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The dysregulated adipose tissue: A connecting link between insulin resistance, type 2 diabetes mellitus and atherosclerosis

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Abstract An emerging paradigm supports the view that adipose tissue (AT) dysregulation might play a crucial role in the pathogenesis of insulin-resistance and atherosclerosis. The net result of such a dysregulation is a state of low-grade, chronic, systemic inflammation that, in turn, links both the metabolic and the vascular pathologies. Overwhelming evidence shows that high circulating levels of markers of chronic inflammation predict the development of T2DM and atherosclerotic manifestations. Therefore, atherosclerotic cardiovascular disease and T2DM seem to arise from a ''common soil'', and chronic inflammation is a candidate. In this scenario, the dysfunctional AT provide a common hallmark for these apparently divergent disorders.

An important question then is whether dysregulated and inflamed AT can be converted to healthy fat and, consequently, the development or the progression of metabolic and vascular impairment can be prevented or reversed by the modulation of the inflammatory profile. The beneficial effects of weight loss on obesity-related complications are clearly associated with the modification of the inflammatory profile in the AT. Furthermore, the thiazolidinediones (TZDs) possess both anti-inflammatory and anti-atherogenic properties. Intriguingly, in contrast to the paradoxical weight gain, TZDs influence favorably the pattern of adipokines.

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In conclusion, accepting the paradigm of AT dysfunction, the use of TZDs will represent an additional therapeutic approach that, in association with lifestyle interventions, would improve inflammation, ameliorate insulin sensitivity, and alleviate the related risk of atherosclerosis.

Inflammation, insulin resistance and dysfunctional adipose tissue: a new paradigm?

Obesity, the final result of increased body fat due to increases in fat cell size and/or number, represents a major risk factor for the development of type 2 diabetes mellitus (T2DM) and its associated complications including premature atherosclerosis, as well as for a cluster of metabolic and other disturbances (hypertension, dysfibrinolysis, lipid abnormalities, insulin resistance) that is now defined as the metabolic or insulin resistance syndrome [1,2]. An emerging paradigm supports the view that adipose tissue dysregulation and dysfunction might play a crucial role in the pathogenesis of such apparently divergent metabolic and vascular disorders [3,4]. The dysfunctional fat tissue, which is coupled with excessive fat deposition in muscle and liver as well as with an increased fat cell size [3], is mainly characterized by a derangement in the release of fatty acids, hormones and pro/anti-inflammatory molecules (adipokines); these can induce insulin resistance, inflammation, dyslipidemia, hypercoagulability and, possibly, endothelial dysfunction and vascular remodelling which, in turn, are associated with hypertension and atherosclerosis.

Recent findings support the view that a state of chronic low-grade inflammation is a hallmark of both the obese state [4—7] insulin resistance/T2DM [6—12,38] and the early stages of atherogenesis [7—10], pointing to mechanisms inducing a low-grade systemic inflammation as a putative link that connects adipose tissue dysfunction and the metabolic and vascular pathologies. An interesting feature of the obesity-related inflammatory response is that it appears to be triggered by, and to reside in, the adipose tissue (AT), although other cells and tissues are also involved during the course of the disease [13—18]. The temporal and spatial properties of the inflammatory response in the context of obesity and fat cell dysfunction and the mechanisms whereby inflammation alters insulin sensitivity in several organs (liver, skeletal muscle, fat and vascular smooth cells) remain to be finally elucidated. However, recent studies of the cross-talk between insulin receptor signaling and inflammatory pathways have provided insight into the development of insulin resistance and T2DM [17—19]. Although the signals and the mechanisms that trigger the inflammatory response are not well understood, the possibility that obesity-related insulin resistance is, at least in part, a chronic inflammatory disease initiated in the AT is supported by recent reports demonstrating the accumulation of macrophages (MØ) in the AT of obese subjects as well as their participation in the inflammatory pathways activated in adipocytes [20,21]. Furthermore, the demonstration of resident MØ in human AT, the number of which is positively correlated with BMI, suggests that macrophage infiltration into AT contributes to the dysregulated adipose tissue and the impairment of adipocyte function. Indeed, a rethinking of the entire issue of AT dysfunction and inflammation, insulin resistance and atherosclerosis with respect to MØ is required in the light of the demonstration that progenitors of mature adipocytes, i.e., preadipocyte, have the potential to be trans-differentiated into MØ [22]. This hypothesis fits well with the observation that monocyte chemoattractant protein-1 (MCP-1), a proinflammatory chemokine mainly produced by MØ and endothelial cells, is also secreted from isolated adipocytes [23,24] and, interestingly, circulating as well as AT levels are positively associated with adiposity [23].

A key question is to understand the mechanism(s) whereby the enlarged adipose cells in obesity become inflammatory and increase their secretion of different cytokines which, in turn, can lead to the recruitment of macrophages to the AT. Although currently unclear, the consequences of this are readily understood. Both TNFα and IL-6 impair insulin signaling and action [13,17]. Human AT produces and secretes large amounts of IL-6 and IL-8 [15,17] but not TNFα. Cytokines also inhibit the differentiation of the preadipocytes and induce an inflammatory phenotype in these cells which, in turn, can attract and recruit inflammatory cells to the AT.