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REVIEW TOPIC OF THE WEEK

Imaging Systemic Inflammatory Networks in Ischemic Heart Disease

Matthias Nahrendorf, MD,* Stefan Frantz, MD,†‡ Filip K. Swirski, PhD,* Willem J.M. Mulder, PhD,§‖ Gwendalyn Randolph, PhD,¶ Georg Ertl, MD,†# Vasilis Ntziachristos, PhD,** Jan J. Piek, MD,†† Erik S. Stroes, MD,‖ Markus Schwaiger, MD,‡‡ Douglas L. Mann, MD,§§ Zahi A. Fayad, PhD§

ABSTRACT

While acute myocardial infarction mortality declines, patients continue to face reinfarction and/or heart failure. The immune system, which intimately interacts with healthy and diseased tissues through resident and recruited leukocytes, is a central interface for a global host response to ischemia. Pathways that enhance the systemic leukocyte supply may be potential therapeutic targets. Pre-clinically, imaging helps to identify immunity's decision nodes, which may serve as such targets. In translating the rapidly-expanding pre-clinical data on immune activity, the difficulty of obtaining multiple clinical tissue samples from involved organs is an obstacle that whole-body imaging can help overcome. In patients, molecular and cellular imaging can be integrated with blood-based diagnostics to assess the translatability of discoveries, including the activation of hematopoietic tissues after myocardial infarction, and serve as an endpoint in clinical trials. In this review, we discuss these concepts while focusing on imaging immune activity in organs involved in ischemic heart disease. (J Am Coll Cardiol 2015;65:1583–91) © 2015 by the American College of Cardiology Foundation.

Although acute myocardial infarction (AMI) mortality has declined, cardiovascular patients increasingly face reinfarction and/or the development of heart failure. There are over 20 million patients with heart failure worldwide, underscoring the need to prevent heart failure. Basic science progress in the last decade revealed that local cardiac repair after ischemia is influenced by macrophage function and systemic leukocyte supply (1). Here, we argue that expanding knowledge of the immune system's role provides opportunities for improving ischemic heart disease management. Regulating immune activity may reduce post-myocardial infarction (MI) heart failure and reinfarction. Because extensive pre-clinical and translational research has shed light on immunity in

From the *Center for Systems Biology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; †Comprehensive Heart Failure Center, Universitätsklinikum Würzburg, Würzburg, Germany; ‡Universitätsklinik und Poliklinik für Innere Medizin III, Universitätsklinikum Halle, Halle (Saale), Germany; §Translational and Molecular Imaging Institute, Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, New York; ‖Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ¶Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri; #Medizinische Klinik und Poliklinik I, Universitätsklinikum Würzburg, Würzburg, Germany; **Institute for Biological and Medical Imaging, Technische Universität München and Helmholtz Zentrum München, Neuherberg, Germany; ††Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ‡‡Department of Nuclear Medicine, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; and the §§Center for Cardiovascular Research, Division of Cardiology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri. Dr. Frantz has received a grant from the Federal Ministry of Education and Research (BMBF). Dr. Ertl has served on steering committees for Novartis, Bayer, and Pfizer. Dr. Ntziachristos is a shareholder in iThera Medical GmbH. Dr. Piek has served on the medical advisory board of Abbott Vascular; and has served as a consultant to Miracor. Dr. Schwaiger has received a research grant from the German Research Foundation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Nahrendorf and Frantz contributed equally to this work. James De Lemos, MD, served as Guest Editor for this paper.
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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CMR = cardiac magnetic resonance

FDG = fluorodeoxyglucose

IVM = intravital microscopy

PET = positron emission tomography

USPIO = ultrasmall superparamagnetic iron oxide nanoparticles

atherosclerosis and its comorbidities, clinical progress now appears to be within reach. The first clinical trials investigating neutralizing interleukin-1β (2) and modulating cellular immune responses with low-dose methotrexate (3) are bellwethers for immune targeting strategies in cardiovascular medicine.

