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Adipose Tissue Remodeling in Pathophysiology

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Abstract

Rather than serving as a mere onlooker, adipose tissue is a complex endocrine organ and active participant in disease initiation and progression. Disruptions of biological processes operating within adipose can disturb healthy systemic physiology, the sequelae of which include metabolic disorders such as obesity and type 2 diabetes. A burgeoning interest in the field of adipose research has allowed for the elucidation of regulatory networks underlying both adipose tissue function and dysfunction. Despite this progress, few diseases are treated by targeting maladaptation in the adipose, an oft-overlooked organ. In this review, we elaborate on the distinct subtypes of adipocytes, their developmental origins and secretory roles, and the dynamic interplay at work within the tissue itself. Central to this discussion is the relationship between adipose and disease states, including obesity, cachexia, and infectious diseases, as we aim to leverage our wealth of knowledge for the development of novel and targeted therapeutics.

INTRODUCTION

From the 1980s onwards, we have witnessed the perception of adipose tissue (AT) evolve from that of an inert depot in which to store triacylglycerol to a dynamic and metabolically active endocrine organ (1). It is now accepted that adipose participates in systemic glucose and energy homeostasis, insulin resistance, the immune response, and thermogenesis (2). In that light, it is evident that the AT should actively play a role in disease processes. However, with few exceptions, the contributions of adipose to pathological conditions, such as tissue injury, atrophy, and fibrosis, are less understood. Unlike other organ systems wherein distinct biomarkers can be used to assess a functional or dysfunctional state (e.g., alanine and aspartate aminotransferases in plasma as markers for liver function), there is no clear-cut means to distinguish between healthy and pathological adipocytes. Further confounding the significance of this organ in disease states is the fact that AT itself is a highly heterogeneous community, consisting of adipocytes, adipocyte precursor cells, and immune cells, to name a few (3). The advent of high-resolution techniques such as single-cell RNA sequencing (scRNA-seq) has allowed for further dissection of the complexity in AT while also raising more questions and driving curiosity as to the roles of cellular subtypes (4–6).

Broadly, adipocytes are categorized as being either white or brown, with the two populations demonstrating markedly disparate functions and morphology. White adipocytes contain a large unilocular lipid droplet with relatively few mitochondria, representing the classical perception of AT as a site for energy storage. On the other hand, brown adipocytes have several small multilocular lipid droplets and high mitochondrial density, indicative of their ability to increase energy expenditure (2). This is facilitated by the presence of uncoupling protein 1 (UCP1), which allows for the dissipation of the proton gradient at the inner mitochondrial membrane, thus uncoupling respiration from ATP production (7). A third subset consisting of adipocyte progenitors and white adipocytes that are capable of browning in response to select stimuli and thus adopting characteristics of brown adipocytes are known as beige adipocytes (8). As a generalization, adipocytes exist in distinct depots termed white adipose tissue (WAT) and brown adipose tissue (BAT), which can be further categorized by anatomical location. Visceral fat within the abdominal cavity and surrounding organs is considered unfavorable and is associated with metabolic disorders such as obesity while subcutaneous fat is generally considered protective, but this is an oversimplification (9). Indeed, as we further uncover the developmental origins of adipocytes as well as their unique bioenergetic, metabolic, and immune functions, it is clear that these cells have heterogeneous roles even within the same AT depot.

Uncovering the biomolecular processes regulating adipocyte functionality holds the key to mitigating metabolic disorders. For instance, the ability to stimulate brown and beige adipocyte thermogenesis via β3-adrenergic signaling has opened the door to clinical interventions for obesity and metabolic disorders, albeit with mixed results (10). As of this writing, the β3-adrenergic receptor agonist mirabegron is the leading candidate for β3-mediated treatment of metabolic disease (11). It was recently demonstrated that chronic treatment with mirabegron in humans increases BAT activity and whole-body resting energy expenditure (REE) with noted improvements in glucose tolerance and insulin sensitivity (11). However, the caveat of this study is that the treated group consisted of young and healthy women, whereas chronic use of β-adrenergic agonists in individuals with metabolic disorders would likely induce adverse cardiovascular effects as they raise heart rate, systolic blood pressure, and myocardial oxygen consumption (12). Moreover, mirabegron is approved by the US Food and Drug Administration for the treatment of overactive bladder at lower doses than what is required to observe these beneficial metabolic effects (100 mg daily for 4 weeks) (11). To that effect, harnessing the potential of brown and beige fat to mitigate metabolic

disorders such as obesity would require alternative means of inducing the thermogenic program that would minimize detrimental effects on the cardiovascular system.

Herein, we review the current knowledge on adipocytes with an emphasis on their contribution to human health and pathology. Mechanistically, we cover the underpinnings of adipocyte development, the role of AT as a metabolic sink, and the dynamic cross talk between adipose and other organ systems. Where possible, we describe therapeutic interventions to mitigate maladaptation in adipocytes for select diseases and their clinical significance. While much is known on the role of adipocytes in obesity and cardiovascular health, the overarching aim of this article is to demonstrate that AT dysfunction underlies a wide spectrum of disorders beyond this scope alone.

ADIPOSE TISSUE: A HETEROGENEOUS COMMUNITY

White Adipose Tissue

Expansion of WAT is categorized as either hyperplastic (increase in cell number) or hypertrophic (increase in cell size) (**Figure 1*a***) (13). Mature adipocytes arise from adipose progenitors (APs) located in the stromal vascular fraction (SVF) of WAT, a reservoir of APs, stem cells, and immune cells such as M2 macrophages and T cells (14). It is well known that, owing to constraints on adipocyte volume and fat storage, caloric excess magnifies adipocyte apoptosis and the stress response during obesogenic behavior (**Figure 1*a***) (2). The resultant infiltration of immune cell populations such as $CD8^+$ T cells, M1 macrophages, and IFN-γ^+ Th1 cells induces a low-grade inflammatory state preceding the development of metabolic disorders such as type 2 diabetes (T2D) and cardiovascular disease (15). As such, a number of studies have focused on characterization of the WAT inflammatory profile, with single-cell transcriptomics allowing for in-depth analysis of immune populations. Although the plethora of roles played by immune cells in adipose depots is outside the scope of this review, one must remain cognizant that their function and that of adipocytes are inherently intertwined (16). For instance, $CD206^+$ M2-like macrophages inhibit the differentiation of APs, promoting adipocyte hypertrophy and insulin resistance, which is reversed by depletion of this cell population (17). In murine epididymal WAT, a *$CD9^+Trem2^+$* macrophage subgroup is detectable only after a high-fat diet (HFD) feeding, with Trem2 knockout amplifying insulin resistance and diet-induced obesity (DIO) (18).

