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White Adipose Tissue Browning: a double edge sword

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Abstract

The study of white adipose tissue (WAT) browning has become a “hot topic” in various acute and chronic metabolic conditions, based on the idea that WAT browning might be able to facilitate weight loss and improve metabolic health. However, this view cannot be translated into all areas of medicine. Recent studies identified effects of browning associated with adverse outcomes, and as more studies are being conducted, a very different picture has emerged about WAT browning and its detrimental effect in acute and chronic hypermetabolic conditions. Therefore, the notion that browning is supposedly beneficial may be inadequate. In this review we analyze how and why browning in chronic hypermetabolic associated diseases can be detrimental and lead to adverse outcomes.

Keywords

hypermetabolism; burns; cancer; white adipose tissue; uncoupling protein 1; ER stress

Hypermetabolism in response to injury

The **hypermetabolic response** is characterized by a profound increase in free fatty acids (FFAs) and glycerol release from fat, glucose production by the liver, and amino acids from muscle, ultimately resulting in significant elevations in resting energy expenditure [1] [2] [3]. Catecholamines, corticosteroids, and inflammatory cytokines have been implicated as the primary mediators of this hypermetabolic response [2, 4]. Although this phenomenon may be viewed as an adaptive response to injury, such as thermal injury or cachexia, initially, a prolonged response is potentially futile and becomes devastating for patient outcome [2]. This is because sustained hypermetabolism in these patients results in

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significant muscle wasting, hepatic steatosis, and immunosuppression [2, 5]. Also, during the hypermetabolic phase the skin is significantly depleted of oxygen and becomes hypoxic [6]. Prolonged hypoxia in the skin can have damaging effects on wound healing because it can amplify the levels of reactive oxygen species that foster tissue destruction [7]. This increased free radical activity not only impairs wound closure, but can also impair the activity of macrophages to effectively combat pathogens in the wound bed. [8]. While other organs like the heart (increased cardiac work, tachycardia) and kidney (oliguria, renal failure) [9] are affected by the hypermetabolic response, the majority of the metabolic burden is placed on the liver, skeletal muscle, and adipose tissue (figure 1).

Perhaps the most serious gap in our understanding of the hypermetabolic response is the role of the adipose tissue. In fact, it has recently been suggested that the **‘browning’** of **white adipose tissue (WAT)** in hypermetabolic patients adds fuel to an already highly catabolic state in these patients. As such, in the rest of this review we will converge on the browning of WAT, with a focus on the regulators and the damaging aspects of this browning phenomenon from a hypermetabolic perspective.

‘Browning’ of WAT in hypermetabolic conditions

Reports of browning in traditionally white adipose [10] depots occurred decades ago, when it was observed that mice acclimated to cold developed **brown adipose tissue (BAT)** [11] characteristics, i.e. small, multi-ocular cells enrich in mitochondria, in a subset of cells in the parametrial adipose depots [12, 13]. With regards to humans, there is a dearth of literature concerning the browning of WAT. However, three new studies have recently discovered WAT browning in the development and progression of hypermetabolism in cancer as well as burns [14] [15] [16]. In the first study, Wagner et al observed a phenotypic switch from WAT to BAT [11] in cachexic cancer patients. In the second and third study, Herndon et al found a similar phenotypic switch of WAT to a more BAT-like phenotype in post-burn pediatric patients. Indeed, these same findings were confirmed by Patsouris et al. in adult burn patients, as well as post-burn mice [16]. Overall, these studies reveal the occurrence of WAT browning in humans albeit in the context of pathological conditions (figure 2).

Is the browning of WAT good or bad during hypermetabolism?

Logically, it would not seem beneficial to activate heat production and intense nutrient utilization under conditions of hypermetabolism like those seen in burns, massive trauma, and cancer. While for some aspects of this question the answers are straightforward; this biological occurrence under pathological conditions has remained a mystery. Here we consider how WAT browning is deleterious in the context of hypermetabolic conditions such as burns and cancer (Key figure).

