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REVIEW TOPIC OF THE WEEK

Unraveling Vascular Inflammation

From Immunology to Imaging

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ABSTRACT

Inflammation is a critical factor in early atherosclerosis and its progression to myocardial infarction. The search for valid surrogate markers of arterial vascular inflammation led to the increasing use of positron emission tomography/computed tomography. Indeed, vascular inflammation is associated with future risk for myocardial infarction and can be modulated with short-term therapies, such as statins, that mitigate cardiovascular risk. However, to better understand vascular inflammation and its mechanisms, a panel was recently convened of world experts in immunology, human translational research, and positron emission tomographic vascular imaging. This contemporary review first strives to understand the diverse roles of immune cells implicated in atherogenesis. Next, the authors describe human chronic inflammatory disease models that can help elucidate the pathophysiology of vascular inflammation. Finally, the authors review positron emission tomography–based imaging techniques to characterize the vessel wall in vivo. (J Am Coll Cardiol 2017;70:1403–12) Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CT = computed tomographic

CV = cardiovascular

CVD = cardiovascular disease

FDG = ^{18}F-fluorodeoxyglucose

HIV = human immunodeficiency virus

IFN = interferon

MI = myocardial infarction

MR = magnetic resonance

NaF = ^{18}F-sodium fluoride

NET = neutrophil extracellular trap

PAD4 = peptidylarginine deiminase-4

PET = positron emission tomographic

SLE = systemic lupus erythematosus

VI = vascular inflammation

Cardiovascular disease (CVD) remains the leading cause of death worldwide, highlighting the need to elucidate its pathogenesis. Once considered a passive biological process, CVD is now recognized as an active, immune-driven process that may begin in childhood (1). Current research into the natural history of atheroma development has implicated many immune cells, including phagocytes, lymphocytes, dendritic cells, and neutrophils (2). Because these cells play a major role in initiating plaque development and complication, leukocytes are promising targets for acute and chronic atherosclerosis therapy. However, the complexity of the immune system and its role as a defensive force against infection requires novel tools to precisely identify and treat only the inflammatory cells or processes that promote atherosclerosis. Biomedical engineering, specifically in human imaging, offers unique possibilities for diagnosing and treating atherosclerotic plaque inflammation before cardiovascular (CV) events. Thus, interfacing novel engineering to enhance human imaging with immunology will be essential to accelerate advances in management of this disease.

In this review, we begin with an overview of the emerging understanding of CVD as a systemic inflammatory disorder relating to monocytes, macrophages, neutrophils, and T cells. We then discuss specific human conditions with increased CVD risk to study the natural history of atherosclerosis, including human immunodeficiency virus (HIV), systemic lupus erythematosus (SLE), and psoriasis as human models of vascular disease initiation and progression. Finally, we review current applications of positron emission tomographic (PET) imaging and emerging PET tracer agents used in vascular characterization.

IMMUNOLOGY OF INFLAMMATION AS IT PERTAINS TO THE VESSEL WALL

MONOCYTES AND MACROPHAGES. The most numerous cells in atherosclerotic plaques are macrophages (3), leukocytes that are central to innate immunity. In atherosclerosis, macrophage accumulation commences as bone marrow-derived, Ly6Chigh monocytes infiltrate the lesion. These Ly6Chigh inflammatory monocytes exit the bone marrow in a C-C motif chemokine receptor 2-dependent manner, accumulate in the vessel wall, and differentiate into macrophages, which are sustained through self-renewal (4). Notably, as atherosclerosis progresses, local macrophage proliferation, rather than monocyte recruitment, becomes more important in lesion growth.

In addition to the accumulation of monocytes in atherosclerotic lesions, these innate immune cells contribute to the biological response following a myocardial infarction (MI). Monocytes are both destructive and protective, in that they give rise to infarct rupture and contribute to infarct healing. However, an overabundance of monocytes can interfere with healing, resulting in heart failure. In an acute MI, an oversupply of monocytes to the aorta is rapid, concomitant with a reduction in C-X-C motif chemokine ligand 12 expression in the bone marrow. Diminished C-X-C motif chemokine ligand 12 expression enables myeloid cells and their progenitors to exit the bone marrow and take up residence in the spleen, where they trigger extramedullary hematopoiesis (5). Additionally, differentiated leukocytes, especially monocytes and neutrophils, take up residence in end-organ tissues, giving rise to plaques and inflammation. The vascular sympathetic innervation (i.e., nerve fibers traveling along the aorta and arterioles) plays a role in the increased emergency supply of leukocytes. In the periphery, sympathetic innervation activates endothelial cells on the luminal surface of atherosclerotic plaques, increasing adhesion molecule expression, which augments leukocyte recruitment (6). To directly investigate the role of the vascular sympathetic innervation system in atherogenesis, the role of stress in monocyte proliferation is a topic of ongoing investigation. Stress elevates noradrenaline levels in the bone marrow and activates bone marrow stem cells (7). Hematopoietic stem and progenitor cell proliferation is significantly enhanced, C-X-C motif chemokine ligand 12 is lowered, and monocytes enter the systemic circulation in increased numbers. Collectively, these mechanisms suggest a multiorgan communication system that activates the bone marrow through the sympathetic innervation system, increasing hematopoietic stem and progenitor cell proliferation and thus enhancing leukocytosis. Therefore, current studies aim to unravel the systemic mechanisms that control the production, recruitment, differentiation, and proliferation of monocytes and their descendent macrophages in atherosclerosis, to determine how these processes can be balanced to exert the most benefit, and to elucidate specific control points in atherogenesis.

NEUTROPHILS. Neutrophils are increasingly recognized in the initiation of atherosclerotic plaque development. Neutrophils are the initial immune cell to infiltrate inflammatory sites produced by injury or