An important gap in our knowledge is the molecular workings of diverse adipocyte populations themselves and how distinct cell types contribute to metabolic disease, as understanding the developmental origins of adipocytes can enable predictions as to which populations will demonstrate increases in basal lipolysis, insulin resistance, and endocrine profiles that are common to metabolic disorders and may be amenable to therapeutic interventions (19). Cell surface markers have been identified in SVF progenitor cells that undergo adipogenesis. These include platelet-derived growth factor receptor alpha (PDGFRα), stem cell antigen-1 (Sca1) (in mice), CD13, CD29, CD34, CD44, CD73, CD90, and CD142, but there is a lack of consensus as to the fate of various APs, and it is likely that these progenitors represent multiple states of adipose commitment and differentiation (**Table 1**) (5). To that effect, scRNA-seq and cell trajectory analyses have helped to unravel the origins of mature adipocytes. In a study of subcutaneous inguinal WAT from 12-day-old mice, it was found that cells expressing dipeptidyl peptidase-4 (DPP4) are bona fide multipotent mesenchymal progenitors (20). $DPP4^+$ cells are highly proliferative and maintain their multipotent identity via increased Wnt and transforming growth factor beta (TGFβ) signaling, which, if inhibited, induces the expression of adipocyte genes in $DPP4^+$ cells (20). Inducing obesity in a murine model leads to depletion of $DPP4^+$ cells in the visceral fat, suggesting that reduced precursor differentiation contributes to the pathophysiological remodeling of AT

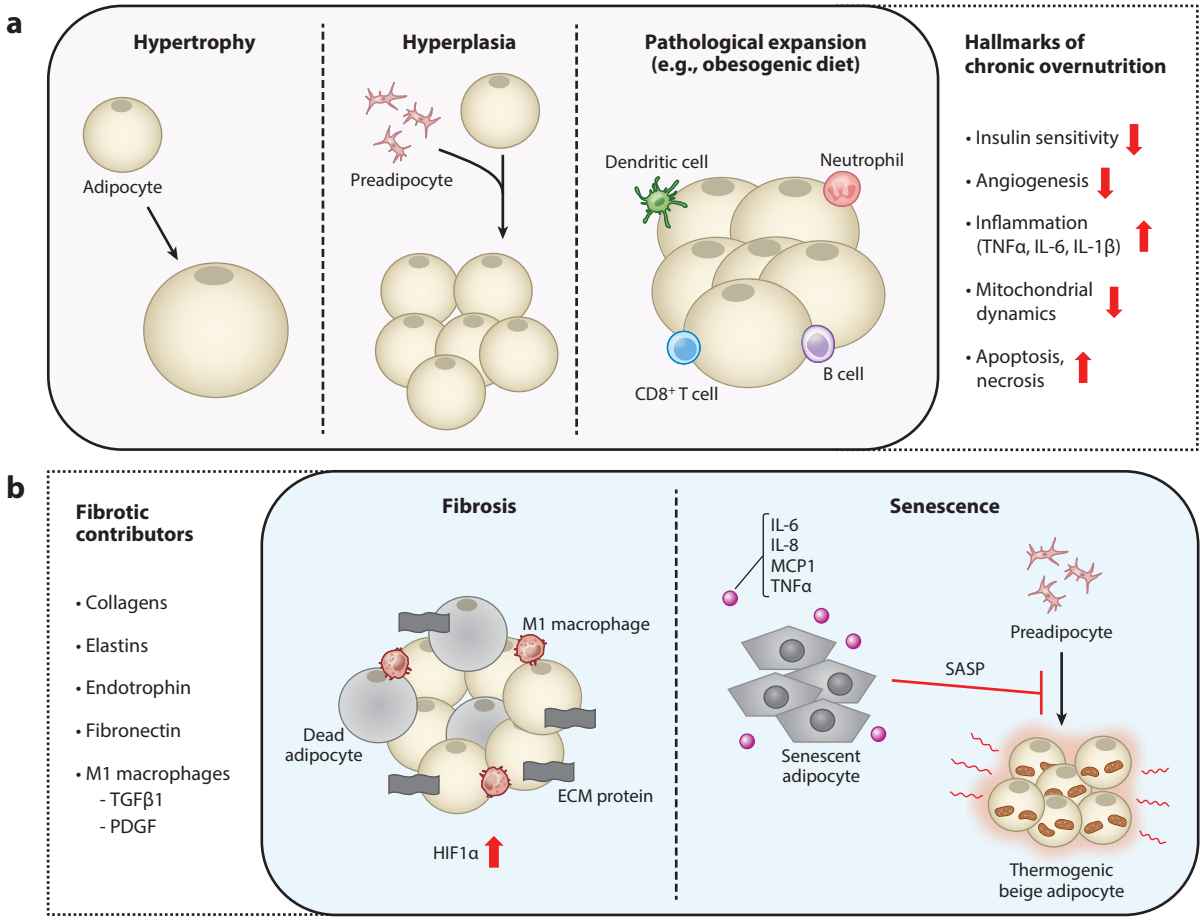

Figure 1

Adipose dynamics in healthy and pathological states. (*a*) Adipose tissue grows through both hypertrophy (increase in cell size) and hyperplasia (increase in cell number). While both processes allow healthy and functional expansion of fat, an excessive increase in size via caloric overnutrition induces a pathological state characterized by inflammation, hypoxia, and decreased blood supply. (*b*) Unresolved chronic inflammation as a result of obesity or other metabolic disorders remodels adipose tissue into a fibrotic state characterized by the accumulation of ECM proteins and persistent hypoxia that is difficult to reverse, limiting the dynamism of adipose depots. Senescent cells, characterized by irreversible cell cycle arrest, are a product of metabolic disorders and aging. The SASP maintains a proinflammatory environment and impedes the differentiation of adipocyte precursors into metabolically beneficial beige adipocytes. This maladaptive state has detrimental sequelae such as insulin resistance, poor glucose uptake, and ectopic fat deposition (lipotoxicity). Abbreviations: ECM, extracellular matrix; HIF1α, hypoxia-inducible factor 1α; IL, interleukin; MCP1, monocyte chemoattractant protein 1; PDGF, platelet-derived growth factor; SASP, senescence-associated secretory phenotype; TGFβ1, transforming growth factor beta 1; TNFα, tumor necrosis factor alpha.

in obesity (20). Moreover, it was demonstrated that DPP4$^+$ progenitors produce ICAM1$^+$ and CD142$^+$ preadipocytes and that analogous DPP4-expressing cells are present in human subcutaneous white adipose tissue (scWAT), pinpointing this population as the root of adipogenesis in both mice and humans (20). Interestingly, these findings conflict with previous data that identified CD142$^+$ cells as adipogenesis-regulatory cells, a population capable of suppressing adipocyte formation (21). As single-cell technologies become more refined, and methodologies are harmonized, these discrepancies should resolve.

Table 1 Molecular markers for adipocyte progenitor cells and preadipocytes

Cell type	Biomarker(s) (positive)	Biomarker(s) (negative)	Reference(s)
Multipotent progenitors (mouse/human)	DPP4/CD26/CD55	NA	20
Committed preadipocytes	ICAM1/CD142/αSMA ZFP423 (mouse)/PDGFRα/PDGFRβ	NA	20, 21, 144
White adipocytes (mouse)	CD34/Sca1 (mouse)/PDGFRα/PDGFRβ/CD44/CD24/VCAM1	CD31/CD45/Lin	145, 146
White adipocytes with high lipolytic flux (human)	CD29/$CD34^{high}$	Lin	24
Myofibroblastic white adipocytes (mouse/human)	PDGFRα/$CD9^{high}$	NA	48
Beige adipocytes (mouse/human)	PDGFRα/Sca1 (mouse)/SMA/CD81/CD29 (human)	Lin/Myf5/Pax3/CD34 (human)	24, 29, 33–35
Glycolytic beige adipocytes (mouse)	MyoD/PDGFRα/CD34/CD29	NA	39
Brown adipocytes (mouse)	Myf5/Pax7/En1/Pax3/Trpv1	Prx1/CD31/CD45	28, 30–32
Aging-dependent regulatory cells (mouse/human)	CD34/PDGFRα/Pref-1/$CD163^{high}$/$CD36^{high}$/$Pu.1^{high}$	NA	63
Dermal white adipocytes (mouse)	PDGFRα (dermal mesenchyme)	CD31/CD45	125

Abbreviations: DPP4, dipeptidyl peptidase-4; En1, engrailed 1; ICAM1, intercellular adhesion molecule 1; Myf5, myogenic factor 5; MyoD, myoblast determination protein 1; NA, not applicable; Pax, paired-box protein; PDGFR, platelet-derived growth factor receptor; Pref-1, preadipocyte factor 1; Prx1, paired-related homeobox 1; Sca1, stem cell antigen-1; SMA, smooth muscle actin; Trpv1, transient receptor potential cation channel subfamily V member 1; VCAM1, vascular cell adhesion molecule 1; ZFP, zinc finger protein.

