Biochimie 116 (2015) 43–51

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Review

Translational applications of molecular imaging in cardiovascular disease and stem cell therapy

Wei Du [a, b, c], Hongyan Tao [a, b], Shihua Zhao [d], Zuo-Xiang He [e, **], Zongjin Li [a, b, c, *]

[a] Collaborative Innovation Center for Biotherapy, Nankai University School of Medicine, Tianjin, China
[b] Tianjin Key Laboratory of Tumor Microenvironment and Neurovascular Regulation, Nankai University School of Medicine, Tianjin, China
[c] The Key Laboratory of Bioactive Materials, Ministry of Education, College of Life Sciences, Nankai University, Tianjin, China
[d] Department of Radiology, Fuwai Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China
[e] Department of Nuclear Imaging, Fuwai Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China

ARTICLE INFO

Article history:
Received 25 February 2015
Accepted 25 June 2015
Available online 30 June 2015

Keywords:
Molecular imaging
Cardiovascular disease
Stem cell therapy
Reporter gene
Clinical translation

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide. Molecular imaging techniques provide valuable information at cellular and molecular level, as opposed to anatomical and structural layers acquired from traditional imaging modalities. More specifically, molecular imaging employs imaging probes which interact with specific molecular targets and therefore makes it possible to visualize biological processes *in vivo*. Molecular imaging technology is now progressing towards preclinical and clinical application that gives an integral and comprehensive guidance for the investigation of cardiovascular disease. In addition, cardiac stem cell therapy holds great promise for clinical translation. Undoubtedly, combining stem cell therapy with molecular imaging technology will bring a broad prospect for the study and treatment of cardiac disease. This review will focus on the progresses of molecular imaging strategies in cardiovascular disease and cardiac stem cell therapy. Furthermore, the perspective on the future role of molecular imaging in clinical translation and potential strategies in defining safety and efficacy of cardiac stem cell therapies will be discussed.

1. Introduction

Cardiovascular disease (CVD) is a common disease with high morbidity and mortality around the world [1]. As a new approach, molecular imaging can directly display biological processes at cellular and molecular level within intact living organisms and is becoming an indispensable tool in CVD diagnosis and therapy [2–4]. This novel diagnostic solution could identify individuals at risk of CVD and initiate early therapy for avoiding irreversible damage occurrence. Many effective therapeutic strategies have been translated into the clinical settings and resulted in considerable improvements in therapy of CVD. However, current treatments fail to address the underlying scarring and cell loss, which is major cause of heart failure after myocardial infarction [5]. Cardiac regeneration with stem cell transplantation is a promising and novel strategy to attenuate cardiac function by promoting-regeneration of injured cardiomyocytes or enhancing angiogenesis. Results from preclinical studies have showed that cardiac stem cell therapy contributes to perfusion and ventricular function enhancement [6,7]. A better understanding of cell fate after transplantation by tracking cell location, engraftment, survival, and cellular fate non-invasively *in vivo* is important for successful implementation of cardiac stem cell therapies. With the capabilities for longitudinal, noninvasive assessment of cellular behavior *in vivo* in the intact animal or human, molecular imaging offers the potential for non-invasive assessment of outcomes and therapeutic mechanisms after stem cell transplantation [8,9].

2. Principles of CVD imaging

Molecular imaging can allow direct, noninvasive, repeatable evaluation of treatment effects by imaging functional molecules, thereby enabling the visualization of the cellular function and

* Corresponding author. Nankai University School of Medicine, 94 Weijin Road, Tianjin 300071, China.
** Corresponding author. Department of Nuclear Medicine, Fu Wai Hospital, CAMS and PUMC, 167 Bei Li Shi Lu, Beijing 100037, China.
E-mail addresses: zuoxianghe@hotmail.com (Z.-X. He), zongjinli@nankai.edu.cn (Z. Li).

http://dx.doi.org/10.1016/j.biochi.2015.06.021
0300-9084/

molecular process in living organisms without perturbing them [2]. Over the last decade, a variety of imaging technologies has been investigated as tools for CVD diagnosis, monitoring the responses to therapies or predicting treatment outcomes to available therapies [2,10]. Comparing with traditional histological techniques, molecular imaging not only could lower the cost of experiment but also provide more visual and accurate assessment for experimental results.

