Adipose Tissue Lymphocytes and Macrophages in Obesity
and Insulin Resistance
Makers or Markers, and Which Comes First?

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Obesity, and more specifically accumulation of adipose tissue in the visceral and subcutaneous abdominal locations, is a major risk factor for the development of cardiovascular pathologies including hypertension and atherosclerosis, as well as metabolic disorders such as type 2 diabetes. During recent years, “metaflammation” or metabolically-triggered inflammation has emerged as a key process involved in the clustering of those conditions. Although several metabolically active organs such as the liver, muscle, and, recently, the intestine certainly play major roles, the white adipose tissue appears as a central and primary player as both a source and site of inflammation. Accumulation of adipose tissue macrophages (ATMs) has been well-described in obese conditions in mice and humans. Moreover, the ATM proinflammatory phenotype has been linked to the development of insulin resistance in mice, although the exact nature of the proinflammatory myeloid cells, ie, macrophages or dendritic cells, remains to be determined. Nevertheless, the causal link between inflammation and insulin resistance was further strengthened by the specific knock-out of the inflammation coordinator IκB kinase beta of myeloid cells, which gave protection against insulin resistance. The study of Kintscher and al in this issue extends those original observations to cells of adaptive immunity. The authors suggest that the accumulation of T-lymphocytes, assessed mainly through gene expression analyses and immunohistochemistry, occurs in the perigonadal adipose tissue of mice on a high-fat diet before the accumulation of macrophages. Moreover, the increased expression of T-lymphocyte markers was concomitant with the initiation of insulin resistance characterized by a reduction in systemic glucose tolerance and insulin sensitivity, at least compared with counterpart animals that were 5 weeks younger. Given these new findings in rodents, the authors suggest that early lymphocyte infiltration of the adipose tissue might be considered as a primary event that orchestrates the adipose tissue inflammation (Figure). This provocative and attractive idea poses a number of questions and requires further clinical investigations to validate its relevance in humans.

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One of the most important tasks is to define the process underlying the accumulation of immune cells and the nature of the ATMs within the adipose tissue. Cells of adaptive immunity are able to home to healthy extralymphoid peripheral tissues, including adipose tissue, where they are thought to carry out peripheral immune monitoring and to reside as long-lived resting memory T cells. Alternatively, effector T cells efficiently home into sites of inflammation and are destined to die. Chemokines and their receptors represent a critical element in immune cell trafficking. Adipose tissue produces a wide range of chemokines, the production of which is modulated by the degree of adiposity. The potential contribution of MCP1/CCL2 in ATM accumulation, through its interaction with the monocyte receptor CCR2, has given conflicting results. In the current work, the authors suggest that resident adipose tissue cells, particularly stromal and endothelial cells (in agreement with a previous study), could release the chemotactrant SDF1/CXCL12 and so behave as lymphocyte recruiter cells. In turn, lymphocyte-derived interferon gamma (IFNγ) would stimulate preadipocyte-derived MCP1 release, which would attract circulating monocytes. This simplistic view has to be reconciled with the fact that the main receptor of CXCL12, CXCR4, is widely expressed on all leukocytes including monocytes, making it unlikely to participate alone in the selective lymphocyte trafficking into adipose tissue. In-depth analysis of the adhesion molecules and chemokine receptors expressed on ATMs might reveal the specific repertoire determinant for adipose tissue homing. Moreover, as the authors point out, the expression of CD3, as well as CD4 and INFγ, is not restricted to Th1 CD4+ effectors but is found in other T cell subsets such as memory and regulatory T cells as well as NKT cells that are present in adipose tissue, at least in mice. Another interesting point will be to determine clearly whether changes in the degree of adiposity are associated
with modulation in the number and phenotype of the ATLs. Indeed, dynamic changes in ATM numbers and phenotype have been demonstrated during the development of obesity on high-fat diets in mice. The ATM shifted from a reparative resident phenotype in lean animals to inflammatory newly recruited ATM in obese mice. In humans, ATMs appear less polarized and possess a proliferative capacity associated with a remodeling proangiogenic phenotype, the hallmark of cells involved in chronic inflammation. By correlative analyses and using gene expression analyses only, the present study suggests a recruitment of Th1 CD4+ cells with obesity. Therefore, the detailed characterization of ATL subsets in both human and mice adipose tissue is necessary to determine, whereas the growth of adipose tissue impacts on the phenotype, function and numbers of resident or infiltrated T cells.

Finally, the pathogenic role of ATLs in obesity remains to be established. Although correlative data analyses show a clear association between lymphocyte gene markers and waist circumference in patients with type 2 diabetes, similar approaches with nondiabetic patients will determine whether ATLs are markers or players in adipose tissue growth and obesity-associated pathologies. A recent study has suggested that perivascular fat may serve as reservoir for activated effector T cells which in turn promote vascular dysfunction and hypertension. Moreover, local intercellular cross-talk is probably more complex than suspected. Although one might expect local interactions between ATLs and ATMs, adipocyte-derived products, including the main adipokines, leptin and adiponectin, and free fatty acids, which have been shown to modulate T-lymphocyte function and proinflammatory responses, are probably major variables to be taken into account. In this field and for long time, the work of C.M. Pond has stressed the close interactions between lymphoid cells in lymph nodes and the surrounding adipose tissue. In addition to this local cross-talk, interactions with adjacent tissues might contribute to the pathogenicity of ATLs. Moreover, although increasing lines of evidence point to the links between the innate and adaptive immune systems and metabolism in rodents, we must keep in mind that the jump to patient-related problems is not easy and requires a number of additional clinical studies. Indeed, there are major differences between young mice submitted to an acute nutritional stress promoted by a high-fat diet and patients who could be at different ages and stages of obesity. ATLs and ATMs, makers or markers? The question is undoubtedly there, but its definite answer and its relevance to humans remains open and clearly further complementary investigations are needed.

Disclosures
None.
References


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