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INFLAMMATION IN DIABETES AND VASCULAR DISEASE

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Key Points

- Adipose tissue can elaborate proinflammatory cytokines that can influence atherothrombosis.
- In addition to innate immunity due to activated macrophages, adaptive immunity, characterized by activated T lymphocytes, also operates in intra-abdominal (visceral) adipose tissue.
- Adaptive immune regulators such as interferon-γ can alter aspects of systemic metabolism, such as glucose tolerance, as well as aggravate atherogenesis.
- Lifestyle modifications that limit intra-abdominal adiposity should help to quell inflammation that promotes atherosclerosis and atherothrombotic events.

Abundant evidence supports the fundamental contribution of inflammation to the genesis of atherosclerosis and its complications. We recognize the recruitment of inflammatory leukocytes from the blood as an early step in atherogenesis. The molecular mediators of leukocyte recruitment, including endothelial adhesion molecules and chemoattractant cytokines, increase in response to risk factors including constituents of modified lipoproteins or angiotensin II. Not only does early atherogenesis involve inflammation, but so do the thrombotic complications that lead to clinical events, such as myocardial infarction or ischemic stroke. The propensity of a plaque to rupture and provoke thrombosis depends on the content of collagen in the plaque's fibrous cap. Inflammatory signalling tightly controls the level of interstitial collagen in the plaque. For example, activated inflammatory cells secrete proteinases that can break down collagen, elastin, and other constituents of the arterial extracellular matrix, rendering the plaque fragile and susceptible to rupture, a common cause of thrombotic complications.

While indubitable evidence supports the operation of inflammation during all stages of atherosclerosis, our knowledge of the triggers for this inflammation remains incomplete. While traditional risk factors, such as high levels of LDL or hypertension, link causally with inflammation and oxidative stress, tight control of blood pressure and of LDL has not eliminated the complications of this disease. Therefore, we must seek novel triggers for inflammation to understand this process more fully and to identify

novel therapeutic targets. The residual burden of cardiovascular risk demands a deeper understanding of the triggers of atherosclerosis.

In this context, burgeoning evidence supports obesity [and particularly intra-abdominal (visceral) adiposity] and diabetes as instigators of inflammation. The former concept of adipose tissue as an energy storage depot where triglyceride droplets push an inactive nucleus to the side of the adipocyte has undergone remarkable revision in the last decade. We now recognize that the adipocyte itself, and inflammatory cells that accumulate in adipose tissue, secrete abundant proinflammatory cytokines. In particular, intra-abdominal adipose tissue is strategically located to inundate the liver with proinflammatory cytokines via the portal circulation. These mediators from intra-abdominal adipose tissue impinge directly on the liver and can alter the program of hepatic protein synthesis. Among the proteins of the acute phase response solicited by inflammatory cytokines, fibrinogen and plasminogen activator inhibitor-1 participate causally in thrombus formation and accumulation. Levels of these proteins increase in obese subjects and in patients with diabetes. These alterations likely contribute to the thrombotic diathesis associated with these conditions. Among the acute phase reactants, C-reactive protein serves as a readily measured analyte that can disclose inflammatory status in a reliable way. Indeed, C-reactive protein levels increase in proportion to accumulation of intra-abdominal adipose tissue, a finding that underscores the inflammatory burden associated with intra-abdominal fat accumulation.

While numerous studies over the last decade have highlighted the role of innate immune cells such as the mononuclear phagocytes in intra-abdominal adipose tissue, the role of adaptive immunity in adipose tissues has remained relatively unexplored until recently. As considerable crosstalk characterizes the operation of innate and adaptive immunity, our group [1] and others have recently hypothesized that T lymphocytes may regulate the inflammatory response in adipose tissue. In particular, we have found evidence of activated T lymphocytes in intra-abdominal adipose tissue in obese mice. Local overexpression of class II histocompatibility antigens served as the signature of elaboration of the T helper cell type 1 (Th1) cytokine interferon-gamma (IFN-γ) locally in intra-abdominal adipose tissue. Subsequent studies have shown that IFN-γ could induce numerous proinflammatory mediators, including chemokines that can recruit further lymphocytes to the plaque. Mice deficient in IFN-γ rendered obese by a high-fat diet showed not only decreased chemokine and inflammatory cell accumulation, but also improved glucose tolerance. Work from the laboratories of Ballantyne and Marx [2-4] has also highlighted the operation of adaptive immunity in intra-abdominal adipose tissue.

The presence of inflammatory stimuli often elicits counter-regulatory mechanisms to mute the inflammatory response and prevent an untrammeled phlogistic amplification of inflammation. In this regard, several investigators have hypothesized a role for adiponectin as an endogenous anti-inflammatory mediator related to obesity. Individuals with intra-abdominal adiposity have lower circulating levels of this anti-inflammatory adipokine than do their lean counterparts. We explored the anti-inflammatory effects of adiponectin on human macrophages, and identified a coordinate suppression of the expression of T lymphocyte chemoattractants of the CXCR3 ligand family due to

adiponectin treatment. In vivo experiments in mice genetically engineered for atherosclerosis susceptibility and absence of adiponectin showed increased T cell accumulation and a modest but significant increase in atherosclerotic lesion size at the level of the aortic root [5]. While not all laboratories have found increased atherosclerosis in adiponectin-deficient animals, these findings together indicate that adiponectin not only suppresses innate immune responses, but also may limit adaptive immunity. Thus, inflammation represents a common thread that unites the fundamental aspects of the pathophysiology of atherosclerosis, obesity, and diabetes.

References

1. Rocha VZ, Folco EJ, Sukhova G, et al. Interferon-gamma, a Th1 cytokine, regulates fat inflammation: a role for adaptive immunity in obesity. Circ Res 2008; 103: 467-76.

2. Kintscher U, Hartge M, Hess K, et al. T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. Arterioscler Thromb Vasc Biol 2008; 28: 1304-10.

3. Wu H and Ballantyne CM. Inflammation, adipose tissue, and T cells: what is the "straight skinny" on lean versus fat mice? Circ Res 2009; 105: e3-4.

4. Wu H, Ghosh S, Perrard XD, et al. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. Circulation 2007; 115: 1029-38.

5. Okamoto Y, Folco EJ, Minami M, et al. Adiponectin inhibits the production of CXC receptor 3 chemokine ligands in macrophages and reduces T-lymphocyte recruitment in atherogenesis. Circ Res 2008; 102: 218-25.