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Review

Oxidative stress and lipid peroxidation by-products at the crossroad between adipose organ dysregulation and obesity-linked insulin resistance

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ABSTRACT

Obesity has been proposed as an energy balance disorder in which the expansion of adipose tissue (AT) leads to unfavorable health outcomes. Even though adiposity represents the most powerful driving force for the development of insulin resistance (IR) and type 2 diabetes, mounting evidence points to "adipose dysregulation", rather than fat mass accrual *per se*, as a key pathophysiological trigger of the obesity-linked metabolic complications. The dysfunctional fat, besides hypertrophic adipose cells and inflammatory cues, displays a reduced ability to form new adipocytes from the undifferentiated precursor cells (ie, the preadipocytes). The failure of adipogenesis poses a "diabetogenic" milieu either by promoting the ectopic overflow/deposition of lipids in non-adipose targets (*lipotoxicity*) or by inducing a dysregulated secretion of different adipose-derived hormones (ie, adipokines and lipokines). This novel and provocative paradigm ("expandability hypothesis") further extends current "adipocentric view" implicating a reduced adipogenic capacity as a missing link between "unhealthy" fat expansion and impairment of metabolic homeostasis.

Hitherto, reactive oxygen species have been implicated in multiple forms of IR. However, the effects of stress on adipogenesis remain controversial. Compelling circumstantial data indicate that lipid peroxidation by-products (ie, oxysterols and 4-hydrononenal) may detrimentally affect adipose homeostasis partly by impairing (pre)adipocyte differentiation. In this scenario, it is tempting to speculate that a *fine tuning* of the adipose redox status may provide new mechanistic insights at the interface between fat dysregulation and development of metabolic dysfunctions. Yet, in humans, the molecular "signatures" of oxidative stress in the dysregulated fat as well as the pathophysiological effects of adipose (per)oxidation on glucose homeostasis remain poorly investigated.

In this review we will summarize the potential mechanisms by which increased oxidative stress in fat may impair (pre)adipocyte differentiation and promote the adipose dysfunction. We will also attempt to highlight the conundrum with the adipose redox changes and the regulation of glucose homeostasis. Finally, we will briefly discuss the scientific rationale for proposing the adipose redox state as a potential target for novel therapeutic strategies to curb/prevent adiposity-linked insulin resistance.

1. Historical background: the regulation of energy balance and body weight

The maintenance of adequate nutrition and energy stores is essential for survival and reproductive capacity of individuals. Humans, like other mammals, are characterized by a tight control of energy homeostasis by coordinated changes in food intake and energy expenditure through mechanisms that allow the

Abbreviations: AT, adipose tissue.

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maintenance of a stable body weight [1,2]. Numerous control pathways, involving both neural networks and circulating signals, have evolved to maintain energy balance at an optimal level [1,2].

Adipose tissue (AT) serves a primary role in the setting of energy homeostasis because it represents the body's main depot for energy storage and mobilization. Homeostatic circuits that regulate body fat mass include, among others, those based on insulin and leptin. These hormones, which circulating concentrations are proportional to fat mass, may act as "adiposity signals". Insulin, on the one hand, displays adipogenic actions and stimulates the storage of triglycerides in adipose cells, which became enlarged. The size of adipocytes, on the other, may be "sensed" to the brain via the secretion of leptin [1,2], which, in turn, acts on the central nervous system to reduce feeding and increase energy expenditure to restrain fat mass expansion. Besides the "adiposity signals", gut hormones, such as the gastric hormone ghrelin (see below), are also known to signal to the brain inducing a central integration according to the dietary intake and nutrient requirements. Evidence is mounting to suggest extensive cross-talks between adiposity signals, gut hormones and insulin [3,4].

Ghrelin, the orexigenic protein secreted by X/A-like cells of the gastric oxyntic glands, emerges as a suitable candidate linking fat mass expansion, control of food intake and glucose homeostasis. Independently of the orexigenic action, both the acylated and desacylated ghrelin forms may stimulate lipid accumulation in human visceral adipocytes and, as compared with obese normoglycemic subjects, obese patients with type 2 diabetes (T2D) exhibit higher acylated ghrelin concentrations [3]. Further insights into ghrelin effects on adipobiology have been provided by the discovery of aquaporins (AQP) [5]. Aquaporin-7 (AQP7), the adipose-specific water–glycerol transporter present in the plasma membrane of adipocytes, operates as a glycerol channel *in vivo*, whereby fat cell permeability and delivery of glycerol into plasma display a key role in the regulation of fat accumulation and insulin resistance [5]. Recent data indicate that, under physiological conditions insulin mediates a coordinated regulatory loop between fat-specific AQP7 and liver-specific AQP9 in order to maintain glucose homeostasis through modulation of glycerol output from adipocytes and glycerol uptake for hepatic gluconeogenesis according to the nutritional status [6]. On the other hand, the expression of AQP7 in human visceral adipocytes is repressed by acylated and desacyl ghrelin, supporting the view that ghrelin decreases lipolytic capacity and promotes fat cell enlargement [3]. Notably, insulin is also required for prandial ghrelin suppression in humans [7], and chronic hyperinsulinemia, as well as hyperleptinemia, have been indicated as the most important modulators of ghrelin secretion in obese individuals with or without T2D [4]. It is thus plausible that the disruption of the coordinated regulation between insulin, ghrelin and AQP7/AQP9 might impair glucose homeostasis by increasing glycerol release from adipocytes and glucose production from the liver, thereby perpetuating a *vicious cycle*.

