RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted), Inflammation, Obesity, and the Metabolic Syndrome

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For a long time, white adipose tissue (WAT) has been regarded as an inert tissue for energy storage. With the rapidly rising incidence of the components of the metabolic syndrome—obesity, diabetes mellitus type II, and hypertension—in the industrialized world, these diseases have attracted increasing attention in research and health politics. In parallel, WAT was recognized as an active endocrine and paracrine organ that plays an important role in the metabolic syndrome.

Various studies within the past decade indicated that WAT in obesity is characterized by a chronic low-grade inflammation with secretion of inflammatory cytokines and chemokines (see the Figure). Tumor necrosis factor-α was identified as the first molecular link between inflammation and obesity by Hotamisligil and coworkers: Expression of this cytokine was increased in WAT of obese mice and correlated with obesity-induced insulin resistance. Interleukin-6 (IL-6) is another cytokine critically involved in the pathogenesis of obesity and insulin resistance. The serum levels of IL-6 positively correlate with obesity in humans and predict the risk of development of insulin resistance and diabetes mellitus type 2. IL-6 is produced by a variety of metabolic tissues that include WAT, hepatocytes, β-cells, and skeletal muscle. Thus, circulating IL-6 could mediate a crosstalk between these organs that results in a downward spiral toward systemic insulin resistance and decreased insulin secretion.

Furthermore, obesity was found to be associated with macrophage accumulation in murine and human WAT. Chemokines such as CCL2/monocyte chemotactrant protein-1 (MCP-1) and CCL3/macrophage inflammatory protein-1α were reported to be increased in WAT of obese mice and to contribute to insulin resistance and macrophage recruitment. Recently, a causal relationship between obesity, WAT inflammation, and insulin resistance was characterized for MCP-1 and its receptor CCR2; MCP-1 enhanced macrophage infiltration in WAT; insulin resistance, and hepatic steatosis in obesity. Obese mice with CCR2 deficiency exhibited decreased WAT inflammation and improved systemic insulin resistance. The close relationship between WAT mass, the size of adipocytes in obesity, and the number of macrophages in WAT, as well as the level of inflammatory cytokines and chemokines in WAT, suggests a paracrine crosstalk that involves adipose tissue macrophages and adipocytes. In addition, comitant effects on liver steatosis and systemic insulin resistance imply more widespread endocrine effects of WAT inflammation in obesity.

We learn now from Wu and colleagues in this issue of Circulation that T cells and the chemokine CCL5/regulated on activation, normal T cell expressed and secreted (RANTES) are also increased in WAT in the setting of murine and human obesity (Figure). A previous study did not find elevated CD3-positive cells by immunohistochemistry in WAT of both genetic and high-fat diet-induced mouse models of obesity. Wu and colleagues characterized T cells via flow cytometry, mRNA, and immunofluorescence stainings in WAT samples obtained from obese mice and humans. The discrepancy between the 2 studies remains to be clarified; it may relate to the lower fat content (41% versus 60%) or to the longer diet exposure (24 weeks versus 16 weeks) of mice subjected to diet-induced obesity in the current study by Wu et al.

Furthermore, Wu et al report that both mRNA and protein levels of RANTES were increased in a gender-dependent fashion in WAT of obesity. RANTES levels were particularly elevated in male mice in the stromal/vascular fraction of WAT as compared with its adipocyte fraction. In addition, monoclonal antibodies directed against RANTES reduced T-cell chemotaxis induced by media conditioned by WAT isolated from obese male mice. These findings underscore the role of RANTES-induced T-cell chemotaxis by WAT in obesity and suggest an opportunity for pharmacological interventions. Interestingly, obese female mice exhibited less WAT inflammation and lower levels of RANTES and CCR5 expression and were also less resistant to insulin than their male counterparts. The reason for this phenomenon remains to be determined.

With regard to RANTES receptors, the authors find that CCR5, the major receptor for RANTES, and CCR3 were both induced in WAT of obese mice by its stromal/vascular as well as its adipocyte fraction. This increase in RANTES, CCR5, and CCR3 in WAT of obese mice may create a positive auto-

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and paracrine feedback loop, as well as provide a potent signal for the recruitment of macrophages and T cells.

Wu’s group further reports higher expression of RANTES in visceral compared with subcutaneous WAT of morbidly obese humans. An abnormal increase in visceral fat constitutes a prominent risk factor for atherosclerosis and was found to be associated with elevation of the inflammation marker C-reactive protein. In summary, Wu et al report for the first time an accumulation of T cells in obese WAT that is gender dependent and associated with increased expression of RANTES as well as its main receptor CCR5. What is the potential impact of these findings?

Other organs involved in metabolic responses are likely to be affected by similar cellular, molecular, or endocrine pathways (Figure), as suggested recently by Lazar. The most striking similarities relate to atherosclerosis. WAT in obesity is characterized by low-grade chronic inflammation. Likewise, atherosclerosis is recognized as a chronic inflammatory disease in which macrophages and lymphocytes play a crucial role. The chemokine MCP-1 or its receptor CCR2 mediate deleterious effects in obesity. In parallel, MCP-1 or CCR2 deficiency decreased atherogenesis in atherosclerosis-prone mice. The current findings by Wu et al match a study by Veillard et al, who showed that RANTES expression colocalized with macrophages and T cells within murine atherosclerotic lesions and that the RANTES antagonists Met-RANTES reduced progression of atherosclerosis in mice. These findings suggest that pharmacological inhibition of chemokines may exert beneficial pleiotropic effects in several metabolically active organs. In particular, it would be interesting to determine whether RANTES antagonists affect diet-induced WAT inflammation and insulin resistance. Similar pharmacological interventions or genetic approaches that modulate RANTES or its receptors in mice would also clarify the causal role of RANTES related to metabolic and inflammatory effects after diet-induced obesity.

A paracrine crosstalk between atherosclerosis and periadventitial adipose tissue that releases inflammatory chemokines and cytokines was suggested by studies that correlated human and rodent tissue samples. The concept that adipocytes and macrophages integrate metabolic and immune responses through shared mechanisms has been formulated previously. The study by Wu et al in the present issue suggests that some of these responses may also be shared by T cells.

The liver constitutes another metabolically active organ and has been shown to be affected by genetic modulations of both MCP-1 or CCR2. In the study by Wu et al, RANTES mRNA was induced less in liver than in WAT, which suggests that RANTES may exert only minor alterations in liver metabolism of diet-induced obesity. The relevance of RANTES in this context remains to be determined, however.
The pancreas is also at the crossroads of metabolism. Chronic hyperglycemia in diabetes mellitus type II is detrimental to pancreatic β-cells, which leads to impaired insulin secretion. Maedler et al demonstrated the critical role of inflammatory cytokines in this context. They showed that high glucose increased IL-1β levels and impaired β-cell function. An IL-1 receptor antagonist protected cultured human islets from these deleterious effects.20 Investigation of the role of RANTES in this context may be another interesting avenue to pursue.

In conclusion, the study by Wu et al supports the paradigm that inflammatory cytokines and chemokines, macrophages, and T cells are important players in the inflammation of adipose tissue in obesity. It also suggests paracrine and endocrine interactions among organs involved in the metabolic syndrome. A better understanding of these local and systemic interactions will have major implications for decreasing the rates of morbidity and mortality associated with sequelae of the metabolic syndrome.

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Disclosures
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