Adipose tissue wasting

The association of adipose tissue with metabolic disease, weight gain, and unpleasant aesthetics has largely vilified this organ as something to purge the human body from. However, more and more studies are showing that having some extra fat tissue is protective in certain chronic diseases. Such a phenomenon has been coined the “obesity paradox” in

which obese and overweight patients with chronic diseases have higher survival rates compared to their healthier weight counterparts [17]. This realization began with a number of studies observing that cancer patients who were characterized as obese had improved survival rates compared to those classified as having a healthy body weight [18]. These same findings have later been corroborated in other conditions like burns, in which it was demonstrated that mild obesity was protective against severe burn injury [19]. Although it is difficult to reconcile why all the obese patients had a better outcome, it seems that excess fat tissue in these patients provides fuel reserves to bridge the gap between decreased intake and elevated requirements post injury.

Cachexia and muscle wasting

Given its central role in energy hemostasis, it is no surprise that adipose exerts a profound influence on neighboring tissues; this appears to be particularly true for muscle tissue. For instance, in burns and cancer you have the occurrence of **cachexia**, a devastating condition characterized by severe weight loss, systemic inflammation, muscle and adipose tissue wasting [20–23]. The WAT remodeling and heightened energy expenditure that occurs in cancer and burn patients has been implicated in triggering cachexia (Key figure). Although few studies have directly investigated the association of WAT browning in mediating cachexia, it is clear that WAT browning is a culprit if not the main facilitator of cachexia [14]. It is postulated that enhanced lipolysis drives cachexia via muscle wasting. This idea emerges from observations by Das et al, in which they have shown that attenuating lipolysis via genetic ablation of adipose triglyceride lipase not only prevents WAT wasting, but also preserves lean muscle mass [24]. Studies have also shown that attenuating WAT browning via β -adrenergic blockade reduces the severity of cachexia [14].

Atherosclerosis and hepatic steatosis

Interestingly, evidence has shown that BAT activation and WAT browning, with their associated increased plasma lipid profiles, accelerates the development and progression of **atherosclerosis** [25]. Two different but complimentary mechanisms have been put forth to explain browning induced atherosclerosis. In the first case, browning of WAT leads to high levels of blood cholesterol, especially LDL and VLDL, core lipids involved in atherosclerotic plaques (32). Equally, circulating adiponectin levels are decreased post browning, which facilitates further plaque buildup as adiponectin has been reported to suppress lipolysis. Similarly, it has been speculated that the well-documented **hepatic steatosis** in burn patients may be linked to WAT browning-induced lipolysis [3] [26] (Key figure) in the liver.

What are the regulators of WAT browning during the hypermetabolic response?

Catecholamines

In burns, marked increases in catecholamines have been noted in patients years after the initial injury [4]. This sustained catecholamine surge in burns has recently been shown to initiate WAT browning and the cascade of events leading to the hypermetabolic response

[15, 16]. It has long been assumed that the adrenal glands were the only source of catecholamine secretion, however, this has recently changed with the discovery that macrophages can secrete catecholamines as well. In this study it was shown that upon activation, polarized M2 macrophages are recruited to subcutaneous WAT and secrete catecholamines to activate WAT browning [27]. This browning effect of macrophages was shown to depend on interleukin 4 (IL-4) signaling, as mice lacking IL-4 signaling exhibited impairments in browning [28]. However, it was recently shown that palmitate, an abundant FFA in the serum of burn patients can also regulate macrophage polarization [29] [30, 31]. This macrophage-adipose tissue cross talk is intriguing as it may suggest a vicious feed forward loop, as WAT browning-induced lipolysis causes FFA efflux which in turn polarizes macrophages, thus sustaining WAT browning during the hypermetabolic response.

