Turning ACS outside in: linking perivascular adipose tissue to acute coronary syndromes

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ACUTE CORONARY SYNDROME (ACS) typically occurs when an atherosclerotic plaque suddenly destabilizes in a patient with previously stable coronary artery disease (CAD) (7). Traditionally, the research emphasis in this area has focused on pathology occurring within the vessel lumen and the intima. The prevailing concept is that CAD pathology progresses “inside out” with endothelial dysfunction, infiltration of inflammatory cells, transcytosis of cholesterol-rich atherogenic lipoproteins from plasma to the intima, oxidative modification, foam cell formation, and smooth muscle pleiocytosis, subsequently leading to stable plaque growth (23, 24). Plaque rupture at the shoulder region of atherosclerotic lesions allows the precarious exposure of prothrombotic and proinflammatory mediators, thereby triggering ACS with its attendant morbidity and mortality. These concepts have been recently challenged by reports that the adventitia is the major site of vascular inflammatory cell accumulation in hyperlipidemic, atherosclerosis-prone apolipoprotein E-deficient mice (16). However, the causes of adventitial inflammation and its potential contribution to intimal disease and clinical events such as ACS are largely unknown.

Mounting evidence suggests that perivascular adipose tissue (PVAT) plays a key role in triggering adventitial inflammation in atherosclerosis. For example, inflammatory cell infiltration was reported to be markedly increased in PVAT surrounding atherosclerotic human aorta compared with nondiseased aorta (8). Moreover, inflammatory gene expression was shown to be upregulated and the expression of anti-inflammatory adiponectin downregulated in PVAT surrounding diseased human coronary arteries (2, 9, 15). In rodents fed high-fat diets, PVAT accumulates at sites prone to the development of atherosclerosis and secretes potent chemokines that attract monocytes and T cells to the adventitial interface (16). While much of the inflammation in PVAT is attributed to infiltrating macrophages and T cells, the adipocytes themselves exhibit a proinflammatory phenotype and may play an important role in triggering and propagating the inflammation in PVAT (3). Adipokines such as leptin and resistin released by PVAT may perturb the function of vascular wall cells in an autocrine fashion. Indeed, the cross talk between PVAT and the blood vessel wall is a complex process that likely influences not only inflammation but also smooth muscle cell proliferation, angiogenesis, and vasoreactivity (17, 21).

In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Langheim et al. (13) describe adipokine secretion patterns of human coronary artery PVAT, termed epicardial adipose tissue (EAT) in their article, highlighting three groups of patients: ACS, CAD, and patients with angiographically normal coronary arteries (control). While several studies have examined the inflammatory profiles of EAT and PVAT in stable CAD patients undergoing coronary artery bypass grafting (CABG) (2, 9, 12, 15), the most interesting and novel aspect of this research is the focus on adipokine secretion by PVAT in patients with ACS. This enabled the investigators to determine whether patterns of adipokine secretion by PVAT could be specifically associated with ACS.

The investigators measured the expression of a number of cytokines and adipokines, including adiponectin, leptin, resistin, IL-6, IL-10, monocyte chemotactic protein 1 (MCP-1), and plasminogen activator inhibitor-1. Among these mediators, resistin stood out as exhibiting the highest level of mRNA expression in PVAT harvested from patients with ACS. Likewise, the secretion of resistin protein into the media by EAT from ACS patients was significantly higher compared with patients with stable CAD or controls. An examination of the tissue histology suggested that much of the resistin colocalized with infiltrating macrophages in the EAT. Resistin has been shown in one study to be systemically elevated in CAD patients (18). However, other studies and the one by Langheim et al. (13) show that this association is not significant after an adjustment for other cardiac risk factors and markers (13, 14). While these findings are intriguing, it is nevertheless conceptually difficult to understand how resistin released by EAT in the outer adventitia could be directly linked to the pathology of ACS, which is traditionally viewed as an intimal process.

Resistin, also known as FIZZ3 or adipocyte-specific secretory factor, is secreted in humans mostly by cells of the monocyte/macrophage lineage but perhaps also by adipocytes (5, 25). Increased serum levels of resistin have been variably associated with diabetes and obesity (1, 4, 6, 19). It is important to note that in the study by Langheim et al. (13), the stable CAD and ACS patients had similar body-mass indexes, so differences in resistin secretion cannot be attributed to different degrees of obesity. In vitro experiments in mice showed that resistin expression is upregulated by LPS and the inflammatory cytokines IL-1, IL-6, and tumor necrosis factor-α (10). In addition to its effects on insulin signaling, resistin also appears to promote endothelial cell activation by inducing endothelin-1 release, upregulating VCAM-1 and MCP-1 expression, and downregulating tumor necrosis factor receptor-associated factor-3 expression (22). In their study, Langheim et al. (13) also present novel evidence that resistin released from PVAT increases endothelial cell permeability, an index of potential involvement in ACS. The data presented were obtained in human umbilical vein endothelial cells and thus may not reflect with complete fidelity the functional effects of resistin on coronary endothelium. Nevertheless, these findings highlight the importance of resistin, compared with other proinflamma-
tory mediators released by PVAT, as a pathological cause of endothelial injury.

It is important to point out that in coronary arteries, endothelial cells reside not only within the vessel lumen but also within the vasa vasorum, which is encased by PVAT. In that resistin is being secreted by the PVAT, endothelial cells within the vasa vasorum are likely exposed to higher resistin concentrations compared with endothelial cells lining the coronary artery lumen. In advanced atherosclerotic lesions, the vasa vasorum can penetrate into the intima, suggesting a mechanism whereby resistin and other mediators released from PVAT could travel from the outermost to the innermost regions of the blood vessel wall, thereby contributing to diseases such as ACS. If the resistin is able to disrupt endothelium in vasa vasorum, it could help to trigger intraplaque hemorrhage, which has been associated with ACS in a subset of patients (11). Further pathobiological studies will be required to delineate the relationship between resistin secretion by PVAT and the mechanism of ACS within this complex system. Even if such a relationship could be established, proving causality will be difficult but might be aided by the recent development of an adipose tissue transplantation model to the blood vessel wall (20).

In summary, Langheim et al. (13) are to be congratulated for conducting such a challenging and insightful study in a cohort of humans with ACS. Their article sheds light on the potential role of locally secreted adipokines, and more specifically resistin, not only on vascular function but also on acute vascular disease. Further studies are needed to determine whether the relationship between resistin and ACS is associative or causal and to address the underlying mechanisms. Such studies may not only refine our understanding of atherosclerosis but they may lead to an “outside in” approach to treating patients with ACS.

DISCLOSURES

No conflicts of interest are declared by the author(s).

REFERENCES