Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular and Cellular Cardiology 41 (2006) 921–933
Journal of Molecular and Cellular Cardiology
www.elsevier.com/locate/yjmcc

Review article

Molecular imaging of myocardial infarction

Farouc A. Jaffer [a,b,*], David E. Sosnovik [a,b], Matthias Nahrendorf [a], Ralph Weissleder [a]

[a] *Center for Molecular Imaging Research, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02129, USA*
[b] *Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA*

Received 12 August 2006; accepted 5 September 2006
Available online 24 October 2006

Abstract

Molecular tools are rapidly elucidating the molecular and cellular processes underlying myocardial infarction. To further understand these biological processes *in vivo*, investigators are embracing the burgeoning field of molecular imaging. Here we review important aspects of molecular imaging technology and then devote the majority of the text to studies that shed light on the *in vivo* pathogenesis of myocardial infarction. In particular, we focus on post-infarction healing and remodeling and discuss molecular imaging of proteolytic activity, angiogenesis, transglutaminase activity, and apoptosis. In the future, novel reporter agents and high-resolution cardiac imaging systems should enable imaging of emerging targets such as activated macrophages and myeloperoxidase activity, as well as stem cell-based and gene therapy-based myocardial regenerative strategies, in both experimental and clinical subjects.

Keywords: Molecular imaging; Myocardial infarction; Remodeling; Protease; Angiogenesis; Apoptosis; MRI; Optical imaging; Nuclear imaging

Contents

1. Introduction

Molecular tools are unraveling the biology underlying myocardial infarction, a leading cause of death and disability worldwide. To further elucidate the molecular and cellular processes governing myocardial infarction, investigators are embracing the burgeoning field of molecular imaging. Molecular imaging aims to visualize key aspects of biology *in vivo* by utilizing chemically engineered imaging agents for magnetic resonance imaging (MRI), nuclear imaging (single photon emission computed tomography (SPECT), positron emission tomography (PET)), near-infrared fluorescence (NIRF) imaging,

* Corresponding author. MGH-CMIR, 149 13th St., Rm. 5406, Boston, MA 02129, USA. Tel.: +1 617 726 5788; fax: +1 617 726 5708.
E-mail address: fjaffer@partners.org (F.A. Jaffer).

0022-2828/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.yjmcc.2006.09.008

and ultrasound (US) imaging. Molecular imaging technology has demonstrated applications for biology, pharmacological and genetic intervention assessment, drug and imaging agent discovery, and personalized medicine [1–7].

Here we review some recent developments in molecular imaging of myocardial infarction (MI). We first briefly review important aspects of molecular imaging technology and then devote the majority of the text to studies that shed light on the *in vivo* pathogenesis of myocardial infarction. In particular, we present promising molecular imaging studies that assay the biology of post-MI ventricular remodeling, including matrix metalloproteinase activation, angiogenesis, transglutaminase activity, and apoptosis.

2. Molecular imaging: integrating biology, imaging agents, and detection systems

Molecular imaging aims to visualize key molecular or cellular targets of a disease of interest. In many cases, targets are identified from fundamental biological investigations. However, not all targets will furnish successful imaging agents for *in vivo* imaging. Imaging of low-abundance intracellular targets such as DNA (2 copies/cell) remains challenging; recent work however has demonstrated the feasibility of imaging RNA molecules in live cells [8]. Successful imaging targets are often highly and uniquely expressed under disease conditions; thus intracellular, membrane-bound, and extracellular proteins have served as the largest target class for molecular imaging. Favorable targets are also amenable to chemical or biological signal amplification schemes including: protease-activatable agents for optical imaging [9], enzyme-dependent water access for MRI [10], oligomerization of magnetic substrates [11,12], trapping of radioactive agents by phosphorylation (^{18}F-FDG [13] and HSV-TK [14]), multivalency [15], binding to internalizing receptors (transferrin receptor) [16] or vascular cell adhesion molecule-1 [17,18], concentration of iron-oxide-based magnetic nanoparticles within endosomes [16], or covalent binding of imaging agents [19]. These amplification schemes provide strong enhancements in the target-to-background ratios and can often determine the success of an agent for *in vivo* imaging. An alternative approach employs transgenes to reduce background (e.g. luciferases for bioluminescence imaging or engineered fluorescent proteins); these methods are covered in more detail elsewhere [20–23]. Additional important features in selecting biological target for molecular imaging (Table 1) include a clear understanding of its biological role, and the availability of suitable targeting ligands, discussed below.

Table 1
Ideal characteristics of a biological target for molecular imaging

Well-understood, important role in the disease of interest
High expression in target (diseased) tissue
Low expression in non-target tissues, particularly blood
Availability of specific affinity ligands/substrates with favorable attachment chemistry to imaging reporters
Amenable to chemical (e.g. FRET dequenching) and/or biological (e.g. phosphorylation) amplification

Injectable imaging agents typically consist of two components: a signal-emitting compound (radioisotope, fluorochrome, magnetic moiety, sonic enhancer), and an affinity ligand (small molecule, peptide, protein, carbohydrate, antibody or antibody fragment, aptamer) that recognizes the molecular/cellular target of interest. While substrate identification has historically stemmed from top–down approaches (e.g. compounds with known mechanisms and biochemical properties), newer approaches may employ screening methodologies (library approaches utilizing nanoparticles, small molecules, or phage display) to identify novel ligands. Advantages of screening include the rapid and broad assessment of numerous compounds, often in high-throughput fashion [24]. An important consideration of compounds derived from screening-based approaches is that additional experimental validation is required to verify their targeting mechanism of action, specificity, and the absence of harmful biological effects on cells, both *in vitro* and *in vivo*.

Another key aspect of any molecular imaging study is the employed imaging modality (MRI, nuclear, optical (fluorescence/bioluminescence), US). Considerations include the desired molecular sensitivity, spatial and temporal resolution, noninvasive capability, existence of mouse/preclinical imaging systems, the need for clinical translation, and the need to acquire anatomical and functional measurements in the same imaging session. A promising recent advance is the integration of nuclear imaging with computed tomography (PET-CT and SPECT-CT systems), permitting high-resolution co-registration and concomitant assessment of ventricular function. Further advances in murine CT technology (rapid acquisition, gating) will further enhance its utility in molecular imaging of the heart [25]. Similarly, the integration of PET imaging with MRI (high-resolution and highly versatile for cardiovascular imaging without utilizing ionizing radiation [26]) may provide additional molecular–structural correlation in a clinically relevant platform [27]. Bioluminescence is a promising approach to image reporter gene expression, but is likely to remain restricted to small animals in the near future [28]. For an in-depth discussion of these concepts and aspects of specific molecular imaging platforms, the interested reader is referred to several recent reviews [3,5,28,29].

3. Molecular imaging of post-infarction ventricular remodeling

In response to MI, the heart initiates the complex reparative process of ventricular healing and remodeling, where specific biochemical, morphological, and structural alterations occur in both the infarct and non-infarct zones [30–35]. The intended goal of adaptive post-MI healing is the formation of a stable mechanical scar. However, illustrative of the complexity of this process, impaired healing of the infarct zone may predispose to infarct thinning, aneurysm formation, and fatal ventricular rupture, while late adverse remodeling may promote global ventricular dilatation and heart failure [30–32,34,35]. Manipulation and control of the remodeling process are thus of paramount clinical importance, yet *in vivo* methods to image,