THE CELLULAR IMMUNE SYSTEM IN HEALTHY CARDIOVASCULAR ORGANS

The cardiovascular system is in constant, intimate contact with immune cells, and does far more than transport circulating leukocytes and cytokines. The vascular endothelial layer regulates cell recruitment, signaling the stroma's status to circulating leukocytes via expression of adhesion molecules and chemokines. Some immune cells, including monocytes and neutrophils, patrol the endothelium by crawling along or below its surface (4–7). The endothelium is less of a barrier than previously thought: even in steady state, leukocytes extravasate. Extravasation is subject to circadian rhythms and may be partly regulated by nervous signals (8). There is a surprisingly dense network of tissue-resident leukocytes (9) in healthy vascular (10) and myocardial tissue (11–14). Tissue-resident macrophages are numerous and create a close-knit network interspersed within the stroma. The high number and organization of the cells, whose delicate dendrites increase their reach and surface area, could only be observed using the recently-devised technique of applying fluorescence microscopic imaging to thicker cardiac tissue sections (**Figure 1**). Expression of bright fluorescence reporters in tissue-resident macrophages revealed their number and organization in the hearts of transgenic mice (12,14). These cells are assumed to pursue sentinel functions and support stromal cells' tissue-specific tasks.

THE CELLULAR IMMUNE SYSTEM IN ATHEROSCLEROSIS

Immune cell phenotype, number, and function in the arterial wall change drastically in atherosclerosis. Macrophages increase 20-fold in apolipoprotein $E^{-/-}$ mice on a Western diet (10). Pre-clinical (15,16) and clinical (17) studies show that activated endothelium recruits monocytes, neutrophils, and lymphocytes, even in the early stages of atherosclerosis (1,18,19). Innate immune cells should remove cholesterol deposits from the intima, but they fail to do so, and instead give rise to inflamed plaques. Monocytes adopting inflammatory phenotypes differentiate into macrophages and foam cells and engage in tissue destruction by releasing cytokines and proteases that weaken the stromal architecture (20). Prototypical sequelae include plaque rupture and erosion, with subsequent thrombotic stenosis or occlusion of arteries and tissue ischemia. Dendritic cells and lymphocytes also participate in disease progression or regulation (21). Presentation of autoantigens, including oxidized lipoproteins, to lymphocytes may trigger their proliferation and activation (18). B cells pursue regulatory functions (21), for instance, by instructing increased innate immune cell production (22). In addition, regulatory T cells have protective roles (23). Imaging data support many of these insights. Pre-clinical optical imaging, especially intravital microscopy (IVM), shows immune cell interactions with stromal cells and with each other. In the past, the rigorous and rapid motion of cardiovascular organs posed a problem for IVM; however, recent progress in tissue stabilization, gating image acquisition, and/or reconstruction has overcome these hurdles (24,25) (**Figure 1**).

THE IMMUNE SYSTEM IN AMI

Whereas atherosclerotic lesions develop due to chronic low-grade inflammation, the ischemic events triggered by atherosclerosis induce high-amplitude acute inflammatory responses. In patients and in mice, AMI triggers robust blood leukocytosis (1). These events have recently been studied in more detail, and we now understand which immune cells or cell subsets react to MI. The changes observed in blood are the "tip of the iceberg": circulating components mirror systems-wide increases in immune cell numbers and activity in the ischemic myocardium, the remote nonischemic myocardium, nonculprit plaques, heart-draining lymph nodes, the spleen, and bone marrow. Sampling blood reveals immune cell migration from storage or production sites to the atherosclerotic plaque or failing myocardium. Tissue is more difficult to assay than blood. Imaging and flow cytometry of digested myocardium and arteries enable quantitative approaches and provide the cell recruitment timeline after ischemic injury. The most numerous and fastest responders are innate immune cells. Neutrophils and the inflammatory monocyte subset begin to infiltrate the distressed myocardium within the first 30 min after ischemia onset (24), while resident macrophages disappear (14), most likely due to local death or emigration. The neutrophil response wanes quickly, and inflammatory monocytes continue to infiltrate at high rates for the first 4 days after ischemia (11). The number of