The identification of precursor cells contributing to the pathological expansion of WAT in obesity is of great therapeutic interest. For instance, it has been shown that promoting the differentiation of $PDGFR\beta^{+}$ adipocytes leads to healthier visceral fat expansion in obesity with improved glucose homeostasis (22). Moreover, the balance of PDGFRα/PDGFRβ signaling in APs may determine differentiation into white or thermogenic beige adipocytes (23). In a recent single-cell analysis of 25 adipose samples (12 visceral, 13 subcutaneous) from individuals with obesity, APs were demarcated by their stage of adipogenesis by the expression of *CFD*, which encodes the adipokine adipsin (6). This study also identified glutathione peroxidase 3 (*GPX3*) as being a protective gene in APs derived from individuals without T2D (6). On the other hand, genes associated with the progression of T2D and identified by scRNA-seq in humans included *WISP2* and *ATF3*, thus revealing potential therapeutic targets for the treatment of insulin resistance and restoration of euglycemia (6). Using fluorescence-activated cell sorting followed by metabolic and proteomic analysis, the complex nature of human APs was further established by demonstrating that rates of basal and stimulated lipolysis are increased in adipocytes derived from progenitors with high CD34 expression versus those with low or absent CD34 (24). Moreover, these alterations in lipolysis were detected in APs stemming from abdominal and gluteofemoral subcutaneous adipose depots but not from the omentum (24). As such, the potential contributions of APs to disease

states can be further distinguished by not only surface markers but also their anatomical location. Higher-resolution technologies such as spatial transcriptomics complimented by scRNA-seq revealed that APs have distinct localization patterns within AT (25). For instance, collagen-rich progenitors appear to cluster in proximity to M2 macrophages to form adipogenic niches (25). Additionally, spatial mapping followed by hyperinsulinemic-euglycemic clamps has demonstrated that mature adipocyte subpopulations in humans have markedly distinct sensitivities to insulin, with only those enriched for adiponectin demonstrating a robust response to the hormone (25). The degree to which specific APs contribute to the heterogeneity of these mature white adipocytes and metabolic disorder in human WAT is an ongoing query.

Brown and Beige Adipose Tissue

Thermogenic beige and brown fat appears to not only increase energy expenditure but also improves glucose clearance, reduces fibrosis, and exerts anti-inflammatory effects leading to systemic benefits (26). Recently, a retrospective study on individuals subjected to ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography showed that simply the presence of BAT is associated with lower blood glucose, decreased white blood cell count, and triglycerides as well as increased high-density lipoproteins (27). It was also determined that individuals with BAT have decreased prevalence of T2D and ectopic fat accumulation in the liver (27).

Developmentally, embryonic brown adipocytes arise prenatally from precursors expressing the somite markers engrailed 1, myogenic factor 5 (*Myf5*), paired-box protein 3/7, and mesenchyme homeobox 1 (28–31). Recently, vascular smooth muscle cells expressing the temperature-sensitive cation channel TRPV1 have also been identified as a source of brown adipocytes in response to cold exposure (32). Beige adipocytes, on the other hand, stem from *Myf5*-negative APs and mature from precursors expressing PDGFRα, Sca1 (in mice), smooth muscle actin, and CD81 (28, 29, 33–35). Beige adipocytes are unique in that they express a functional thermogenic program only upon exposure to beiging stimuli such as cold and β3-adrenergic signaling (2). When these signals are withdrawn, beige fat undergoes whitening, a process relying on mitochondrial clearance via mitophagy that leads to the readoption of WAT characteristics (36, 37).

Not unlike WAT, brown and beige adipose tissues are also highly heterogeneous with respect to cell composition. Using scRNA-seq and 3D tissue profiling, it was demonstrated that there are both low- and high-thermogenic brown adipocytes, demarcated by an increase in UCP1 and adiponectin expression in the highly thermogenic fat cells (38). Interestingly, these two subpopulations are dynamic and interconvertible, with cold exposure converting low-thermogenic adipocytes into a high-thermogenic population and thermoneutrality (30°C) having an opposing effect (38). This cellular complexity also extends to beige fat where, using a murine model lacking all three forms of β-adrenergic receptors, it was demonstrated that *Myod*$^+$-derived beige adipocytes exist that are thermogenic and highly glycolytic, suggesting that it is possible to increase energy expenditure independently of β3 signaling in select AT cells (39). Just as there are subpopulations of adipocytes that promote thermogenesis and the differentiation of brown and beige precursors, there are also populations that suppress it. Recently, by applying single-nucleus RNA sequencing, it was demonstrated that CYP2E1$^+$ ALDH1A1$^+$ cells in the interscapular BAT of mice depress thermogenesis at higher temperatures by secreting acetate (40). Recognition of this metabolite by G-protein-coupled receptor (GPR) 43 effectively downregulates UCP1 and mitochondrial respiration (40). Further advances in single-cell technologies, as well as an improved understanding of the autocrine and paracrine effects of secreted metabolites, should shed greater light on the heterogeneity of thermogenic fat and modulation thereof.

ADIPOSE TISSUE FIBROSIS

A hallmark of obesity and aging, fibrotic adipose tissue is demarcated by an accumulation of extracellular matrix (ECM) proteins, limiting the pliability and capacity of AT to remodel itself in response to a changing metabolic landscape (41). While ECM proteins such as collagen, elastin, and fibronectin are essential for AT expansion, their excessive accumulation is linked to infiltration of proinflammatory M1 macrophages and, consequently, insulin resistance and increased risk of T2D (42). Indeed, using a whole-body knockout model of the ECM protein collagen VI (Col6), it was demonstrated that lack of Col6 leads to decreased inflammation with improved glucose metabolism and insulin sensitivity (43). PRDM16, a transcription factor and powerful inducer of beige and brown adipocyte formation, has been shown to block precursor fibrogenesis via the secretion of β-hydroxybutyrate (44). Importantly, fat-specific repression of adipose tissue fibrosis by the cold-inducible transcription factor GTF2IRD1 in the PRDM16 complex is sufficient to improve glucose homeostasis and AT insulin sensitivity independently of changes in body mass (45). Collectively, these data demonstrate that fibrotic proteins themselves are a source of systemic dysfunction and not simply a by-product of adipose maladaptation. In obesity, chronic overnutrition is at the root of AT fibrosis, leading to the expansion of lipid droplets in adipocytes to reaches beyond the diffusional limit of oxygen (41). As a result, impaired angiogenesis and a persistent hypoxic state promote the activation of hypoxia-inducible factor 1α (HIF1α), which induces the transcription of profibrotic and proinflammatory genes (**Figure 1*b***) (46).