Interleukin 6

Since its discovery, interleukin 6 (IL-6) has been characterized primarily by its immunological and pro-inflammatory functions in response to infection and injury [32]. However, it is now appreciated that IL-6 is more than a cytokine, as it also has hormone-like properties to affect glucose and energy balance [33, 34]. In fact, there is an increasing awareness that IL-6 exerts a profound influence in the browning of WAT. For example, mice lacking the IL-6 gene have impaired WAT browning in response to burn injury. Other recent data also support these findings, as prolonged activation of IL-6 signaling induces WAT browning and increases energy expenditure in the context of cancer [71]. It is believed that IL-6 mediates WAT browning during the hypermetabolic response via macrophage polarization, as it has been shown to do so in other metabolic conditions like obesity [35]. While the involvement of catecholamines and IL-6 in WAT browning is now undisputed, many questions regarding this process remain unanswered (see Outstanding Questions).

Parathyroid hormone related protein

For decades, **Parathyroid hormone related protein (PTH-rP)** has been recognized for its beneficial effects on skin, cartilage, placenta, and bone development [36] [37] [38]. However a more detrimental picture has emerged in regards to its function during hypermetabolic conditions. In fact, a new study has recently implicated PTH-rP in promoting browning of WAT during cancer in humans and rodents [39]. Specifically, circulating PTH-rP released from the tumor has been implicated in driving the browning program, thereby fuelling a hunt for cancer drugs to target this “tumorkine”. Uncovering the signaling pathway that is activates during hypermetabolism will be key to the medicinal utilization of agents that target PTH-rP induced thermogenesis.

Mechanisms of metabolic dysfunction during hypermetabolism:

Lipotoxicity and the browning of WAT

Here, we focus on the by-product of WAT browning, namely the excessive release of lipids that ultimately causes tissue dysfunction. Specifically, we consider the lipid profile (both good and bad) in hypermetabolic patients, and their mechanisms of action in causing hepatic and adipose tissue dysfunction, as well as inflammation.

What is the lipid profile in hypermetabolic patients?

Of the numerous lipids that accrue during the hypermetabolic response, long-chain FAs (LCFA) are amongst the most deleterious because they disrupt insulin sensitivity and mitochondrial metabolism [40]. Lipodomic profiling in burn and cancer patients has revealed increased saturated FFAs (e.g., palmitate) linked to pro-inflammation and metabolic dysfunction [41] [42] [29]. In contrast, the expression profiles of good lipids such as polyunsaturated FAs (PUFAs) that have been shown to attenuate inflammation are significantly depleted in these hypermetabolic patients [43] [29]. Specifically, the metabolites of these PUFAs termed specialized pro-resolving mediators (SPMs), which are enzymatically derived from essential fatty acids (ω -3 and ω -6), have important roles in orchestrating the resolution of systemic inflammation [43].

How do lipids mediate hypermetabolism?

One emerging mechanism that links **lipotoxicity** to metabolic dysfunction involves the endoplasmic reticulum (ER). In burns, two possibilities have been put forth in regards to **ER stress** activation. First, the ER stress may be induced by the increased demand for protein synthesis to meet the energy demands and insulin production post-burn injury. Second, the excess nutrients themselves like FFAs may serve as signals inducing ER stress [44] [45]. To alleviate ER stress and restore homeostasis, the ER activates an adaptive response known as the **unfolded protein response (UPR)** [46]. If restoration of ER homeostasis is not possible, the UPR activates cellular apoptosis [46]. It was recently shown that endoplasmic reticulum (ER) stress is a hallmark feature in burned patients, which is observed in peripheral blood leukocytes, fat, and muscle in parallel with insulin resistance and that can last for up to a year [47].

ER stress and WAT browning: is there a link?

Although a lot of work has been done on hepatic ER stress and the adverse consequences of fat accumulation in hepatocytes, far less work has been done on investigating ER stress in adipose tissue. Several groups have highlighted that adipose tissue from obese mice display signs of ER stress [45] [48]. Similar findings have also been shown in mice and humans post-burn injury, where the key ER stress markers CHOP, ATF-6, BiP, and IRE-1 are all significantly up regulated in WAT and implicated in adipocyte apoptosis [49] [29]. However, the mechanism by which ER stress activates apoptosis in adipocytes is currently unknown. Does it involve abnormal MAM formation and calcium overload? Is mTORC2 signaling involved, given that it has been shown to regulate MAM formation as well as WAT browning.

