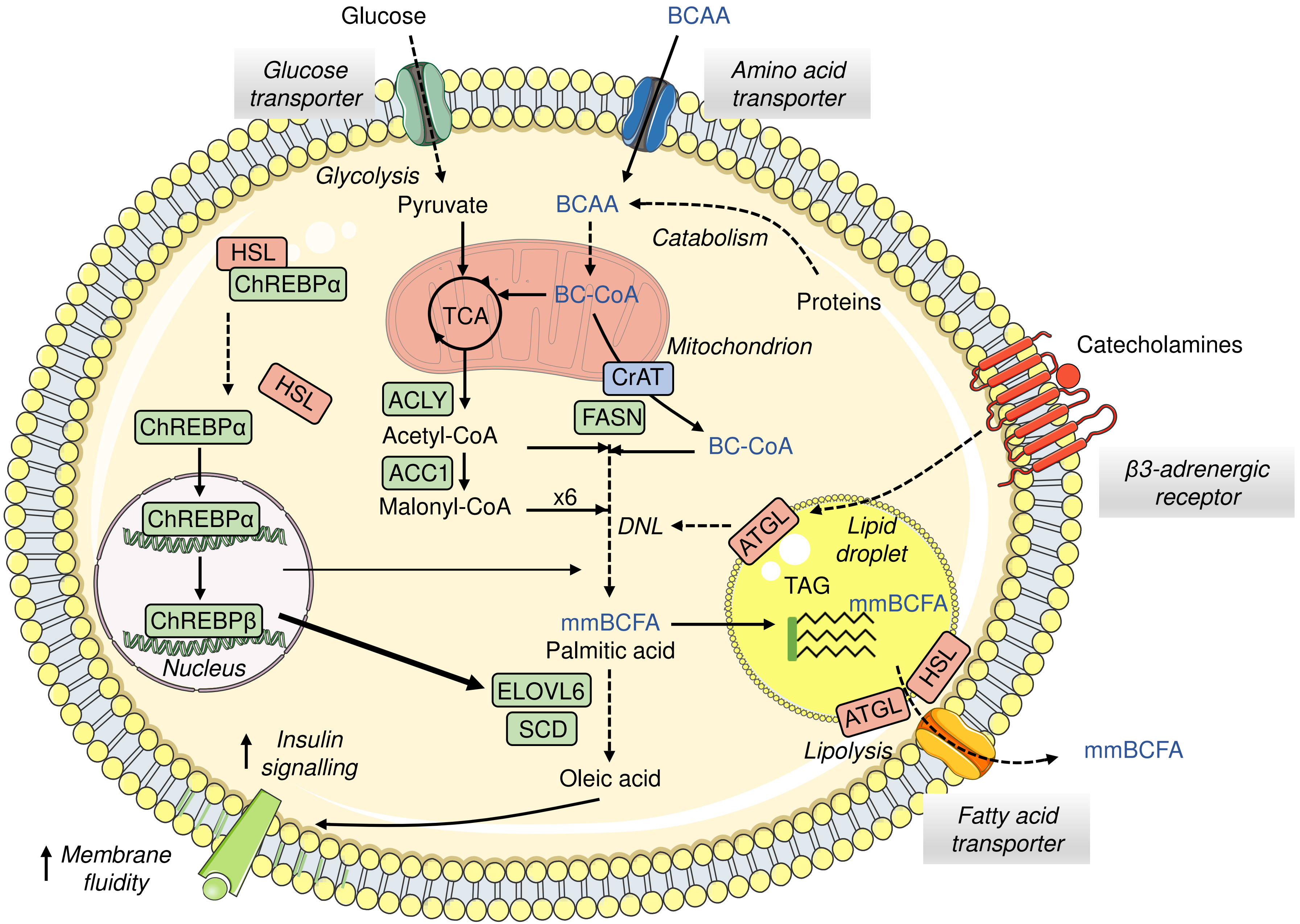
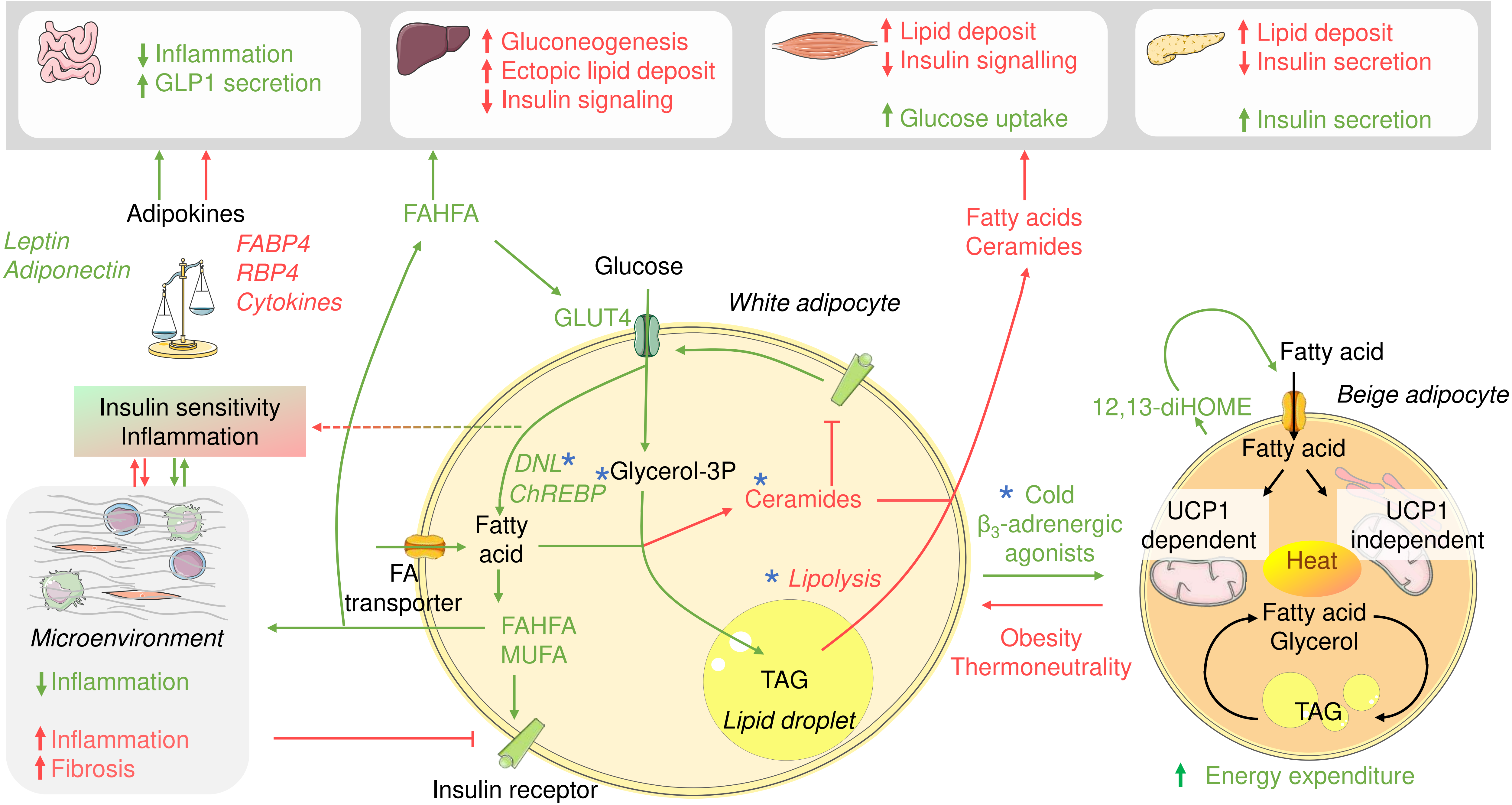