The heterogeneity of this inflammatory environment renders it difficult to narrow down the source of fibrotic deposits. Macrophages are known to secrete TGFβ1 and PDGF, activators of fibroblasts that modulate ECM production (47). However, macrophages are not the only actors inducing AT fibrosis. Recently, the role of APs in this process has been described. In obese mice prone to visceral fibrosis, PDGFRα^{+} progenitors with high CD9 expression drive the pathological remodeling of adipose, adopting a myofibroblastic phenotype and promoting ECM production (48). In human omental WAT, PDGFRα^{+} CD9^{high} cells were correlated to insulin resistance and the severity of fibrosis (48). Adipocytes arising from the gonadal AT of mice originate from PDGFRβ^{+} cells (49). Using scRNA-seq in a DIO model, a population of profibrotic and antiadipogenic progenitor cells was identified that suppresses peroxisome proliferator-activated receptor gamma (PPARγ) activity in a HIF1α-dependent manner via its phosphorylation on serine 112 (49). To that end, targeting HIF1α therapeutically via a specific inhibitor such as PX-478, or indirectly with the PDGFR inhibitor imatinib, leads to marked improvement in adipogenesis, fibrosis, inflammation, and glucose tolerance (49, 50). This finding raises the intriguing possibility that AT fibrosis can be reversed pharmacologically, encouraging healthy adipocyte dynamics.

Given the importance of blood supply for AT thermogenesis and lipolysis, targeting angiogenesis in AT is an attractive prospect for treating metabolic disorders (51). Control of angiogenesis in adipose is multifactorial, involving interplay between pro- and antiangiogenic molecules as well as cross talk between adipocytes and endothelial cells (52). AT angiogenesis may also be autoregulatory, as it releases the angiogenic factors angiopoietin-2 and vascular endothelial growth factor (VEGF) (53). Additionally, leptin has been shown to upregulate and act synergistically with VEGF, while adiponectin has been demonstrated to both promote and inhibit angiogenesis (51). Clinical modulation of angiogenesis for metabolic disorders, however, is a subject of debate. As with cancerous tumors, initial efforts in treating obesity were aimed at reducing angiogenesis to starve AT of oxygen and nutrients with inhibitors such as TNP-470, which targets methionine aminopeptidase-2 (54). In murine models on a HFD, this strategy reduces body weight while increasing insulin sensitivity (55). However, as with β-adrenergic stimulation, limiting fat mass expansion by systemically inhibiting angiogenesis would exacerbate hypertension and cardiovascular disorders. Moreover, increasing energy expenditure through beige and brown fat requires

angiogenesis (56). To that end, polymeric nanoparticles targeted to adipose tissue vasculature for the delivery of rosiglitazone or a prostaglandin E2 analog have been demonstrated to increase vascularization of AT (57). In a murine DIO model, these nanoparticles decreased circulating cholesterol and triglycerides while impeding weight gain and increasing expression of thermogenic markers in inguinal WAT (57). The application of nanomedicine-based approaches to attenuate metabolic disorders specifically in AT holds potential as a means to avoid off-target effects from systemic drug administration.

ADIPOSE TISSUE SENESCENCE

With a predicted population of 2 billion people by 2050, the elderly represent one of the fastest-growing fragments of society, one with a predicted health-care burden that has stoked intensified research efforts into the pathophysiology of aging (58). This focus has also extended to adipocytes, which demonstrate an age-related impairment in angiogenesis along with increased fibrosis and the appearance of a senescence-associated secretory phenotype (SASP) (59). Despite their inability to divide, senescent adipocytes continue to release proinflammatory moieties such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor alpha (TNFα) (**Figure 1*b***) (60). Furthermore, SASP prevents the formation of metabolically beneficial beige fat, which can be reversed genetically via deletion of the senescence marker *Ink4a/Arf* in mice (61). Aging is also associated with the redistribution of AT, with an overall loss of scWAT and accumulation of visceral and intramuscular fat, which is linked to the development of metabolic syndrome (59). The loss of protective scWAT is often attributed to a decline in both the number and differentiation potential of APs (62). Recently, a subpopulation of APs designated as aging-dependent regulatory cells (ARCs) has been identified in 48- and 72-week-old mice (63). While these cells were $CD34^+$, $PDGFR\alpha^+$, and $Pref\text{-}1^+$, common markers for adipose progenitors, they also demonstrated high expression of the inflammatory markers CD163, F4/80 (Adgre1), Lgals3, CD36, and NFkB1 that increased further in the oldest cohort (63). Importantly, ARCs had increased expression of Pu.1, a transcription factor known to inhibit preadipocyte differentiation via downregulation of PPARγ (64). As such, ARCs are incapable of differentiation, while also exhibiting a secretory profile that inhibits the differentiation of neighboring APs, overall contributing to the loss of scWAT in the elderly.

It has also been demonstrated that aging is associated with the loss of adipocyte Rubicon, a downregulator of autophagy (65). The increased autophagic activity in aged cells prompts the degradation of SRC-1 and TIF2, coactivators of PPARγ, thus impeding adipogenesis and causing detrimental sequelae such as glucose intolerance and hepatic fat accumulation (65). Consistent with metformin's purported benefits in increasing health span and life span in mice, this biguanide was used to treat adipose-derived stromal cells from the scWAT of aged adult women (>55 years) where it was found to improve adipogenesis, glucose uptake, oxidative stress, and mitochondrial function via the activation of AMP-activated protein kinase (AMPK) (66, 67). While metformin's AMPK-mediated benefits in aging, cancer, and neurodegenerative disease are well described, this compound also exerts effects independently of this energy sensor through mechanisms that remain to be fully delineated and are likely to be concentration dependent (68, 69). After hepatic uptake, circulating metformin levels are reduced to 10–40 μM, an important mechanistic consideration for the clinical treatment of peripheral adipose tissue (69).

MECHANISMS OF ADIPOSE TISSUE THERMOGENESIS

The classical and most well-known mechanism by which organisms increase thermogenesis is via sympathetic nerve-mediated β3-adrenergic signaling (2). Upon binding to catecholamines (e.g., norepinephrine), these GPRs activate adenylate cyclase to produce cAMP (70). Subsequent

