Adipose tissue inflammation and liver pathology in human obesity

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Abstract

The increase in circulating inflammatory factors found in obese subjects and the recent discovery of macrophage infiltration in white adipose tissue (WAT) have opened up new fields of investigation, allowing a reevaluation of the pathophysiology of human obesity. The so-called ‘low-grade’ inflammatory state, which characterizes this complex disease, is revealed by the moderate, but chronic, systemic rise of a growing panel of molecules with proinflammatory functions. The qualitative and quantitative alterations in the production of these molecules (free fatty acids, cytokines) by the different WAT cell types, particularly in the omental fat depot, are considered new factors with the potential to modify local WAT biology and to contribute, via the portal system, to liver alteration. The aim of this review is to present the most up-to-date knowledge regarding the relationships between inflammatory processes in WAT and non-alcoholic liver disease in human obesity.

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Résumé

Inflammation du tissu adipeux et pathologie hépatique chez l’obèse

L’augmentation des facteurs inflammatoires circulants chez les sujets obèses et la découverte récente d’une infiltration macrophagique du tissu adipeux blanc sont des avancées majeures qui ont conduit à une réévaluation de la physiopathologie de l’obésité humaine. L’état inflammatoire « à bas bruit » qui caractérise cette maladie complexe se traduit par une augmentation modérée, mais chronique, d’une série de molécules qui possèdent des propriétés pro-inflammatoires. Les modifications qualitatives et quantitatives de la production de ces facteurs (acides gras libres, cytokines) par les différents types cellulaires présents dans le tissu adipeux blanc, plus particulièrement dans le tissu adipeux omental, sont considérées comme des nouveaux facteurs pouvant modifier localement la biologie du tissu adipeux blanc et contribuer, via le système porte, aux altérations hépatiques. Dans cette revue, nous présentons l’état des connaissances actuelles concernant les liens entre processus inflammatoires dans le tissu adipeux blanc omental et pathologie hépatique non alcoolique dans l’obésité humaine.

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Obesity is characterized by an increase in adipose tissue mass. The number of obese subjects is growing worldwide, reaching epidemic proportions in adults and children in some countries [1]. The progression of obesity-linked pathologies, including type 2 diabetes, increased cardiovascular risk and liver diseases, is to be expected and necessitates the identification of the underlying mechanisms. An emerging theory suggests that inflammation is a major contributing factor to obesity co-morbidity. Animal models and human studies have identified white adipose tissue (WAT) as a major site of inflammatory damage in obesity, which is revealed by macrophage infiltration [2-5]. Although the subject of intensive investigations, the consequences of adipose tissue inflammation and macrophage accumulation remain elusive in the human diseases related to obesity. Non-alcoholic fatty liver disease (NAFLD) is a frequent complication of human obesity [6,7] and has been linked to the amount of visceral fat [8,9]. Here, we review the recent hypothesis linking adipose tissue inflammation with liver histopathology in human obesity.

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1. Inflammation in obesity

The increase in fat mass—particularly in the splanchnic region (visceral fat) of the body—is associated with chronic elevation of circulating levels of inflammatory mediators. This includes non-specific markers such as C-reactive protein, acute-phase inflammatory proteins and proinflammatory cytokines [10,11]. Adhesion and remodelling molecules of the extracellular matrix are part of these systemic changes [11-13]. The liver and lymphoid organs are the usual production sites of inflammatory factors but, in obesity, WAT is converted into a major producer of these molecules, leading to a chronic and constant local and systemic inflammatory milieu [14]. The role of WAT as a major site of production of proinflammatory molecules was first suggested about 15 years ago by Hotamisligil et al. [15], who showed that WAT synthesizes tumor necrosis factor-α (TNF-α) and that the expression of this proinflammatory cytokine was elevated in adipocytes of obese mice. Moreover, insulin sensitivity could be improved by the action of TNF-α in neutralizing antibodies administered to obese insulin-resistant rats. These pioneer observations underscored the link between a proinflammatory cytokine produced and secreted by WAT, and the development of insulin resistance in rodents. More recently, the expression and secretion of a myriad of factors linked to inflammation have been identified in WAT. They include members of the cytokine family (interleukins (IL)-1, IL-1Ra, IL-8, IL-18 and IL-10), growth factors such as transforming growth factor-β (TGF-β), proteins secreted in the acute phase of inflammation (IL-6, plasminogen activator inhibitor-1), haptoglobin, serum amyloid A (SAA), chemokines (monocyte chemoattractant proteins; MCP-1, -3, -4), angiopoietins, metallothioneins, macrophage inflammatory protein-1α (MIP-1α), complement factors and retinol-binding protein-4 (RBP4) [16-19]. Even though the expression of a large number of cytokines is found in WAT, some of which may influence local biological processes, these molecules are not necessarily significantly secreted into the circulation to exert a major systemic role. Within WAT itself, there are factors that are produced specifically by adipocytes (such as leptin, adiponectin and SAA) and those that are produced by other, non-adipocyte cell types (described below).

