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Regeneration of infarcted myocardium by genetically modified stem cells

Nilanjana Maulik[1], Sumanth Channapatna Suresh[1,2], Vaithinathan Selvaraju[1], Mahesh Thirunavukkarasu[1], Aaftab Husain[1], Juan A Sanchez[1,2] and **J Alexander Palesty[1,2]**
[1]University of Connecticut Health Center, USA
[2]Saint Mary's Hospital, USA

Implantation of mesenchymal stem cells (MSC) is becoming an exciting new method for promoting repair of infarcted myocardium. In this study, we use an adenoviral vector encoding Thioredoxin-1 (Ad.Trx1) to genetically modify MSCs prior to implantation. Trx-1 has been established as a redox regulator of growth and transcription-factors as well as a cofactor. It has also been shown to be a potential antioxidant. We wanted to study whether Trx-1 engineered MSCs are capable of improving cardiac function and angiogenesis in a rat myocardial infarction (MI) model. In order to do so, rat MSCs were cultured and divided into three groups: MSC, MSC-LacZ and MSC-Trx1. The cells were assayed for survivability, proliferation and differentiation potential. Additionally, rats were randomized into control Sham (CS), control MI (CMI), MSC-LacZMI (MLZMI) and MSC-Trx1MI (MTRXMI) groups (n=20 per group). MI was induced by permanent occlusion of the LAD immediately after which MSCs preconditioned with either Ad.LacZ or Ad.Trx1 were administered at 4 peri-infarct areas. We observed increased proliferation of MSC-Trx1 cells *in vitro* that maintained pleuripotency to divide into cardiomyocytes, smooth muscle and endothelial cells. In treated rats, capillary density increased in the MTRXMI group when compared to the both the CMI and MLZMI groups. Western blot analysis showed increased expression of VEGF, HO-1 and CXCR4 and decreased expression of TXNIP in the MTRXMI group. Increased intercellular connections, measured by Cx-43 expression, were seen in the treatment group. Echocardiography showed improved ejection fractions and fractional shortening in Trx-1 treated mice when compared to LacZ and control mice. Additionally, picro-sirus red staining showed Trx-1 treated mice had decreased levels of fibrosis in the myocardium. Trx-1 pretreated MSCs provide protection against myocardial injury via induction of VEGF expression, promotion of neovascularization, reducing fibrosis and increasing functional recovery. Ischemic damage cause by decreased blood flow may be reversed in various cardiovascular diseases by treatment with MSCs preconditioned with Trx-1. The long term clinical management of illnesses, such as MI or peripheral vascular disease, may benefit from the angiogenic properties of Trx-1.

Biography

Nilanjana Maulik has completed her PhD in 1990 from University of Calcutta, India. She has joined the Department of Surgery at University of Connecticut, School of Medicine, USA as a Post-doctoral Fellow in 1991. After completing Post-doctoral Fellowship, she joined the Faculty of the University of Connecticut, School of Medicine, Department of Surgery where she currently serves as a Tenured Professor. She is the Director of the Molecular Cardiology and Angiogenesis Laboratory. She serves several NIH study sections and Editorial Board Member of several prestigious journals. She is the Editor-In-Chief of Molecular Biology Report, Springer. She has published more than 190 articles, 35 book chapters and three books (CRC and Springer press) related to cardiovascular disease and epigenetics.

nmaulik@uchc.edu

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