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

Christian M. Matter, MD; Christoph Handschin, PhD

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.1

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.8 Obese mice with CCR2 deficiency exhibited decreased WAT inflammation and improved systemic insulin resistance.8 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, concomitant effects on liver steatosis and systemic insulin resistance imply more widespread endocrine effects of WAT inflammation in obesity.

We learn now from Wu and colleagues10 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.7 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.10 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-

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From Cardiovascular Research, Institute of Physiology (C.M.M.), and the Zürich Center for Integrative Human Physiology (C.M.M., C.H.), Institute of Physiology (C.H.), University of Zürich; and the Clinic of Cardiology, CardioVascular Center, University Hospital Zürich (C.M.M.), Zürich, Switzerland.

Correspondence to Dr Christian M. Matter, Cardiovascular Research, Institute of Physiology, University of Zürich, and Cardiology, CardioVascular Center, University Hospital Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland. E-mail cmatter@physiol.unizh.ch

(Circulation. 2007;115:946-948.)

© 2007 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/CIRCULATIONAHA.106.852390
Inflammatory chemokines and cytokines in obesity and the metabolic syndrome. Obesity leads to chronic low-grade inflammation of WAT. Activated macrophages (Macroph) and T cells within WAT produce increased levels of inflammatory chemokines such as CCL2/MCP-1 and CCL5/RANTES as well as cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6. Release of these mediators of inflammation is increased by the WAT in obesity and may affect other organs involved in the metabolic syndrome by paracrine or endocrine effects. For example, these chemokines/cytokines may promote atherosclerotic plaque formation, liver steatosis, and pancreatic β-cell degeneration, which lead to diabetes mellitus type II. Many of these chemokines/cytokines are also produced by these organs and have been shown to play a role, particularly in atherosclerosis. The degree of local and systemic interactions between the different organs affected by the metabolic syndrome remains to be determined.

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. Investigation of function. An IL-1 receptor antagonist protected cultured human islets from these deleterious effects.20

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.

**Sources of Funding**

Dr Matter has received research grants from the European Union (G5RD-CT-2001-00532 and Bundesamt für Bildung un Wissenschaft), the Swiss National Science Foundation (31-114094/1 and 3100-068118), the Swiss Heart Foundation, and the University Research Priority Program “Integrative Human Physiology” at the University of Zürich. Dr Handschin has received research grants from the Swiss National Science Foundation (31-114094/1 and Bundesamt für Bildung un Wissenschaft), the Swiss Heart Foundation, and the University Research Priority Program “Integrative Human Physiology” at the University of Zürich. 

**Disclosures**

None.

**References**

RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted),
Inflammation, Obesity, and the Metabolic Syndrome
Christian M. Matter and Christoph Handschin

Circulation. 2007;115:946-948
doi: 10.1161/CIRCULATIONAHA.106.685230

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/115/8/946

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/