In this scenario, the occurrence of obesity may be seen as a result from the failure or breakdown of the homeostatic mechanisms regulating energy balance. Many attempts have thus been made to explain how genetic and environmental factors can overcome normal energy homeostatic control and cause obesity. This fertile area of research is continuously open to new areas of understanding and could potentially open novel therapeutic targets for tackling adiposity epidemic.

2. Obesity and type 2 diabetes: not only a matter of fat

Overwhelming evidence has proven that obesity plays a central role in the development of insulin resistance and T2D [8–10]. While in obesity AT expands to accommodate increased lipid partitioning [11], fat mass accrual by itself is unlikely to be the only instigator of the adiposity-associated unfavorable metabolic outcomes. Different epidemiological trials showed that some morbidly obese patients (and up to 25% of obese individuals) are "metabolically healthy", while about 18% of non-obese subjects demonstrate biochemical characteristics of the insulin-resistance syndrome [12–14]. Accordingly, some authors have recently suggested a reappraisal of the cutoffs to diagnose overweight and obesity. Indeed, 29% and 80% of subjects classified as lean or overweight according to their body mass index (BMI), respectively, are actually "obese" as estimated by their body fat percentage. More importantly, these subjects already exhibit similar cardiometabolic risk factor profile as obese patients [15]. Altogether, these observations support the assumption that fat mass expansion is neither sufficient nor necessary for development of the metabolic dysfunctions.

AT is now emerging as a remarkably active "organ", with functional pleiotropism and high remodeling capacity [16]. Although basically adipose tissues are generally regarded as connective tissues without a specific anatomy, accumulating data support the idea that fat tissues are organized to form a large "organ" with discrete anatomy, specific vascular and nerve supplies, complex cytology, and high physiological plasticity [17]. Obesity implies extensive changes in AT ultrastructure involving the enlargement of existing adipocytes, the formation of new fat cells from committed (pre)adipocytes, (adipogenesis), extracellular matrix proteolysis, and the coordinated development of the tissue vascular network (angiogenesis). Arguably, while fat is by far the most plastic organ in our body, the limit of fat mass expansion appears defined for any given individual [18]. Indeed, if insulin resistance would be a direct consequence of an increased fat mass, all the subjects would develop metabolic complications at the same degree of adiposity. In contrast, on an individual level, there is no clear cut point of "adiposity", as conventionally ascertained by the BMI, clearly separating distinct insulin sensitive from insulin resistant sub-phenotypes [13].

Although different and partly conflicting hypotheses have been put forward to explain such an apparent paradox, one provocative and seemingly counterintuitive paradigm postulates that a reduced ability of the adipose organ to further expand, rather than fat mass accrual *per se*, may be the key determinant underlying the adiposity-induced metabolic dysfunctions ("expandability hypothesis") [19–21].

3. Impaired adipogenesis characterizes the "hypertrophic", metabolically unhealthy obesity

The cellular composition of AT is heterogeneous [11]. In adults, the majority (~35–70%) of adipose mass volume comprises adipocytes, which account for only 25% of the total cell population. Notably, diverse cell-types, which include the adipose precursor cells among others, are found in the so-called "stroma-vascular fraction", and account for the remaining 75% of the whole cell population.

Recent evidence points to substantial AT "remodeling" in obesity, which appears of particular interest in the setting of metabolic homeostasis [21]. Mature adipocytes are derived from a pool of undifferentiated precursors (ie, the adipose-derived mesenchymal stem cell, ASC), which become "committed" toward the adipogenic lineage (ie, preadipocytes). However, not all the progenitors become adipocytes simultaneously [22]. Our current understanding of AT development in humans is that the major pool of precursor cells is primarily recruited before puberty, while in adulthood there is a 10% annual adipocyte turn-over [23,24]. This implies that fat mass expansion in adult age is mainly a consequence of adipocyte