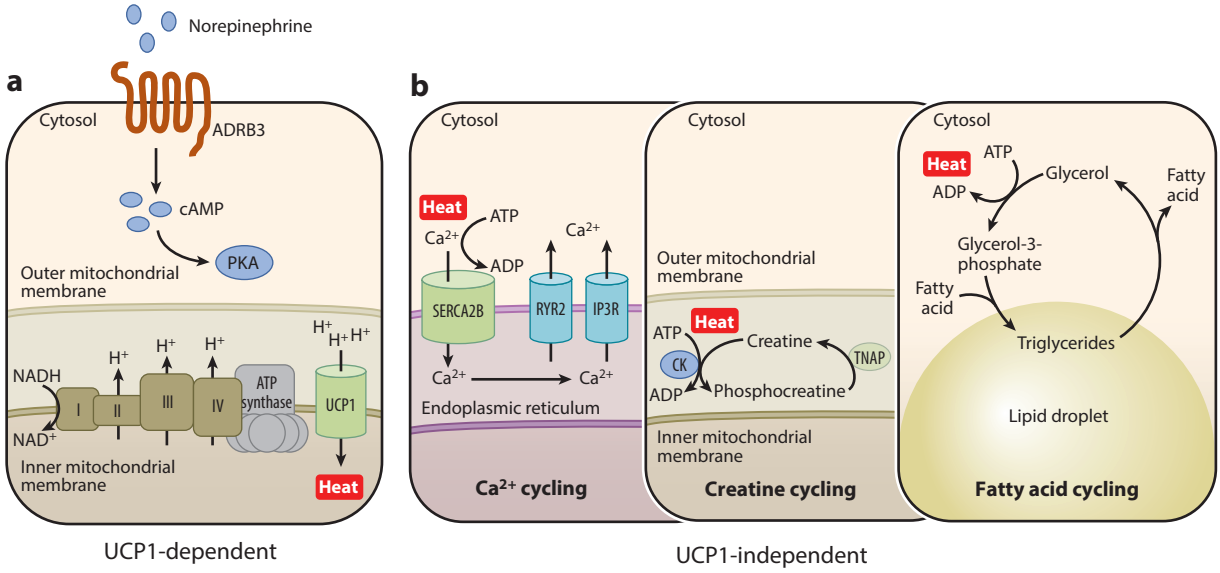

Figure 2

Mechanisms of adipocyte thermogenesis. (*a*) Classically, β3-adrenergic stimulation increases cytosolic cAMP, activating PKA and promoting the thermogenic program, thus dissipating the mitochondrial proton gradient as heat through UCP1 and sacrificing ATP production. (*b*) Absence of UCP1, however, via its genetic ablation or in mammals lacking a functional thermogenin, does not impede thermogenesis. Alternative futile cycles involving calcium, creatine, and fatty acids also generate heat via the cleavage of ATP without accomplishing functional work. Abbreviations: cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; SERCA, sarco/endoplasmic reticulum Ca^{2+} ATPase; TNAP, tissue-nonspecific alkaline phosphatase; UCP1, uncoupling protein 1.

stimulation of protein kinase A (PKA) activity leads to the phosphorylation and, consequently, activation of hormone-sensitive lipase (HSL) and the transcription factor CREB (70). The resultant increase in mitochondrial biogenesis via PGC-1α and uncoupling of the electron transport chain by UCP1 leads to increased heat generation and energy expenditure using long-chain fatty acids generated by lipolysis to mediate proton conductance (**Figure 2*a***) (2, 71). As we now know, however, there is a litany of mechanisms by which adipocytes induce thermogenic machinery independently of β3 ligands. These mechanisms include signaling by cardiac natriuretic peptides and the hepatokine fibroblast growth factor 21 but may not involve extracellular ligands at all (72, 73). In line with the notion that β3 signaling is not the sole regulator of adipose thermogenesis, the concept of UCP1 as the only mammalian thermogenin has also been dismissed, and it is now acknowledged that alternative pathways are activated to enhance heat production in AT.

Calcium Futile Cycling

When mapping *Ucp1* sequences from 133 mammals on a species tree, it was found that several organisms (e.g., cetaceans, horses) evolved extreme cold tolerance in the absence of a functional UCP1 gene (74). To that effect, it is reasonable to conclude that alternative and perhaps redundant pathways exist to ensure temperature homeostasis in changing environments. Sarco/endoplasmic reticulum Ca^{2+} ATPases (SERCAs) are a family of enzymes that couple the energy from ATP hydrolysis to the transport of calcium from the cytoplasm to the sarco/endoplasmic reticulum (75). It is known that uncoupling of SERCA1 in skeletal muscle, whereby the two-to-one stoichiometry of Ca^{2+} transported to ATP hydrolyzed is disrupted, generates heat, and increases REE (76, 77). However, it has only recently been demonstrated that a similar mechanism is at

play in beige adipocytes, where SERCA2b is required for the norepinephrine-induced increase in oxygen consumption rate in the presence and absence of UCP1 (78). Indeed, in a porcine model that lacks functional UCP1, it was demonstrated that SERCA2b and Ca^{2+} cycling thermogenesis mediate the increase in oxygen consumption rate in response to beiging stimuli (**Figure 2*b***) (78).

Several attempts were made to activate Ca^{2+} cycling thermogenesis in vivo. An allosteric SERCA activator CDN1163 was shown to decrease the endoplasmic reticulum (ER) stress response, hepatic gluconeogenesis, and lipogenesis in a genetic murine model of obesity and glucose intolerance (*ob/ob* mice) (79). Treated animals had an increase in energy expenditure, lowered fasting blood glucose, and increased glucose tolerance accompanied by an increase in UCP1-dependent thermogenesis in adipose (79). The extent to which systemic administration of SERCA2b activators provide benefits through UCP1-independent fat thermogenesis remains unknown. To that effect, it has recently been demonstrated that adipocyte-specific intracellular Ca^{2+} cycling can be stimulated wirelessly in a murine model using optogenetics, a technique common to neuroscience that allows for the opening of ion channels via light stimulation (80, 81). Adipocyte-specific activation of Ca^{2+} cycling through the cation channel channelrhodopsin-2 sufficiently increased whole-body energy expenditure by ~35% without the need for cold exposure in mice (80). Calcium influx was also increased with optogenetics in UCP1-null adipocytes, providing proof of concept that thermogenesis and energy expenditure can be enhanced independently of mitochondrial uncoupling (80).

Futile Creatine Metabolism

In addition to Ca^{2+} cycling, a creatine-driven futile cycle is also known to increase beige fat thermogenesis (82, 83). Here, creatine kinase B (CKB) is trafficked to mitochondria in response to thermogenic stimuli such as cold exposure where it phosphorylates creatine, consuming ATP and generating ADP and heat (84). In turn, mitochondrial tissue-nonspecific alkaline phosphatase regenerates creatine from phosphocreatine, closing the cycle (**Figure 2*b***) (85). Indeed, fat-specific genetic deletion of either component accelerates weight gain in mice fed a HFD, with knockout of CKB specifically demonstrating impaired glucose tolerance and reduced insulin sensitivity (84, 85). On a HFD, β3-adrenergic agonist-dependent energy expenditure was increased in mice when diet was supplemented with creatine (84). To demonstrate the translatability of this finding, human adult vegetarians with low creatine bioavailability had their diets supplemented with 20 g of creatine monohydrate daily for 7 days followed by testing (86). Contrary to the hypothesis, creatine supplementation did not significantly alter energy expenditure or BAT activation as measured via ^{18}F-FDG PET–magnetic resonance imaging, with the caveat that this clinical trial was performed on lean individuals without a β3-adrenergic agonist (86).

Lipolytic Cycles Turn Up the Heat

Another futile pathway by which ATP is consumed without performing functional work consists of lipolysis and reesterification cycling (87). Here, the catabolism of triglycerides into free fatty acids (FFAs) and glycerol occurs in tandem with the generation of glycerol-3-phosphate catalyzed by glycerol kinase (**Figure 2*b***) (88). Chronic β-adrenergic simulation with CL 316,243 enhances both de novo lipogenesis and oxidation of fats in all murine depots, regardless of UCP1 content, suggesting futile lipolysis and reesterification increases energy expenditure independently of mitochondrial proton leak (88). With indirect calorimetry and infusion of [1-(14)C]palmitate, it was demonstrated that leptin injection causes an 85% increase in this futile cycling, contributing to a 14% difference in metabolic rate versus saline treatment (87). Thiazolidinediones (TZDs), high-affinity ligands for PPARγ and antidiabetic compounds, also induce futile lipid cycling and

thus decrease the release of FFAs into circulation, partially accounting for their insulin-sensitizing mechanism (89). However, PPARγ agonists such as pioglitazone and rosiglitazone are associated with weight gain and fluid retention, possibly via their ability to promote AP differentiation into adipocytes (90). TZDs also inhibit the mitochondrial pyruvate carrier (MPC) complex, thus limiting pyruvate catabolism and encouraging the consumption of fats as an alternative fuel source (91). To that end, second-generation TZDs such as MSDC-0602K, which are designed to inhibit the MPC complex while minimizing PPARγ agonism, hold promise in treating metabolic disorders without the detrimental side effects of classical TZDs (92). In a randomized, double-blind, placebo-controlled study, MSDC-0602K reduced glucose, insulin, and markers of liver damage in patients with nonalcoholic steatohepatitis without PPARγ agonist–associated side effects such as edema and fractures (92).