Unfortunately, the significant presence of ER stress in the adipose tissue of burn patients leads to even more important questions than answers. What are the origins of ER stress in burns, particularly in adipose tissue? This crucial answer is unknown, but several prospects exist. For instance, catecholamines may be the culprit as they remain elevated in burn patients years after the initial insult [4]. Indeed, studies have already shown that catecholamines induce ER stress and apoptosis in cardiomyocytes, and that beta-blockers are effective at reversing these adverse effects [50] [51]. Another potential culprit is the cytokine IL-6, which also persists in burn patient's years after the injury has resolved [3]. Although,

IL-6 stimulating ER stress in WAT has not been directly studied, it has been shown to induce lipolysis, apoptosis, and mitochondrial dysfunction, which are hallmarks of ER stress activation in adipocytes [52] [53].

Perhaps the biggest remaining question is whether ER stress triggers WAT browning or is it a by-product? Some inroads have been made in answering this “chicken and egg question”, with conflicting reports. For example, several studies have reported that ER stress negatively regulates WAT browning as overexpression of the chaperone GRP78/BiP, or genetic knockout of ATF-4 and CHOP in mice increases **thermogenesis** [54] [55] [56]. By contrast, it has also been shown that IRE1 α -XBP1 activation is crucial for the transcriptional induction of UCP-1 in brown adipocytes [57]. These are all exciting questions that should yield important insights regarding both mechanisms and potential therapeutic applications in the field of adipose tissue biology (see Outstanding Questions).

Understanding the cellular changes to hypermetabolism

The hepatic lipid overload is thought to be at the origin of the chronic ER stress seen in burn patients. Indeed, numerous studies have shown that the UPR is activated in the livers of obese, diabetic, and burn rodents [10] [58] [59]. A number of clinical studies have found that liver impairments mediated by fatty liver infiltration worsens prognosis in burn patients [26] [60] [5]. The exact mechanism by which a cutaneous burn induces hepatic dysfunction is not fully defined, but likely involves activation of programmed cell death in hepatocytes. The inositol triphosphate receptor (IP3R) is the primary calcium release channel on ER membranes and has been implicated in facilitating ER stress-mediated hepatocyte apoptosis [61]. In fact, increased levels of IP3 receptor have been observed in the livers of obese and burned mice [62] [63]. Additionally, hepatic ER stress has been shown to increase the mitochondria-associated membranes (MAMs) [64], thereby tethering the ER to the mitochondria [62]. The MAMs are involved in Ca²⁺ and lipid transfer between the two organelles, as well as in mitochondrial dynamics and autophagosome formation [65].

Although it is unclear which signaling pathway the UPR activates to promote MAM enrichment, it likely involves mammalian target of rapamycin (mTOR). In particular, mTORC2 has been shown to not only localize at MAMs, but also regulate MAM formation [66]. Therefore, it remains to be seen whether the increased MAM enrichment observed in obesity and burns is due to decreased mTORC2 signaling. What is known, however, is that the increased MAM enrichment facilitates Ca²⁺ flux via the IP3R from the ER to mitochondria post-burn injury [62] [63]. Chronic Ca²⁺ overload becomes detrimental for mitochondrial function as it progressively leads to impairment in oxidative phosphorylation. This is in line with reported progressive reduction of ATP synthesis and mitochondrial respiration in hepatocytes of burned mice [63]. Initially, this ER stress calcium-mediated pathology is limited to the mitochondria, but quickly progress to cellular apoptosis when pro-apoptotic mitochondrial contents become released into the cytoplasm. Specifically, cellular apoptosis is triggered upon the irreversible opening of IP3Rs through the binding of mitochondrial cytochrome c at the MAM [67] (figure 4).

