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Molecular Imaging of Myocardial Inflammation With Positron Emission Tomography Post-Ischemia

A Determinant of Subsequent Remodeling or Recovery

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SUMMARY

Inflammation after myocardial ischemia influences ventricular remodeling and repair and has emerged as a therapeutic target. Conventional diagnostic measurements address systemic inflammation but cannot quantify local tissue changes. Molecular imaging facilitates noninvasive assessment of leukocyte infiltration into damaged myocardium. Preliminary experience with ^{18}F-labeled fluorodeoxyglucose ([^{18}F]FDG) demonstrates localized inflammatory cell signal within the infarct territory as an independent predictor of subsequent ventricular dysfunction. Novel targeted radiotracers may provide additional insight into the enrichment of specific leukocyte populations. Challenges to wider implementation of inflammation imaging after myocardial infarction include accurate and reproducible quantification, prognostic value, and capacity to monitor inflammation response to novel treatment. This review describes myocardial inflammation following ischemia as a molecular imaging target and evaluates established and emerging radiotracers for this application. Furthermore, the potential role of inflammation imaging to provide prognostic information, support novel drug and therapeutic research, and assess biological response to cardiac disease is discussed. (J Am Coll Cardiol Img 2018;11:1340–55)

Advances in revascularization techniques have greatly improved survival following first myocardial infarction (MI) (1), but cardiovascular disease remains a major burden on the health system, especially due to the increased number of patients who develop advanced heart failure after ischemic insults (2). Standard medical therapy targeting neurohumoral activation, afterload, and lipid levels improve long-term outcome on a population basis, but these strategies lack personalization (3). The individual biology of myocardial repair early after insult and reperfusion provides novel options for personalized molecular interventions and is increasingly emerging as a therapeutic target. Growing evidence emphasizes the influence of acute local and systemic inflammation on subsequent ventricular remodeling, culminating in worse cardiac outcomes. Novel therapeutic strategies target inflammation to limit infarct expansion, support endogenous cardiac repair, and stabilize collagen-rich scar (4,5). Because inflammation involves many leukocyte subtypes and evolves, it can be difficult to identify the appropriate target cells and timing for optimal intervention. Molecular imaging interrogates inflammatory cells directly and noninvasively (6). New molecular probes may provide greater insight into specific leukocyte populations involved in the infarct healing process, which may help in selecting the right patient and the right timepoint for novel inflammation-targeted therapies.

CARDIAC INFLAMMATION AFTER ISCHEMIA

POST-INFARCT INFLAMMATION. Atherosclerosis and plaque rupture may lead to complete coronary occlusion. Resultant loss of myocardial oxygen delivery evokes localized cell death and secretion of chemical signals to initiate apoptosis and inflammatory cell recruitment. Adhesion molecules on cardiac endothelial cells are acutely upregulated and mediate

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extravasation of circulating leukocytes. The dominant immune cell population in the heart after acute infarction consists of peripheral leukocytes mobilized from the bone marrow and spleen, which persist over a period of days, depending on the specific subtype (7,8). The role of resident inflammatory cells in MI response is less defined and thought to be comparatively minor (9).

CELLULAR BASIS. The inflammatory cascade following infarction is mediated by chemical signals to recruit circulating cells (7). Within minutes after the initial insult, granulocytes and patrolling monocytes begin to infiltrate the tissue to isolate the damaged region and promote localized inflammation (10). Neutrophils and other granulocytes predominate at 24 h after infarction and secrete proinflammatory cytokines, including interleukin (IL)-1β, IL-12, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, to augment the inflammatory response and recruit additional cell populations (11). Granulocytes also secrete proteases, which intensify the vascular and tissue injury (11). Damaged and dying cardiomyocytes secrete chemokine (C-C motif) ligand 2 (CCL2), which attracts $Ly6C^{high}$ monocytes (8,10), which differentiate into M1-like macrophages responsible for removing cellular debris, minimizing the area of apoptosis, and segregating injured from healthy tissue. These proinflammatory cells are dominant in the infarct zone 3 to 5 days after infarction and perpetuate the inflammatory signal through proinflammatory cytokines and proteases, recruiting additional activated leukocytes to the site of injury and destabilizing the tissue (12). After several days, the damaged heart initiates cell recruitment through chemokine (C-X3-C motif) ligand 1 (fractalkine) (CX3CL1) to attract $Ly6C^{low}$ monocytes, which differentiate into M2-like reparative macrophages within the tissue. This 'chemotactic switch' begins the reparative phase of the healing process, whereby invading leukocytes secrete cytokines supportive of endogenous tissue repair including vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-β (8,12). Lymphocytes, including T helper cells, are present at low levels after infarction and are suggested to mediate the transition from proinflammatory to reparative cell recruitment. Together, these cells orchestrate the healing process, stimulating angiogenesis to restore blood supply to the area at risk and border zone of the infarct, and stimulating fibroblast reorganization and extracellular matrix synthesis to generate a stable, collagen-rich scar (13,14).

ALTERED INFLAMMATION. The diversity of invading cell populations and their distinct roles dictate a precise balance to optimize the healing process (Figure 1). Changes in the number, proportion, or timing of inflammatory cell invasion can have deleterious effects on ventricular remodeling and contractile function. Elevated neutrophil content can lead to excessive apoptosis, robust macrophage recruitment, and unstable scar (15). Neutrophil depletion leads to higher fibrosis, larger infarct size, and worse contractile function (16). Similarly, elevated M1-like macrophages impair scar stability and impart higher left ventricular rupture rate. Extended proinflammatory response involving neutrophils and/or M1-like macrophages can also impede the repair process (17). However, complete suppression of inflammatory cell infiltration also results in higher mortality (18), underscoring the necessity of inflammation to limit cellular damage and stabilize the infarct.

ABBREVIATIONS AND ACRONYMS

[^{18}F]FDG = ^{18}F-labeled fluorodeoxyglucose

CCL12 = chemokine (C-C motif) ligand 12

CX3CL1 = chemokine (C-X3-C motif) ligand 1 (fractalkine)

CXCR4 = chemokine (C-X-C motif) receptor type 4

Ly6C = lymphocyte antigen 6 complex locus C

MI = myocardial infarction

RGD = arginine-glycine-aspartate amino acid sequence (αvβ3 integrin)

SSTR2 = somatostatin receptor type 2

TSPO = mitochondrial translocator protein (12 kDa)

INFLUENCE ON HEART FAILURE. Blood levels of inflammatory cytokines tend to be elevated in patients after MI, which may predict functional decline. Patients with highest leukocyte count at time of admission exhibited double the rate of cardiac death, congestive heart failure, or a new MI over 30 days (19). Increased inflammatory cytokines IL-6 and TNF-α are commonly associated with both acute MI and later stage heart failure (20). Acute inflammation influences the rate of left ventricular rupture in mice, analogous to infarct expansion in humans (18). Studies in genetically modified animals identified interactions between early inflammatory response and subsequent healing, through impaired angiogenesis (21), suppressed growth factors (22), and elevated oxidative stress (23), culminating in greater functional decline. Larger infarct size directly correlates with severity of ventricular remodeling and declining contractile function, both in experimental animals and clinically (24,25). Blood-borne biomarkers provide insight into the systemic inflammatory response but cannot specifically investigate localized tissue inflammation, the specific target of novel therapies. Local tissue biomarkers may provide more insight into the progressive and dynamic inflammatory response as local environmental cues can drastically affect the distribution and profile of the expressed/enriched leukocyte subpopulations (8).

TARGETED ANTI-INFLAMMATORY THERAPY

Novel therapeutic techniques aim to enhance protective aspects of inflammation while minimizing