PATHOLOGICAL BROWNING: TOO MUCH OF A GOOD THING?

While the lion's share of literature has focused on the beneficial metabolic effects of inducing adipose thermogenesis, there are notable examples where brown or beige adipocytes appear to contribute to a pathological state. As seen in other biological phenomena (e.g., reactive oxygen species, the unfolded protein response), there is likely a molecular "Goldilocks zone" of thermogenic activation characterized by positive systemic effects, whereas chronic and hyperstimulation of browning may accompany or even precede the development of detrimental sequalae.

Cancer Cachexia

Cancer-associated cachexia (CAC), a condition demarcated by the wasting of skeletal muscle and adipose depots, affects nearly half of cancer patients and contributes to 20% of cancer-related deaths (93). Although no direct link to browning was made at the time, the connection between fat breakdown and skeletal muscle loss was reported in mice with CAC induced by subcutaneous injection of Lewis lung carcinoma (LLC) cells (94). Adipose triglyceride lipase (ATGL) and HSL are the enzymes primarily responsible for the hydrolysis of triacylglycerols and diacylglycerols, respectively (95). Ablation of either in a murine model of CAC was sufficient to protect against loss of WAT, myocyte apoptosis, and muscle degradation, with HSL knockout conferring less protection (94). Mechanistically, AT lipolysis induces the bulk of its downstream effects via ectopic deposition of FFAs in the liver, heart, and skeletal muscle (96). When de novo lipogenesis exceeds the rate of fat breakdown via β-oxidation in these tissues, lipotoxicity is known to occur (97). FFAs can activate c-Jun N-terminal kinase, a key player in the development of insulin resistance and the induction of apoptotic pathways (97).

A number of clinical reports have demonstrated the association of brown fat with cachexia in cancer patients, leading to efforts to elucidate the underlying mechanisms stimulating thermogenesis in chronic disease (98, 99). Indeed, it has been postulated that the ability of beige and brown fat to dissipate energy as heat likely contributes to the negative energy balance observed in cachectic patients (100). By applying murine models of liver, lung, and pancreatic cancers, it was shown that browning of WAT is an early event in the progression of CAC, with gene expression of UCP1 and browning markers detectable even in precachectic mice (100). Therein, the authors observed that lowering the circulating levels of the pleiotropic cytokine IL-6 with a monoclonal antibody decreases the browning response and reduces the loss of fat and muscle mass, suggesting that there is potential for mitigating CAC with early anti-inflammatory treatment (**Figure 3*a***) (100). Tumor-derived parathyroid-hormone-related protein (PTHrP) also drives the adipose tissue thermogenic program in an LLC model of CAC (101). Neutralization of PTHrP with

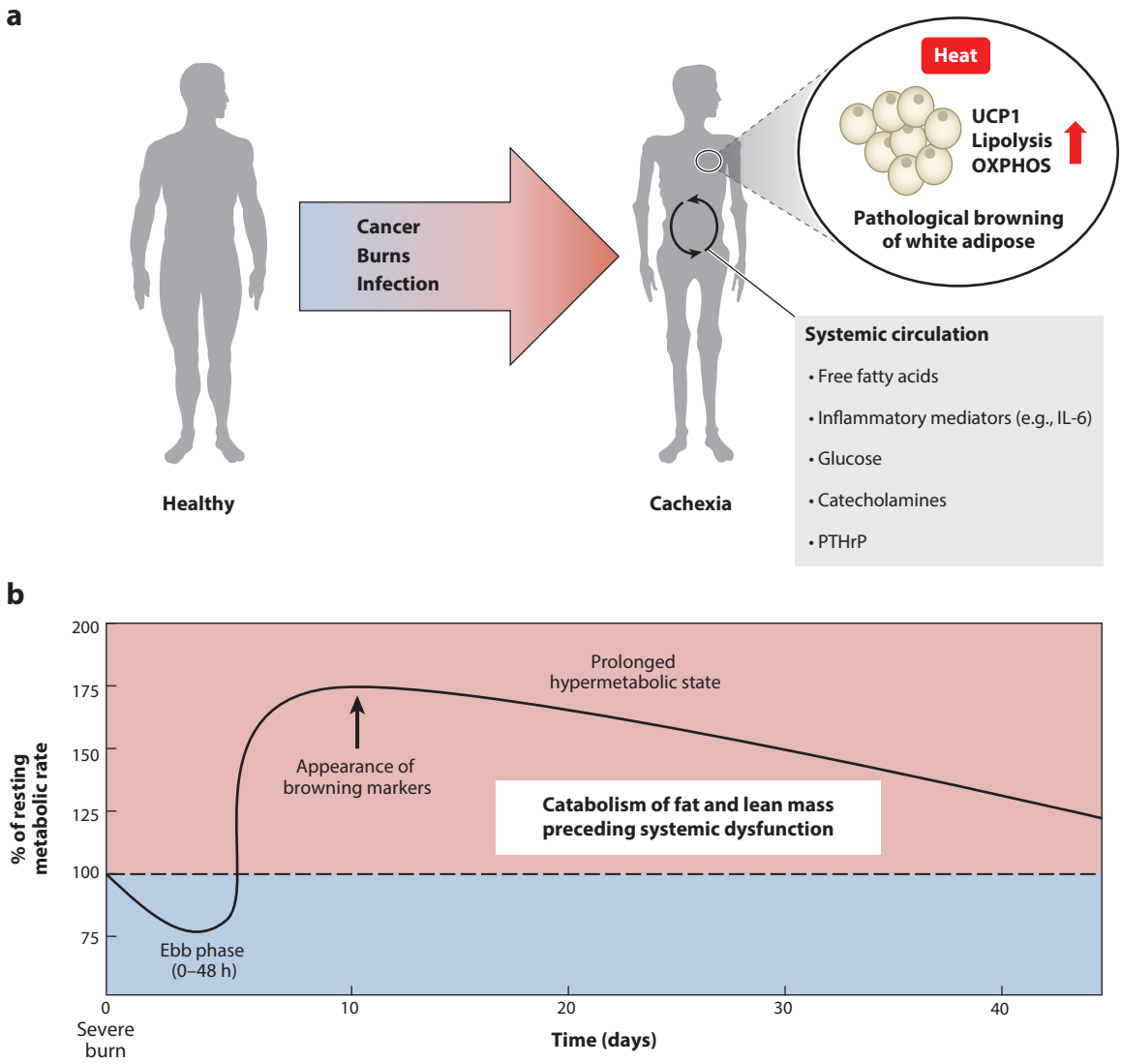

Figure 3

Pathological adipose tissue remodeling in cachexia and burns. (*a*) While browning is often heralded for its benefits in metabolic disorders, increased lipolysis and UCP1-mediated thermogenesis appears to be detrimental in cachectic conditions such as in cancer and severe burns. (*b*) Severe burns, in particular, are demarcated by a prolonged hypermetabolic response. Browning of subcutaneous white adipose tissue in addition to increased lipolysis and a proinflammatory environment contribute to systemic lipotoxicity, organ failure, sepsis, and death. Abbreviations: IL, interleukin; OXPHOS, oxidative phosphorylation; PTHrP, parathyroid-hormone-related protein; UCP1, uncoupling protein 1.

antibodies was sufficient to rescue against fat and muscle wasting while decreasing thermogenic gene expression and lowering O_2 consumption (101). The importance of PTHrP may also extend to clear cell renal cell carcinoma (ccRCC), where it was recently shown to promote browning of perinephric adipose tissue (102). In turn, lactate released from this AT depot appears to fuel growth of ccRCC, creating a vicious cross talk between tumor cells and nearby adipocytes (102).