Lipids mediate inflammation during hypermetabolism

Lipids, particularly the saturated FAs (SFAs), are also key players in the etiology of inflammation in burns and cancer. In fact, the activation of the NLRP3 inflammasome in the adipose tissue of burn patients has been implicated in insulin resistance and hyperglycemia [68]. It is believed that SFAs and in particular palmitate, an abundant FFA in the serum of burn patients, can induce the activation of the NLRP3-ASC inflammasome, subsequently causing interleukin 1 (IL-1 β) secretion in both hepatocytes and adipocytes [69] [70, 71]. In addition, the enhanced inflammatory environment of obese fat pads has also been associated with tumor growth, through the secretion of cytokines like interleukin 18 [72]. It has been hard to decipher what causes what in terms of ER stress and inflammation, as the activators of ER stress (e.g., SFAs, inflammatory cytokines) are also the consequences.

Thus, it is clear that pathways that generate excessive lipids such as WAT browning have important consequences for hepatic and adipose function, and inflammation, ultimately fuelling a hypermetabolic response that results in poor outcomes for patients.

Emerging roles of lipids in hypermetabolism

Palmitoylation—In addition to their energy production roles, lipids are also critical in the post-translational modification of proteins. In fact, proteins are covalently modified with a great variety of lipids: most frequently palmitate and myristate, abundant FFAs in hypermetabolic patients [29] [41]. Traditionally, protein **palmitoylation** has been thought to only mediate protein trafficking and stability [73]. However, recently it has been discovered that palmitoylation of proteins is essential for their signaling function, particularly in the context of cellular apoptosis [74]. Apoptosis is generally initiated by two principal pathways, the intrinsic pathway emerging from the mitochondria discussed earlier, and the extrinsic pathway activated by the Fas ligation of death receptors. Two distinct mechanisms have been put forth for how palmitoylation regulates apoptosis. In the first case, it has been shown that palmitoylation localizes the death receptor Fas to membrane microdomains where it recruits Fas-associated death domain protein (FADD) and procaspase-8 to form the death-inducing signaling complex (DISC), ultimately leading to cell death [74]. Conversely, Lck, an essential component of the Fas signaling pathway undergoes palmitoylation to regulate Fas-mediated apoptosis [75]. Interestingly, hyperactive Fas/FasL signaling has been suggested to mediate liver dysfunction during hypermetabolism. In fact, Fas signaling has been implicated in obesity-associated fatty liver and increased susceptibility to liver damage, which are also phenotypes observed in burn and cancer patients [76]. In the context of burn injury, Fas-mediated apoptosis likely involves ER-mediated calcium release in a mechanism dependent on the IP₃R channels [77] [63]. In cancer, Fas signalling has been shown to facilitate cancer metastasis, making this pathway an exciting new target in cancer therapy [78] [79].

Autophagy—Lipids are also important in regulating signalling pathways that control cell survival such as autophagy. **Autophagy** is a self-degradation program that is essential for the removal of defective cells, proteins and organelles, which is induced during the hypermetabolic response to injury. A number of studies have shown that lipids, in particularly palmitic acid, can activate autophagy [80] [81]. Although autophagy normally

leads to cell death, highly autophagic cells during the hypermetabolic response can actually survive and resume exponential growth [82] [83]. In fact, autophagy promotes survival in cancer cells by providing a continuous supply of energy and macromolecular raw materials to support growth and avert death [84]. Aside from FFAs, ER stress has also been shown to activate autophagy during the hypermetabolic response [85].

Paradoxically, hyperactive autophagy in hypermetabolic patients may actually be beneficial as it can impede WAT browning. Intriguingly, selective inhibition of autophagy in mice recovers BAT-like features in autophagy-deficient WAT [86]. In the perspective of hypermetabolism, this regulation of the phenotypic switch from WAT to BAT by autophagy activation may attenuate not only the excessive release of lipids but also attenuate cachexia in these patients [87]. Thus, it's becoming more apparent now that excess FFAs in the cytoplasm are not only harmful to cells, but can also activate or disrupt critical signaling pathways in cell metabolism.