Glucose
BCAA
Glucose transporter
Amino acid transporter
Glycolysis
Pyruvate
BCAA
Catabolism
Proteins
HSL
ChREBPα
TCA
BC-CoA
Mitochondrion
Catecholamines
HSL
CrAT
ACLY
FASN
ChREBPα
Acetyl-CoA
BC-CoA
β3-adrenergic receptor
ACC1
Malonyl-CoA
x6
ChREBPα
DNL
ATGL
Lipid droplet
TAG
mmBCFA
ChREBPβ
mmBCFA
Palmitic acid
HSL
Nucleus
ELOVL6
ATGL
SCD
Insulin signalling
Lipolysis
mmBCFA
Oleic acid
Fatty acid transporter
Membrane fluidity

Figure 7



Inflammation
GLP1 secretion
Gluconeogenesis
Ectopic lipid deposit
Insulin signaling
Lipid deposit
Insulin signalling
Glucose uptake
Lipid deposit
Insulin secretion
Insulin secretion
Adipokines
Leptin
Adiponectin
FABP4
RBP4
Cytokines
FAHFA
Fatty acids
Ceramides
Glucose
GLUT4
White adipocyte
Insulin sensitivity
Inflammation
DNL
ChREBP
Glycerol-3P
Ceramides
Fatty acid
FA transporter
Lipolysis
FAHFA
MUFA
TAG
Lipid droplet
Microenvironment
Inflammation
Inflammation
Fibrosis
Insulin receptor
Cold
β3-adrenergic agonists
Obesity
Thermoneutrality
Fatty acid
12,13-diHOME
Beige adipocyte
Fatty acid
UCP1 dependent
UCP1 independent
Heat
Fatty acid
Glycerol
TAG
Energy expenditure