Burn Injuries and Sepsis

Severe burns are unique in that, while the injurious event may take only seconds, the metabolic consequences can persist for years. As with CAC, burn patients are in a persistent catabolic state, with the loss of fat mass and lean muscle mass predisposing the individual to an increased risk of infections, sepsis, and, ultimately, death (103). While improvements in nutritional guidelines have greatly improved mortality rates for severe burns (>20% of the total body surface area), many patients have supraphysiological nutritional requirements with profound insulin resistance and poor glucose control (104). To that effect, intensive insulin therapy to maintain glucose levels below 120 mg/dL is the gold standard for treating severe burn patients, but this only mitigates the hypermetabolic response while failing to address the underlying causes (105). The origins of burn-induced hypermetabolism are multifactorial and include stress hormones, an inflammatory cytokine storm, and a chronic persistence of circulating catecholamines (**Figure 3*b***) (106). In one study, urinary norepinephrine was detected in pediatric burn patients at levels significantly higher than healthy controls 2 years out from the initial injury (107). As such, it is of no surprise that this persistent β-adrenergic stimulation markedly increases UCP1 levels and the browning of scWAT in burn patients and murine models of thermal trauma (108, 109). Much like in CAC, genetic deletion of IL-6, a causative agent of pathological browning, or UCP1 leads to improved systemic results such as increased fat mass and body mass while diminishing the fatty burden on the liver (110, 111). Moreover, clinical interventions with proven benefits in burn patients appear to diminish the UCP1-mediated increase in REE. β-Adrenergic blockade with propranolol or activation of protein phosphatase 2A in adipocytes with metformin decrease AT lipolysis, ER stress, and bioenergetics with benefits in murine and human studies (111, 112). Inhibitors of lipolysis, such as acipimox and the murine-specific ATGL inhibitor atglistatin, also decrease browning and the downstream consequences such as hepatic steatosis (113–115). Taken together, these results appear to demonstrate that mitigating the physiological changes to AT postburn, including adipose browning, is beneficial to burn patients.

AT browning has also been demonstrated in lean mice with a cecal ligation and puncture model of sepsis (116). As with burns, sepsis is associated with increased adrenergic and inflammatory stimuli. Interestingly, mice on a HFD regimen failed to upregulate browning markers after induction of sepsis (117). Moreover, the HFD cohort was protected from liver injury and had decreased TNFα and IL-6 levels versus their lean counterparts (117). Severe obesity is often viewed as a comorbidity in pathological states. However, in critically ill patients with burns, sepsis, or cancer cachexia, there exists an obesity paradox whereby mild obesity appears to be protective and associated with lower in-hospital mortality (118–120). As these conditions are hypercatabolic and characterized by wasting of fat tissues, it has been postulated that an increase in metabolic reserves stemming from AT in obese patients is conducive to improved outcomes (119). To that effect, limiting UCP1-mediated browning and its associated increase in lipolysis and energy expenditure would be protective (112). From an evolutionary perspective, it is not yet known why thermogenesis increases in these pathologies. In burns, for instance, loss of the skin barrier may impair the ability to thermoregulate, thus necessitating a browning response to maintain body temperature homeostasis. To that end, in a murine model of thermal trauma, beige adipocyte markers persist for up to 60 days after the initial injury, long after wound closure (121). It is possible, therefore, that pathological browning is simply an epiphenomenon of chronic sympathetic nervous system overactivity.

Drug-Induced Hyperthermia

In some cases, browning of AT may amplify drug-induced hyperthermia via interorgan cross talk. Malignant hyperthermia (MH) is a condition triggered by volatile anesthetics and characterized

by muscle rigidity, increased heart rate, and high body temperature that, if left unchecked, is fatal (122). The bulk of MH cases are a result of mutations in ryanodine receptor 1 (RYR1), the channel allowing for Ca^{2+} release from the sarcoplasmic reticulum in muscle (122). Drug-induced increases in cytosolic concentrations of Ca^{2+} can initiate futile cycling by the aforementioned SERCA to generate heat but also activate glycogenolysis in muscle via calmodulin (123). It has recently been demonstrated that lactate, the end product of glycogenolysis and glycolysis, is released into circulation and results in significantly increased BAT thermogenesis in mice harboring a mutation to *Ryr1* versus wild-type controls (123). Genetic ablation of UCP1 improved the survival of *Ryr1* mutant mice upon heat exposure, suggesting thermogenic fat exacerbates the life-threating MH-like response (123). Consistent with the knowledge that children are more prone than adults to MH episodes in response to anesthetics, the transgenic mice aged 8 weeks or less did not survive heat exposure (37°C for 15 min) (123). The increased prevalence and activity of BAT in pediatric patients may therefore present as a significant risk factor for the onset of MH, though this remains to be demonstrated clinically.

UNRAVELING THE ROLES OF DERMAL ADIPOCYTES

Often erroneously considered to be a continuation of the subcutaneous fat, a distinct population of adipocytes now known as dermal white adipose tissue (dWAT) exists adjacent to the epidermis (124). In murine models, dWAT is distinguishable from scWAT, as the two are separated by the striated muscle panniculus carnosus (124). While the latter is lacking in humans, dWAT exists as cone-shaped structures with a portion in the dermis and another in scWAT, housing the root of hair follicles (124). Lineage tracing in mice has demonstrated that dWAT is established in the dermal mesenchyme, further delineating it as a separate depot from scWAT (125). While dWAT may play a role in insulation during thermal stress, it acts distinctly from brown and beige AT depots, thickening over the course of several days while not expressing traditional thermogenic markers such as UCP1 (126). Local dermal adipocytes also expand in response to pathogens. For instance, *Staphylococcus aureus* infection triggers the expansion of dWAT as evidenced by increased expression of PREF1 and ZFP423, markers for committed preadipocytes (127). Treatment of mice with pharmacological inhibitors of PPARγ and, thus, adipogenesis, increased their susceptibility to infection (127). It was also demonstrated that *S. aureus* increased the expression of cathelicidin antimicrobial peptide in dWAT as a measure to directly kill bacteria, pinpointing this AT depot as a frontline defensive barrier against invading organisms (127).