Concluding remarks and future perspectives

We have highlighted just a few of the questions that have been sparked by recent findings that revealed WAT browning may be detrimental for burn and cancer patients. The aim of this review was to stimulate debate and research, and to address an area of WAT browning that has largely been ignored. For instance, we have illustrated how the browning process and its byproduct leads to a number of alterations in hepatocytes, adipocytes, and immune cells. Ultimately, these alterations facilitate and manifest into the metabolic dysfunction seen during hypermetabolic conditions. However, key questions remain (see Outstanding Questions) in regards to the molecular mechanisms underlying browning-mediated hypermetabolism. As more intriguing avenues on WAT browning continue to open up that is sure to revolutionize how we treat the metabolic syndrome, we must focus on strategies that retain the “good” potent insulin-sensitizing effects and simultaneously reduce or eliminate the “bad” associated side effects like cachexia and lipotoxicity.

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Glossary

Atherosclerosis

a condition characterized by the deposition of plaques of fatty material on the inner walls of the arteries.

Autophagy

is an intracellular recycling program, whereby organelles, cytoplasmic proteins, protein aggregates, and lipids are delivered to lysosomes for catabolic breakdown to be reused by the cell for energy and macromolecular synthesis.

Beige/Brite Adipose Tissue

UCP1-positive adipocytes appearing predominantly in white adipose tissue (WAT) in response to cold, injury (thermal injury), disease (cancer) and exercise. This inherent property of burning fat might be beneficial in counteracting obesity and diabetes.

Brown Adipose Tissue (BAT)

adipocytes highly enriched in UCP1, predominantly involved in dissipating chemical energy in the form of heat, in response to cold. This inherent property of dissipating energy might be beneficial in counteracting obesity and other metabolic diseases.

Browning

The emergence of brown adipocytes and or the conversion of white adipocytes into beige adipocytes in WAT—a process that represents adaptation to increased thermogenic demand, exercise, injury (thermal injury), and disease (cancer).

Cachexia

is a wasting syndrome characterized by systemic inflammation, body weight loss, atrophy of WAT and skeletal muscle. Commonly observed in burn and cancer patients.

Endoplasmic Reticulum stress (ER stress)

under conditions of cellular stress where the demand for protein folding is high, mis-folded proteins may accumulate in the lumen of the ER. Prolonged ER stress triggers the unfolded protein response (UPR).

Hepatic steatosis

is a condition of excessive accumulation of fat in the liver.

Hypermetabolic response

is the physiological state of increased rate of metabolic activity and is characterized by an abnormal increase in the body's basal metabolic rate. It is a common feature during injury and disease.

Lipotoxicity

The oversupply of fat in the form of free fatty acids to tissues not suited for lipid storage. Ectopic accumulation of lipids in tissues induces cellular stress ultimately leading to tissue dysfunction.

Palmitoylation

is the reversible attachment of the fatty acid palmitic acid to a cysteine residue on a membrane protein. Palmitoylation has many different functions in proteins. For instance, it functions in membrane attachment, intracellular trafficking, and membrane micro-localization.

Parathyroid hormone-related protein (PTHrP)

is a family of hormones that have a wide range of endocrine functions, from bone and mammary development to calcium regulation in the body.

Thermogenesis

the process of heat production in organisms. Thermogenesis can be induced/ activated by exposure to cold temperatures, exercise, injury (thermal injury), diet, and disease (cancer).

White Adipose Tissue (WAT)

contains adipocytes that are UCP1-negative, and is predominantly involved in storing chemical energy as lipids. This inherent property of (excessive) fat storage contributes to obesity.

Unfolded protein response (UPR)

A signaling pathway triggered by accumulation of mis-folded proteins in the lumen of the ER. It is primarily activated to help restore homeostasis by improving folding capacity) but if the attempt to minimize accumulation of mis-folded proteins fails, it activates cellular apoptosis.

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Outstanding Questions

Which source of IL-6 (myeloid or tissue origin) regulates WAT browning in hypermetabolic conditions?

Is WAT browning in Cancer and Burns reversible or a permanent response to injury?