2. Adipose tissue infiltration with inflammatory and immune cells

Cell types that make up WAT include mature adipocytes, specialized metabolic cells and a variety of other cells lumped together in the so-called ‘stromal vascular fraction’ (SVF), which are yet to be precisely characterized in humans. In WAT, the presence of macrophages, except in specific experimental conditions leading to adipocyte death in mice, has gone virtually unnoticed until recently [20]. It is now established that, in fact, macrophages are scarce in the WAT of normal-weight individuals, but increase markedly in animal models of obesity and in obese humans [2-5]. Transplant studies in mice suggest that these macrophages derive mostly from bone marrow [2] rather than from preadipocyte differentiation in the macrophage lineage [21]. Substantial infiltration of inflammatory cells occurs around necrotic-like adipocytes in experimental models of adipose cell death [20,22]. Interestingly, in 2000, Bornstein et al. noted the presence of CD68+ cells in direct contact with mature adipocytes in normal-weight individuals, but this was initially considered an experimental artifact [23]. More recently, a specific crown-like disposition of macrophages around single adipocytes exhibiting features of necrosis has been reported in obese subjects [5,24] (Fig. 1). In addition, weight loss-induced improvements in systemic inflammation has been associated with a reduction in macrophage infiltration and improved inflammatory profile in subcutaneous WAT [5,25].

The possible infiltration of WAT in obesity by other inflammatory cells is also suggested by recent analyses in mice showing the modulation of T- and NK-cell subtypes in animals fed a high-fat diet [26]. In a mouse model of high-fat-diet-induced insulin resistance, a recent study has shown that infiltration of T lymphocytes into visceral WAT precedes the recruitment of macrophages. The authors hypothesized that proinflammatory T lymphocytes may contribute to local inflammatory cell activation, and play an important role in the initiation and perpetuation of WAT inflammation and the subsequent development of insulin resistance [27]. In humans, our team has recently shown that other lymphoid cells are present within the WAT of obese subjects (Fig. 1). We observed the presence of NK and T lymphocytes in obese WAT, although they appeared to be less abundant than macrophage cells [28]. Only a few comparative studies have described lymphoid cell accumulation in WAT in obese subjects [29]. In type 2 diabetes patients with moderate-to-morbid obesity, a correlation between WAT lymphocyte number and waist circumference has been reported [27].

WAT is composed of distinct, non-contiguous depots with different characteristics [18,19]. We have recently shown that macrophage accumulation in WAT is dependent on anatomical location. Indeed, there are twice as many macrophages in omental as in subcutaneous WAT on comparing these depots in the same obese subject (Fig. 1) [30]. Other studies have shown that CD68+ cells (activated macrophages and lymphocytes) are more frequently seen in visceral than in subcutaneous WAT in lean, overweight and obese individuals [23,31,32]. The degree of macrophage infiltration might represent a new WAT site-related difference in addition to distinct metabolic capacities, gene expression, secretory function and hormonal responsiveness [18,33].
3. Role of adipose tissue macrophages in liver pathology

As a source of proinflammatory factors, WAT macrophages are thought to contribute to various co-morbidities related to obesity. In animal models, a role for WAT macrophages in inducing systemic insulin resistance has been demonstrated through diet-induced, genetic or pharmacological manipulations of macrophage numbers in adipose tissue [3,34-36]. However, in humans, the pathological consequences of macrophage infiltration in WAT remain largely hypothetical. We have recently addressed this point by focusing on non-alcoholic liver pathology, a frequent complication of human obesity [6,7]. In a population of morbidly obese subjects (BMI > 35 kg/m²) undergoing gastric surgery, we obtained paired biopsies of subcutaneous WAT, omental WAT and liver [37]. The number of HAM56+ macrophages in WAT was quantified microscopically, and correlations with clinical and biological parameters, and histological liver lesions, were investigated. Liver histopathology was precisely evaluated by experts of liver anatomopathology. In this population, metabolic risk factors and significant liver histopathology of steatosis, NASH or fibroinflammation were present in roughly half the participants. Only a minority of subjects (9%) showed no detectable histological liver damage, and no severe damage, such as cirrhosis, was found. The proportion of participants with significant liver histopathology was greater in men than in women. We found no evidence that the duration of obesity aggravates liver histopathology. On the contrary, the proportion of subjects with significant liver damage was greater among individuals with late-onset obesity vs those with early-onset obesity. One important finding in the present study was that omental WAT macrophage accumulation was significantly associated with significant hepatic fibroinflammatory lesions (including fibrosis, and portal and lobular inflammation (Fig. 2). To our knowledge, this is the first identified association between macrophage infiltration in WAT and co-morbidity in human obesity. Interestingly, no association was found with the number of macrophages in subcutaneous WAT, thus suggesting a specific link between omental macrophages and liver damage [37].

