



Adipokine Mediators of Inflammation and Cardiometabolic Comorbidity in Rheumatoid Arthritis: Is There a Master Adipokine?

Understanding how immune cells interact with adipocytes to induce the downstream consequences of obesity (i.e., insulin resistance, hepatic steatosis, atherosclerosis, just to name a few) is among the most active areas of current interest among obesity researchers. In fact, that white adipose tissue has secretory capacity is a relatively recent concept. In the early 1990s it was recognized that tumor necrosis factor- α (TNF- α) and leptin are expressed by adipocytes in proportion to adipose tissue mass and that they possess diverse autocrine and paracrine functions relating to energy metabolism and the neurohormonal regulation of feeding impulses^{1,2}. Since then, dozens of secreted adipocyte products have been identified³.

That many proteins termed “adipokines” overlap those considered central to the inflammatory pathobiology of rheumatoid arthritis (RA) is of particular interest to RA researchers. Adipocytes secrete inflammatory cytokines [TNF- α , interleukin 1 β (IL-1 β), IL-6], chemokines (monocyte chemoattractant protein-1), acute-phase reactants (serum amyloid A), and others that parallel the expression profiles of inflamed synovium⁴. Adipokine expression is potentiated through activated macrophages and T lymphocytes within adipose tissue, and represents an additional parallel to the processes occurring in RA synovitis.

Interestingly, many obesity-related complications are also present in patients with RA, even among those who are not obese. Cardiovascular disease (CVD) event rates and atherosclerosis are increased compared with otherwise similar non-RA controls^{5,6,7}, and insulin resistance measures are higher in RA, even after controlling for adipose tissue amount, location, and glucocorticoid use. Across many studies, circulating and synovial fluid levels of several adipokines (e.g., leptin⁸, resistin⁹, visfatin¹⁰, and adiponectin¹¹) are also higher among RA patients compared with controls. While some of this increase could be related to higher fat mass and/or a tendency to accumulate fat in the

visceral compartment in some patients with RA¹², it likely does not explain the entire increase in levels. However, the implied pathogenic effects of adipose-derived “hyper-adipokinemia” in RA have been difficult to support, particularly as there are seemingly paradoxical associations of adiposity with several key adverse outcomes in RA. For example, several high-quality studies have demonstrated that RA patients with a higher body mass index (BMI, a surrogate for adiposity), have lower all-cause and CVD mortality¹³, and tend to be protected from erosive damage¹⁴. This protection is found to exist despite the observation that RA patients with higher BMI tend to have higher measures of disease activity than those with lower BMI, and a diminished treatment response to some biologic disease-modifying antirheumatic drugs¹⁵. Clearly, the relationships that link the inflammatory products of adipose tissue with RA-associated outcomes are complex, dynamic, possibly conditioned on other patient-specific features, and not easily explained using simple correlations and bivariate modeling techniques. The search for an elusive adipokine “master-switch” in RA continues.

Enter chemerin. Chemerin was first described in 2003 as an adipokine that signals through several chemokine receptors¹⁶. Chemerin levels have been shown to be higher in several chronic inflammatory diseases, such as inflammatory bowel disease, psoriasis, systemic lupus erythematosus, and multiple sclerosis¹⁷. TNF- α induces adipocytes to secrete chemerin, which in turn has been shown to upregulate the production of TNF- α , IL-6, IL-1 β , and chemokine ligand 2 in both human chondrocytes and synoviocytes¹⁸. Relevant to this, synovial fluid concentrations of chemerin are elevated in osteoarthritis, psoriatic arthritis, and RA relative to circulating levels, suggesting that the joint may be the site of production¹⁷. Downstream, chemerin may affect insulin sensitivity and promote atherogenesis. Insulin-stimulated glucose uptake into skeletal muscle was decreased upon treatment with chemerin¹⁹;

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however, this effect has not been shown in all studies. In addition, chemerin is expressed in macrophage foam cells of atherosclerosis in proportion to lesion size²⁰. Taken together, it is compelling to implicate chemerin as a potential link between articular inflammation and cardiometabolic comorbidities.

In this issue of *The Journal*, Dessein and colleagues present a cross-sectional analysis of the association of chemerin with cardiometabolic intermediates, RA characteristics, and ultrasonographic measures of atherosclerosis in the common carotid artery²¹. They report that higher circulating chemerin levels were associated with several RA characteristics, including measures of disease activity. Higher chemerin levels were associated with CVD measures only among certain subgroups. Chemerin was associated with circulating markers of endothelial activation only among patients with traditional CVD risk factors, with common carotid intima-medial thickness only among those who were obese or met criteria for the metabolic syndrome, and seemingly counter-intuitively with carotid plaque only among those who were not obese. While these findings fall short of establishing causality, they are hypothesis-generating and provide support for subsequent longitudinal and mechanistic studies.

In designing those followup studies, several important issues are of particular interest. The first is specificity: Does circulating chemerin induce the same effect in RA as it does in healthy controls or even in other non-RA chronic inflammatory conditions? This is particularly relevant for the design and implementation of RA-specific intervention strategies should chemerin prove to be a therapeutic target.

The second is the source of chemerin in RA. Does the excess chemerin in RA driving pathogenic downstream effects originate in inflamed synovium, or is it being produced in greater than expected excess by white adipose tissue, possibly itself stimulated by the systemic inflammation of RA? This has relevance to potential therapeutic targets and is hinted at in the present report, because chemerin was associated with several of the studied CVD outcomes only among those who were obese.

A third issue relates to possible confounders. Adipocytes produce many adipokines in response to inflammatory stimuli. These tend to be highly correlated, and exploring the independent effects of a single adipokine requires eliminating the confounding effects of the many that are upregulated in parallel and that may be carrying the “true” effect. This is quite challenging in the setting of an observational study. While Dessein and colleagues considered several of the most prominent adipokines and adjusted for the most relevant to the analysis (e.g., leptin), there remains a possibility that the effects they observed are due not to chemerin but to a closely associated factor or factors.

Despite these concerns, the work of Dessein and colleagues provides a compelling new springboard for

investigation, one in which the elusive adipokine “master-switch” may be discovered.

JON T. GILES, MD, MPH,

Division of Rheumatology,
Columbia University,
College of Physicians and Surgeons,
Physicians & Surgeons Building, Suite 10-445,
630 W 168th St.,
New York, New York 10032, USA.

Address correspondence to Dr. Giles; E-mail: jtg2122@columbia.edu

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