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Review

White Adipose Tissue Browning: A Double-edged Sword

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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.

Trends

Inducing 'browning' within white adipose tissue (WAT), that is, by increasing uncoupling protein 1 (UCP-1) 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-edged 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.

Hypermetabolism in Response to Injury

The **hypermetabolic response** (see Glossary) is characterized by a profound increase in the release of free fatty acids (FFAs) and glycerol from fat, glucose production by the liver, and amino acids from muscle, ultimately resulting in significant elevations in resting energy expenditure [1–3]. 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 cancer, initially, a prolonged response is potentially futile and becomes devastating for patient outcome [2]. This is because sustained hypermetabolism in these patients results in 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.

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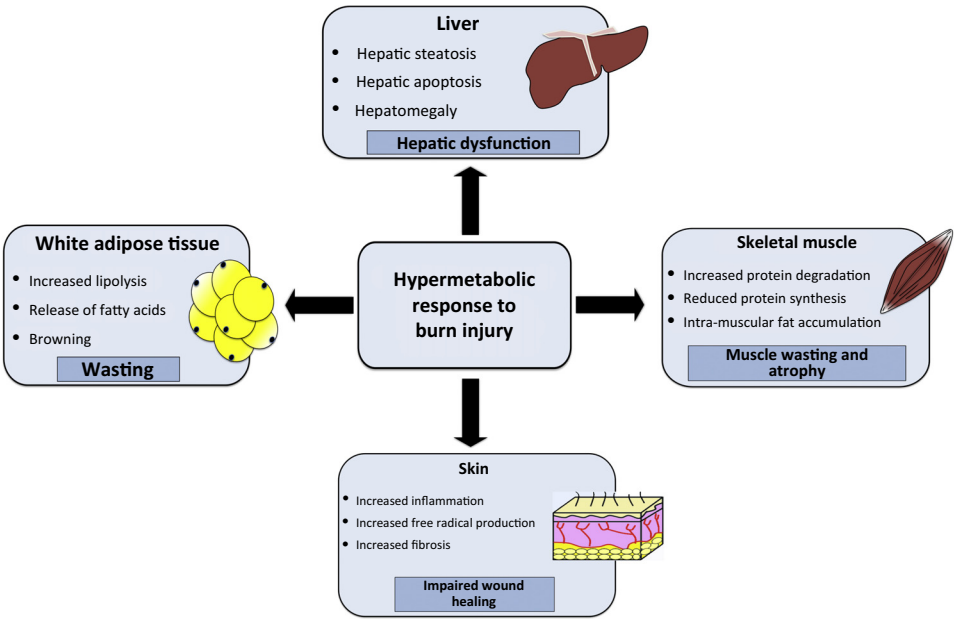

Figure 1. Hypermetabolic Response to Burn Injury. Burn injury results in a number of pathological alterations in various tissues of the body. Alterations in the metabolic tissues of liver, adipose, and skeletal muscle are illustrated post-burn injury. Abnormalities in the function of these metabolic tissues ultimately affect other organs like the skin and impair wound healing.

Browning of WAT in Hypermetabolic Conditions

Reports of browning in traditionally white adipose depots occurred decades ago, when it was observed that mice acclimated to cold developed **brown adipose tissue** (BAT) characteristics, that is, small multiocular cells enriched in mitochondria, in a subset of cells in the parametrial adipose depots [10,11]. 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 [12–14]. In the first study, Wagner *et al.* observed a phenotypic switch from WAT to BAT in cachexic cancer patients. In the second and third studies, Herndon *et al.* found a similar phenotypic switch of WAT to a more BAT-like phenotype in postburn pediatric patients. Indeed, these same findings were confirmed by Patsouris *et al.* in adult burn patients, as well as postburn mice [14]. 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 (Figure 3, 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 from which to purge the human body. However, more and more studies are showing that having some extra fat tissue is protective

Glossary

Atherosclerosis: A condition characterized by the deposition of plaques of fatty material on the inner walls of the arteries.
Autophagy: 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: 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, misfolded proteins may accumulate in the lumen of the ER. Prolonged ER stress triggers the unfolded protein response (UPR).
Hepatic steatosis: A condition of excessive accumulation of fat in the liver.
Hypermetabolic response: 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