Does ER stress mediate adipocyte apoptosis via MAM enrichment and Ca²⁺ toxicity?

Does ER stress trigger WAT browning or is it a by-product?

Is attenuation of WAT browning sufficient to overcome the impaired muscle and liver metabolic processes that have already occurred in the hypermetabolic response to the injury?

TRENDS BOX

Inducing ‘browning’ within white adipose tissue (WAT) i.e., by increasing uncoupling protein UCP1 expression, has attracted much interest in the field of obesity.

WAT ‘browning’ has several beneficial metabolic effects such as increasing energy expenditure and reducing adiposity.

The unique metabolic benefits of ‘browning’ in WAT have recently been overshadowed by its implication in cachexia, atherosclerosis, and hepatic steatosis during hypermetabolic conditions.

WAT ‘browning’ appears to be a double edge sword, beneficial in obesity and diabetes, but detrimental in hypermetabolic conditions.

Understanding the molecular mechanisms underlying ‘browning’ induced hypermetabolism may allow for the development of therapeutic approaches that attenuate or even eliminate the associated adverse metabolic effects.

Figure 1. Hypermetabolic response to burn injury

Burn injury results in a number of pathological alterations in various tissues of the body. Alterations in the metabolic tissues of liver, adipose, and skeletal muscle are illustrated post-burn injury. Abnormalities in the function of these metabolic tissues ultimately affect other organs like the skin and impair wound healing.

Figure 2. Characteristics and properties of the different adipose tissue depots

Immunohistochemistry micrographs illustrating the morphology and properties of human and mouse adipose tissue depots. (A) Left, human WAT (acquired from subcutaneous abdominal depot) have uni-ocular morphology, contain very little mitochondria, and do not express UCP-1. Middle, browning of WAT (induced by burn injury in the image illustrated) leads to the formation of a multi-ocular, mitochondria-rich, and UCP-1-expressing beige/brite adipocytes. Right, human brown adipocytes (acquired from the supraclavicular region of a burn patient) are characterized by a multi-ocular morphology, high mitochondrial

content, and increased UCP-1 expression. **(B)** Left, mouse WAT (acquired from inguinal depot) also has uni-ocular morphology, contains very little mitochondria, and does not express UCP-1. Middle, browning of inguinal WAT (induced by burn injury) leads to the formation of a multi-ocular, mitochondria-rich, and UCP-1 expressing beige/brite adipocytes. Right, mouse BAT (acquired from interscapular region) showing multi-ocular morphology, high mitochondrial content, and increased UCP-1 expression.

Figure 3. WAT browning mediated metabolic dysfunction

During WAT browning, substantial metabolic alterations take place in patients with hypermetabolic conditions (burns, cancer, and heart disease). **Left** WAT browning enhances whole body energy expenditure causing a catabolic state of muscle protein breakdown and increased lipolysis, ultimately leading to *cachexia*; a debilitating condition characterized by muscle and adipose wasting. **Middle:** WAT browning activates lipolysis and increases serum cholesterol levels, ultimately leading to *atherosclerosis*; a condition characterized by plaque growth and instability in the heart. **Right:** WAT browning stimulates lipolysis and FFA efflux ultimately leading to *hepatic steatosis*; a condition characterized by ectopic fat accumulation and liver failure. *Full arrows* indicate well-substantiated findings; whereas *dashed arrows* indicate less characterized findings.

Figure 4. Hepatic ER stress response to burn injury

A schematic diagram illustrating the acute response to burn injury, in which there is increased MAM formation in the liver. Increased MAM formation drives higher Ca^{2+} transfer from ER (via IP3R1) to the mitochondria, leading to Ca^{2+} overload. This excessive uncontrolled influx of Ca^{2+} into the mitochondria leads to mitochondrial dysfunction via impairments in oxidative capacity and swelling. The release of cytochrome C from the mitochondria also sustains chronic ER stress via the phosphorylation of the IP3R receptors to release more calcium, ultimately resulting in cellular apoptosis.