Unlike other populations of mature adipocytes, dWAT also appears capable of dedifferentiation (125). In particular, dermal fat cells dedifferentiate and redifferentiate during hair cycling with observable expansion in size and number of cells while follicles grow and a decrease in fat volume associated with regression of hair follicles (128). In an ex vivo model, using hair follicles embedded in adipose from male patients undergoing hair transplantation procedures, it was demonstrated that dWAT secretes hepatocyte growth factor (HGF) to promote hair shaft production and hair follicle pigmentation (128). In the dermal papilla, HGF downregulates secreted frizzed-related protein 1, leading to activation of Wnt/β-catenin signaling involved in hair follicle growth modulation and melanocyte differentiation (128). HGF also upregulates the inner root sheath keratin genes associated with the hair shaft (128). Given their anatomical location, it is unsurprising that dermal adipocytes also play a key part in wound healing. Using a murine model with an inducible diphtheria toxin receptor in adipocytes (*Adipoq*Cre;mT/mG;iDTR mice), an intradermal injection of diphtheria toxin successfully ablates dWAT without the loss of other AT depots (129). Mice lacking dWAT demonstrated a delay in recruitment of both pro- and anti-inflammatory macrophages to the wound bed, impairing both reepithelialization and revascularization (129).

Using a similar model crossed with *Atgl*$^{fl/fl}$ mice, it was uncovered that dermal adipocyte lipolysis is required for the recruitment of monocyte-derived Ly6C^{hi} macrophages via GPR84 signaling, suggesting that FFAs are needed for the initial inflammatory phase of wound healing (129). Given the benefit of adipocytes in skin repair, autologous fat grafting for the treatment of burn wounds, scars, and diabetic ulcers has shown promising results (130). Keloids and hypertrophic scars are thick raised scars that appear often at the site of a thermal injury and may be associated with pain, itching, and limited mobility (131). Fat injection into scars has been shown to reduce fibrosis and thickness and encourage new collagen deposition, with subjective improvements in aesthetics (130). In one study of 13 patients with burns to the hand, autologous fat transfer improved the range of movement and scar quality (132). While it is clear that skin-adipose cross talk is of great importance in health and pathophysiology, this relationship is understudied relative to the field of adipose biology as a whole. The importance of dWAT vascularization and its role in obesity and aging as well as skin diseases such as psoriasis are currently unclear, particularly in humans.

HOST–PATHOGEN INTERACTIONS AND ACQUIRED LIPODYSTROPHY

Lipodystrophy comprises a series of disorders whereby adipose tissue is lost from one area of the body, generally a subcutaneous region, and redistributed elsewhere (133). This may manifest as increased adipose in the visceral cavity or trunk region but also as ectopic deposition in nonadipose tissues, leading to lipotoxicity and insulin resistance (134). As opposed to rare cases of congenital lipodystrophy [reviewed extensively elsewhere (134, 135)], acquired lipodystrophy is more common, occurring as a result of both infections and combination antiretroviral therapy (cART) (133). Refinements in cART, particularly for human immunodeficiency virus (HIV), have resulted in a decreased risk of lipodystrophy (133). For instance, older-generation nucleoside reverse transcriptase inhibitors (NRTIs) would inhibit mitochondrial DNA (mtDNA) polymerase-γ, substantially reducing adipocyte mtDNA content and inducing lipoatrophy (133). Replacement with less-toxic NRTIs has decreased these symptoms, leading to improvements in management and quality of life for persons living with HIV (133). What is less understood, however, is the cross talk between infectious viruses or parasites and adipocytes themselves, as well as the systemic consequences thereof. Further insight into this relationship is paramount, as AT is a known reservoir for pathogens such as *Trypanosoma* spp., *Mycobacterium tuberculosis*, HIV, and severe acute respiratory syndrome coronavirus 2 (133, 136–138).

Trypanosoma brucei, the causative agent of sleeping sickness, is transmitted through the bite of a tsetse fly and is highly adaptable to a mammalian host (139). While in its bloodstream form, it relies dominantly on glycolysis as an energy source but switches to proline and other amino acids in its procyclic form (140). Recently, it was determined that in addition to the brain and blood, *T. brucei* accumulates in the AT, using myristate as a carbon source via β-oxidation (140). This form of the parasite is replicative and can establish new infections, as fat homogenate from an infected mouse injected into a naïve mouse also induces parasitemia (140). The breakdown of lipid droplets to provide a fuel source for parasitic growth may explain the weight loss associated with sleeping sickness, but whether this involves communication between the parasite and adipocytes or alterations in adipocyte metabolism is currently unknown (140). Chronic alterations in AT function may also result from *T. cruzi* infection, which persists in adipose depots of mice for up to a year postinfection and is linked to the development of diabetes (136).

Tuberculosis (TB) is the leading cause of mortality by infectious disease (137). The bacillus *M. tuberculosis* can persist in a latent state for decades but, when active, results in death within 2–3 years if left untreated (141). Paradoxically, aerosol infection of mice with *M. tuberculosis*

improved systemic glucose tolerance and insulin signaling in adipocytes despite increased inflammation and hypertrophy (137). This was also demonstrated after a HFD feeding, where glucose control was improved over uninfected controls. Biochemical analyses of AT revealed the activation of Akt by serine 473 phosphorylation via increased activity of mTORC2 (137). As activated leukocytes convert to glycolytic metabolism in response to infection, it is possible that increased glucose uptake into peripheral adipose fuels efforts to eliminate the pathogen (137, 142). Later stages of the infection and the switch from latent to active TB are characterized by loss of fat mass and impaired adipogenesis, with an association of high body mass index with protection (141, 143). Indeed, ablation of fat mass in infected mice leads to an increase in pulmonary *M. tuberculosis*, suggesting that loss of AT may be a key driver in the switch between latent and active infection (141). Whether these stages of adipocyte remodeling are orchestrated by the bacillus to promote its survival or by the host as part of an adaptive response to infection are currently unclear.

CLOSING REMARKS

If one were to put a status on the relationship between humans and their fat cells, "it's complicated" would be an apt choice. Adipocytes are often vilified for their contribution to body image and metabolic disorders but have also been shown to play vital roles in wound healing, immunity, and insulation. Activation of UCP1-dependent and independent thermogenesis are desirable as a stratagem to mitigate obesity and metabolic disease, unless they are part of a spiraling catabolic cascade such as with burns or cachexia, and then these same pathways become pathological. While there has been monumental progress in characterizing and modulating cellular pathways in adipocytes, therapeutic interventions aiming to specifically correct adipocyte dysfunction are rarely applied because, ultimately, there is no clinical consensus on what a dysfunctional adipocyte looks like. To that effect, leaps and bounds have been made on research into adipose pathophysiology, and we now have a clearer picture of AT maladaptation. Modulation of angiogenesis and inhibition of fibrosis, particularly in obesity and aging, can restore adipocyte dynamicity and mitigate a proinflammatory environment. Blockade of adrenergic signaling and early inflammatory mediators such as IL-6 in cachexia and thermal injuries can offset the loss of fat mass and prevent ectopic deposition of FFAs in downstream organs such as the liver. The incorporation of fat or adipose-derived stem cells into traditional skin substitutes may enhance wound healing and prevent scar formation.

Progress has been made, but a number of challenges still lie ahead if we are to unlock the therapeutic potential of targeting adipocytes in disorder and disease. As brown fat, UCP1, and mitochondrial content decline with age, thermogenic cycles that operate independently of these organelles hold promise in treating metabolic disorders. However, pharmacological modalities that stimulate these pathways have not been uncovered or, as is the case with TZDs, require optimization to minimize off-target effects. Identifying novel APs and mature adipocytes via scRNA-seq and spatial mapping provides perspective on the heterogeneity of AT, but assigning a metabolic role to individual populations and characterizing their contribution to tissue dynamics and fuel utilization is a more difficult undertaking. We expect that the insights to be gained from answering these questions and others will further inform a precision medicine approach tailored to adipocytes and their role in pathophysiology.

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