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iVIEW

EDITOR'S PAGE

Molecular Imaging

From Deep Pearl Diving to Enlightenment

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Despite major advances in the management of acute coronary syndromes, post-infarct morbidity has not been adequately contained. The incidence of heart failure in the aftermath of myocardial infarction (MI) continues to be sizable, and attempts have been made toward the development of various structural patterns and morphological algorithms that may help identify subjects who are at higher risk for adverse ventricular remodeling and heart failure.

However, while this has been important, one could argue that it has offered limited success, and defining adverse left ventricular structure and function through morphofunctional imaging schemes can do only so much. Although remodeling predicts suboptimal prognosis, we have reached the limit of what it can do, and defining therapy on the basis of morphological or functional imaging has not been helpful in preventing heart failure. In contrast, molecular imaging, at least in experimental milieu, has allowed better understanding of the remodeling process and opportunity for intervention. Such a modality of evaluation has characterized the extent of myocardial damage by the processes of necrosis and apoptosis (and resolution thereof) and estimated the rate of myofibroblastic proliferation. Recently, substantial information has become available pertaining to the role of molecular imaging of the immune system in the repair of infarcted myocardium, which is highly variable, and relatively deficient or exaggerated immune responses may variably contribute to remodeling. Because the dose of the immune response determines the protective or detrimental influence on remodeling, the authors of 2 reports published in this issue of *iJACC* (1,2) propose that immune surveillance for tissue repair post-MI can be a powerful strategy to detect, treat, and predict prognosis, even for conditions that have not traditionally been thought to be in the purview of imaging (3). This might change our concepts from the traditional patient with dilated or not dilated left ventricles, and reduced or preserved ejection fraction to more meaningful connotations, such as at high risk for damage versus not at high risk for myocardial damage, or efficient versus inefficient repairers.

Molecular imaging has been widely applied to differentiate between myocardial cell death in MI attributed to the necrotic and apoptotic processes. Tracers targeting heavy chains of myosin or abundant intracellular heat-shock proteins in the ischemic myocardium have allowed the distinct definition of myocardial necrosis (4,5). In contrast, targeting of cell surface phospholipid alterations by radiolabeled annexin A5 (6) or duramycin (unpublished observations) defines the apoptotic process. Imaging studies targeting 2 modes of cell death have clarified the concept of the nonphysiological apoptotic process, which precedes the onset of necrosis and is reversible upon the resolution of ischemia or restricting apoptotic cycling (7). These studies have clearly demonstrated that the 2 modes of cell death are part of the same spectrum, and an attempt to limit either of them would restrict all kinds of cell death. Imaging studies have also

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demonstrated that the annexin A5 is internalized into the injured cells and influences the cellular rescue.

Extracellular myocardial repair by replacement fibrosis at the site of necrotic debris and the untoward occurrence of interstitial fibrosis in the peri-infarct and remote myocardium have been evaluated by the distribution of enzymes involved in the synthesis and degradation of collagen fibers and the rate of myofibroblastic proliferation. Because collagen deposition and interstitial fibrosis contribute to cardiac remodeling and heart failure after MI, evaluation of myofibroblastic proliferation should provide indirect evidence of the extent of fibrosis. Molecular imaging with a charged radiolabeled RGD peptide with affinity to myofibroblast integrin receptors demonstrated that maximum tracer uptake occurred at 2 weeks in the infarct zone, reducing gradually by 12 weeks (8). In contrast, uptake started to increase in the remote areas by 12 weeks. Tracer uptake was histologically confirmed to bind to myofibroblasts and was directly related to the new collagen production. Quantitative uptake decreased significantly in animals treated with any of the angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or aldosterone receptor antagonists (9). Intervention with 2 or 3 of these neurohumoral antagonists demonstrated further reduction in tracer uptake. The reduced new collagen in the remote area in response to neurohumoral inhibition suggested the beneficial effect. However, the decrease in new collagen synthesis in the infarcted area was not affected in the face of massive replacement collagen content, but suppression of the renin-angiotensin-aldosterone axis allowed rapid maturation of thin to thick collagen fibers in this area and prevented aneurysmal dilation.

The studies reported in this issue have used a gallium-68 based positron emission tomographic tracer, pentixafor, that binds to CXCR4 chemokine receptor. Paired CXCR4 and its ligand, SDF-1, regulate the migration of hematopoietic stem cells, as well as neutrophils and monocytes from bone marrow and spleen (3). These cells provide balanced inflammatory, phagocytic, and reparative responses, wherein excess or deficiency of any component may adversely affect subsequent remodeling process (10). Although inflammatory cell imaging has previously been proposed indirectly and less specifically with ^{18}F-fluorodeoxyglucose and ^{18}F-fluorothymidine (11), pentixafor uptake was seen in the infarcted region early after the event (2), was blocked effectively by a CXCR4 inhibitor, and was substantially reduced by neurohumoral antagonists (3). Not all infarcted segments were pentixafor positive, and the maximum uptake was observed in significantly damaged myocardial segments. High tracer uptake in marrow and spleen was correlated with signal intensity in the myocardium. Although longitudinal studies are necessary, these observations suggest that lower signal might support better outcomes and the higher uptake might be an indication for anti-inflammatory intervention.

From the aforementioned reports of molecular imaging in acute MI and during the clinical course thereafter, it becomes clear that regardless of clinical applicability, these techniques clarify pathogenesis in real time, because molecular imaging is the only strategy that allows interrogation of pathophysiological processes at the subcellular level in a living organism. It is necessary to identify appropriate targets and design appropriate targeting tracer. With better imaging comes better understanding of pathogenetic mechanisms and recognition of yet better targets and hence yet better understanding (12–14). The future of imaging will be not just showing more about chamber or scar size and patterns or just more sensitive measures of myocardial dysfunction—we have reached a plateau for what we can learn from that. It is a distinct possibility that molecular imaging might be able to dynamically uncover what pathways are activated in damage and repair (personalized imaging), and which of those are to be targeted for therapy (personalized therapy). We have said it in the past (12–14) and would like to re-emphasize that molecular imaging is all about unraveling deep-seated clues and all about better learning.

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