2.1. Targets for CVD imaging

The identification of imaging targets has benefited from increased understanding of the pathophysiology of CVD [11]. A series of targets have been identified, including extracellular matrix (ECM), cell surface markers and intracellular molecules, which represent the specific state of disease progression to a certain degree (Fig. 1). The development of reliable biomarkers to monitor the cellular and molecular activities in CVD will flourish the application of molecular imaging. For CVD diagnosis, specific probes can specifically bind to cell surface or intracellular target molecules, and then allow to directly observe the *in vivo* reactions and activities of these molecules, which could reflect the progression of diseases, such as atherosclerosis and myocardial infarction [9]. Probes can be used as potential indicators, which are able to reflect the development of disease by corresponding molecular imaging modality. Furthermore, molecular imaging probes, typically comprising a signal agent, a targeting moiety and a linker connecting the targeting moiety, should be developed for targeting different molecules according to different imaging modalities [2]. The efficacy and safety are usually two of the most important considerations for probes designation. In terms of probes used in CVD diagnosis, nanoparticulate probes have shown great quality for imaging of macrophages, apoptosis, angiogenesis and thrombosis. Recently, various magnetic contrast nanoplatforms such as SPION [10], micelles and liposomes [12,13], have been prepared by conjugating different targeting ligands, such as monoclonal antibodies, small peptides, antibody fragments or recombinant proteins. Both T1 contrast agents and SPION-based T2 contrast agents have been validated with success for molecular imaging of atherosclerosis at preclinical and clinical levels by MRI. Moreover, a ^{99m}Tc-labeled AT1 receptor peptide analog was applied in a murine model of acute myocardial infarction, which showed an excellent targeting to the myofibroblasts that localized to the infarct zone. This study suggested that the probe may be utilized to identify those cardiomyocytes at risk after myocardial infarction [14].

2.2. Molecular imaging of cardiovascular disease (CVD)

CVD is mainly characterized by dysfunction of the heart and blood vessels. Atherosclerosis and its consequences, such as myocardial infarction and heart failure, constitute the main cause of CVD. Traditional imaging modalities provide anatomical definition and functional information, such as myocardial perfusion, viability, stiffness and contractility. The traditional imaging methods are based on anatomy or physiology level and the underlying biology of most diseases could not be directly revealed *in vivo*. To date, molecular imaging is bridging the gap between the traditional imaging and personalized medicine which allows early detection before symptoms showing up, disease staging and tracking of disease progression.

2.2.1. Atherosclerosis

Atherosclerosis is a syndrome that disrupts blood circulation of the body, posing serious cardiovascular complications. Eventually, a set of symptoms such as arterial thrombosis and myocardial infarction can be caused by plaque erosion or rupture. Inflammation plays a key role in all phases of atherosclerosis and the pathogenesis of atherosclerosis include the accumulation of fatty materials such as cholesterol and triglyceride, monocyte and macrophage recruitment, foam cell formation, endothelial cell

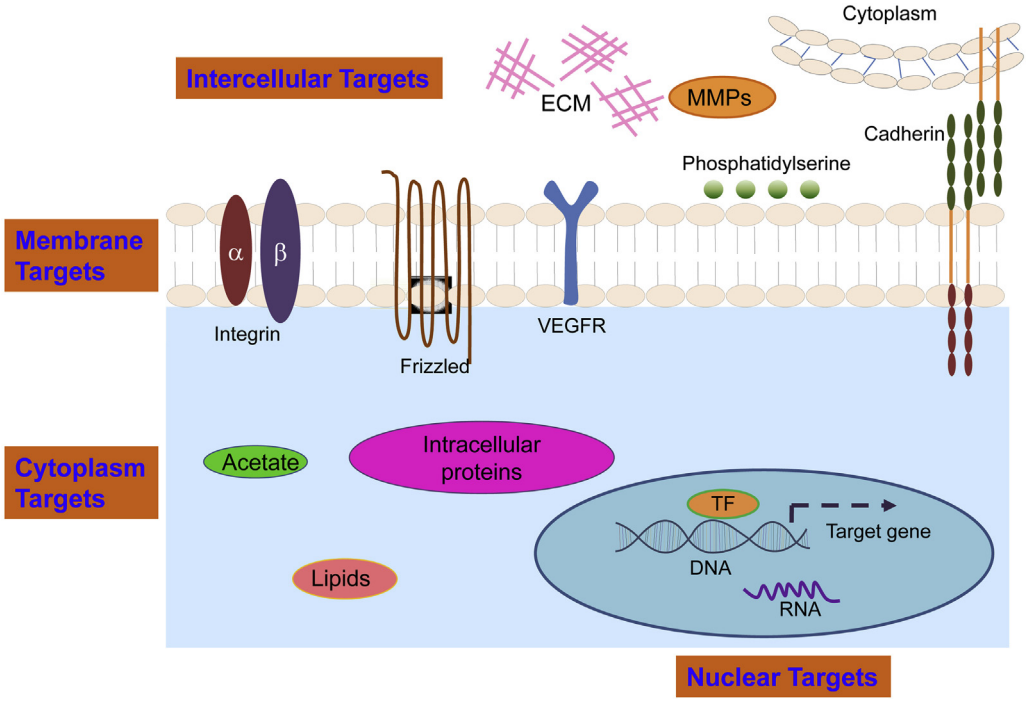

Fig. 1. Molecular imaging targets for cardiovascular diseases. A series of imaging targets can be used for cardiac molecular imaging, including molecules located in cell membrane, cytoplasm, intercellular attachment and nuclear. Imaging probes for various targets can reflect the state of cell or diseases. MMP, matrix metalloproteinase; TF, transcription factor.