4. Potential links between WAT macrophages and liver pathology

The mechanisms underlying the deleterious association between accumulation of macrophages in omental WAT and liver pathology could involve increased free fatty acid
the portal system. The delivery of free fatty acids (FFA) and/or proinflammatory cytokines to the liver via biology by macrophage-secreted factors results in an increased delivery to the liver histopathology in human obesity. Local alteration of obese WAT between accumulation of macrophages in omental WAT and increased liver damage has been recently evaluated in humans [42-44]. Interestingly, in our population of severely obese patients, neither leptin nor TNF-α circulating levels were significantly associated with the severity of hepatic lesions. However, patients with significant hepatic fibroinflammation had reduced adiponectin levels. A similar association of low serum adiponectin with worsening grades of hepatic necroinflammation has recently been reported in different populations, including non-obese and non-diabetic subjects with simple steatosis or NASH [42-44].

The exact phenotype of infiltrating macrophages in WAT is still a matter of debate. The classical M1 macrophages initiate the inflammatory reaction, while the alternative M2 macrophages terminate the inflammatory process [45]. Several markers, including cell-surface receptors, chemokines, cytokines, free-radical-producing enzymes and matrix-degrading enzymes, have all been described as hallmarks of macrophage phenotype. This includes TNF-α, IL-6, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expressed in M1 macrophages, and IL-10 and transforming growth factor-β (TGF-β) expressed in M2 macrophages. In mice, a shift in the activation state of WAT macrophages from an M2 ‘alternatively activated’ state to an M1 ‘proinflammatory state’ has been recently described in response to diet-induced obesity [46]. In response to a high-fat diet, M1 macrophages are recruited from the circulation and accumulate in WAT in addition to resident M2 macrophages [47,48]. However, the macrophage populations found in WAT in humans are not fully defined [49]. Cell-surface markers characterizing the M2 phenotype (CD206 and CD163) have been identified on the basis of gene-expression analyses in subcutaneous WAT in non-obese subjects. Nevertheless, investigation of the secretome of these macrophages revealed the production of proinflammatory cytokines, suggesting a ‘mixed’ phenotype [50]. Similarly, macrophages that are immunodetected from subcutaneous WAT in normal-to-overweight subjects express both markers of M1 and M2 polarization [51]. In the morbidly obese, our observations suggest that the phenotype of WAT macrophages might be influenced by changes in fat mass. Indeed, the M2 marker, IL-10, while not detectable in the subcutaneous WAT of morbidly obese subjects, was readily immunodetected in WAT after drastic weight loss induced by bariatric surgery [5]. More recently, a preliminary study of a limited number of morbidly obese subjects showed a higher proportion of macrophages expressing proinflammatory (M1) markers in omental WAT than in subcutaneous WAT (Wis-
newsky J, unpublished data). The relationship between the phenotype of macrophages infiltrating omental WAT and liver pathology remains to be explored. Indeed, depending on their phenotype, the in vivo paracrine dialogues between inflammatory and adipose cells could be modified.

In conclusion, the discovery of low-grade inflammation in human obesity has provided new concepts in the pathophysiology of this complex disease. From a temporal perspective, human obesity can be considered a set of phenotypes of variable severity that develop successively over time. Progressively biological alterations of WAT probably contribute to the development of obesity-linked metabolic, hepatic and cardiovascular complications. As suggested by studies in mice and, to a lesser degree, in humans, inflammation characterized by the infiltration of various types of circulating immune-system cells appears to follow the different phases of fat-mass accumulation. However, the mechanisms and roles of these inflammatory phenomena in the different stages of human obesity remain to be established. In particular, more information is needed of the dynamics of inflammatory processes (types and phenotypes of cells) and their local roles in the perturbation of preadipocyte and adipocyte biology, and of the development of the complications associated to obesity. Defining precisely these pathophysiological processes in human conditions is mandatory for paving the way towards a greater understanding, and eventually the discovery, of new candidate molecules for therapeutic uses.

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