Noninvasive Imaging of Angiogenesis with a αvβ3 Integrin-targeted Multi-modality Nanoprobe in Myocardial Infarction Model

Di Chang[1]

[1]*Department of Radiology, Jiangsu Key Laboratory of Molecular and Functional Imaging, Zhongda Hospital, Southeast University, Nanjing, Jiangsu, China*

Purpose:

Angiogenesis is a well-recognized mechanism to recover cardiac blood perfusion after acute myocardial infarction (MI). Angiogenic therapy as a novel promising strategy for MI patients is under research and development, which requires a noninvasive, sensitive and repeatable in vivo method for diagnosing and monitoring therapeutic efficacy of myocardial angiogenesis. The purpose of this study was to develop a novel cyclic peptide containing an arginine-glycine-aspartic acid (RGD) based multi-modality probe imaging for evaluation of angiogenesis in MI model.

Methods:

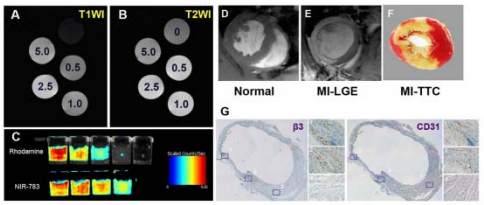

Fig1.(A) T1, (B) T2 weighted MR imaging and (C) NIR optical images of RGD probes. (D) T1-MR imges of normal heart. (E) Gadolinium delayed enhancement (LGE) MR imaging and (F) TTC staining of MI mice. (G) β3 and CD31 immunohistochemical staining of MI mice.

Acute MI was induced in male C57BL/6 mice (8 weeks old, n = 36). Cyclic RGD, Gd-DOTA, IR783 and rhodamine were functionalized into the fifth generation PAMAM dendrimer to synthesize the aiming RGD probe, and the control probe without cyclic RGD was synthesized in the same way. Molecular magnetic resonance (MR) and near-infrared (NIR) fluorescence optical imaging were performed 24 hours after intravenous contrast agent administration on day 1, 3, 7, 14 and 21 after MI. The expressions of αvβ3 integrin and CD31 were detected by microscope at different time points.

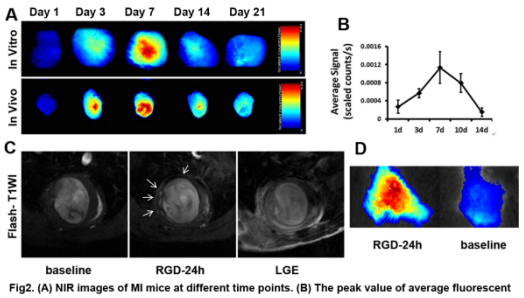

Fig2. (A) NIR images of MI mice at different time points. (B) The peak value of average fluorescent signal intensity was measured at day 7. (C) Cardiac TI-weighted images and (D) NIR images in day 7.

Results:

Injection of RGD probe resulted in a much higher signal intensity that was located mainly in the infarcted myocardium on both MR and NIR fluorescence optical images, indicating more accumulation of RGD probe in MI mice compared with unlabeled control probe. The highest uptake in angiogenic area was achieved on day 7, which was validated by the expression of αvβ3 integrin and CD31 in both pathological staining and western blot analysis. A strong correlation was observed in MR and NIR values ($r^2 = 0.761$, $p < 0.01$). Additionally, the gadolinium content in ischemic myocardium also had linear correlations with both MR ($r^2 = 0.668$, $p < 0.05$) and NIR ($r^2 = 0.615$, $p < 0.01$) values.

Discussion:

To our knowledge, the present study is the first to image cardiac angiogenesis using Gd, IR783 and rhodamine labeled cyclic RGD peptide targeting αvβ3 receptors in ischemic myocardium, which may provide unique information about cardiac angiogenic conditions. RGD probe was found to have a much higher positive contrast enhancement in the infarct region in day 7 after MI and the ex vivo fluorescence imaging showed wonderful colocalization of RGD probes with neovascular endothelium cells, suggesting that RGD probes may be useful to monitor angiogenesis therapy in ischemic myocardium.

Conclusion:

The αvβ3 integrin-targeted multi-modality imaging may be a useful noninvasive method for assessing angiogenesis and monitoring angiogenesis-related therapy in the ischemic myocardium.

References:

1. Oostendorp M, Douma K, Wagenaar A, Slenter JM, et al. Molecular magnetic resonance imaging of myocardial angiogenesis after acute myocardial infarction. Circulation. 2010; 121: 775–783.
2. Makowski MR, Ebersberger U, Nekolla S, Schwaiger M, et al. In vivo molecular imaging of angiogenesis, targeting αvβ3 integrin expression, in a patient after acute myocardial infarction. Eur Heart J. 2008; 29:2201.