



NORTHWESTERN
UNIVERSITY



FEINBERG CARDIOVASCULAR
RESEARCH INSTITUTE

IL-10 modulates mobilization of bone marrow-endothelial progenitor cells (EPC) and enhances their survival and angiogenic properties in ischemic myocardium

Prasanna Krishnamurthy, DVM, PhD

**Feinberg Cardiovascular Research Institute
Northwestern University
Chicago IL-60611**

Financial Disclosures: NONE

Introduction

Preclinical and clinical studies have shown that stem cells hold great promise for cardiovascular regenerative therapy.

However, several reports on stem cell therapy describes the challenges in overcoming the susceptibility of transplanted stem cells in a hostile ischemic tissue microenvironment like inflammation, hypoxia and free radical damage, thereby compromising full benefits of EPC-mediated vascular repair. (*Bishopric, NH., Circ Res 2008; Crisostomo, PR., et al., Surgery, 2008; Rabelink, T.J., et al., Arterioscler Thromb Vasc Biol, 2004*).

As an example-Patients with high serum levels of TNF, a potent proinflammatory cytokine, were associated with significantly lower endothelial progenitor cell (EPC) counts.

(*Grisar, J., et al., Circulation, 2005*).

Most importantly, EPCs mobilized in response to inflammatory stimulus may be functionally impaired. (*Werner, N. & Nickenig, G. Arterioscler Thromb Vasc Biol, 2006*).

Introduction

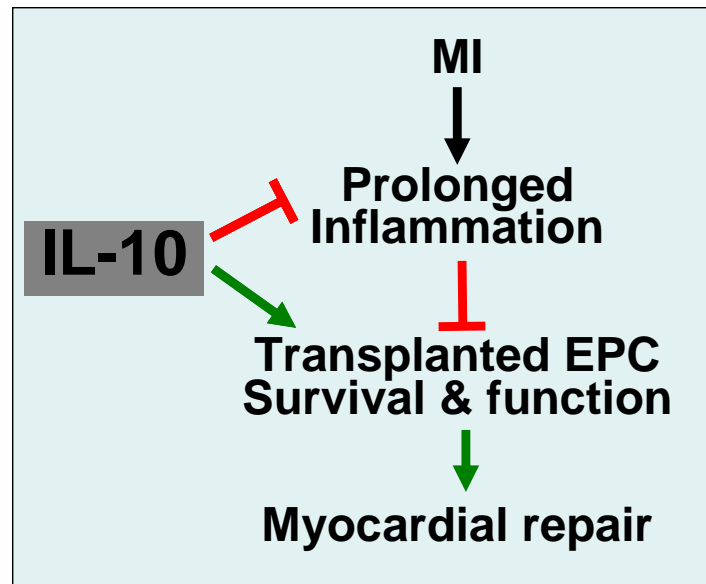
Our laboratory has shown that recombinant IL-10 (an anti-inflammatory cytokine) inhibits inflammation in the myocardium, attenuates left ventricular remodeling and enhanced neovascularization after myocardial infarction via inhibition of mRNA stabilizing protein, HuR and STAT3 activation. (*Krishnamurthy et al., Circ Res 2009; Krishnamurthy et al., FASEB 2010*)

Surprise findings from our lab: Increased mobilization of Sca1+/Flk1+ endothelial progenitor cells (EPC) into the circulation in IL-10-treated mice.

The protective effects of cell therapy with bone marrow mononuclear cells on the infarcted heart may be mediated at least in part through IL-10 production. (*Burchfield, J.S., et al. Circ Res 2008*).

Overarching objective of the Study

Hypothesis: IL-10, an anti-inflammatory cytokine, modulates EPC (Sca1+/Flk1+ cell) biology and enhances EPC survival and function following transplantation in an ischemic tissue micro-environment.

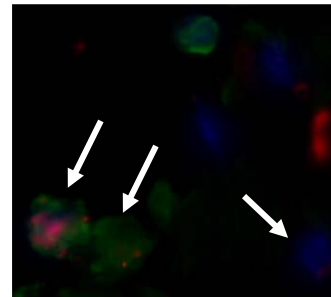


Overview of the study

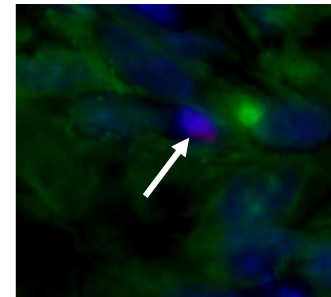
Salient findings

➤ Recombinant IL-10 therapy in mice

- Enhances retention and survival of transplanted EPCs in the ischemic myocardium



EPC+saline



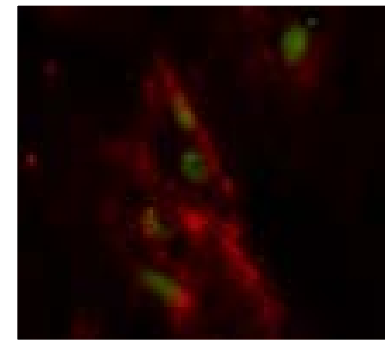
EPC+IL10

GFP-EPC
TUNEL+ cells
DAPI

- Increased EPC-mediated neo-vascularization in the ischemic myocardium



EPC+saline



EPC+IL-10

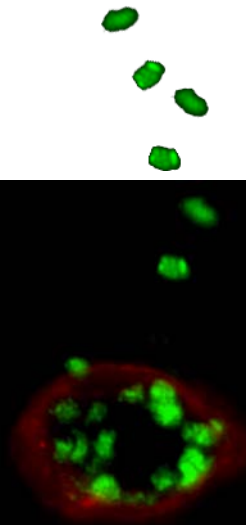
GFP+ EPC
CD31+ cells
(Vascular structures)

Salient findings

- MI-induced EPC (Sca1+/Flk1+ cells) **mobilization into the circulation was impaired in IL-10-deficient-mice** and bone marrow transplantation involving replacement of IL-10-deficient marrow with WT marrow attenuated these effects.
- IL-10 therapy enhanced EPC-mediated **attenuation of MI-induced LV dysfunction and adverse remodeling.**

Implications

Our data suggests a potential therapeutic role for IL-10 in enhancing the regenerative effects of EPC cell-based therapies by modulating EPC biology and tissue microenvironment on one hand and augmenting cell retention and survival on the other.



GFP+ EPC **CD31+ blood vessel**

Acknowledgement

Funding sources

AHA SDG National- 0930219N (PK)

The Davee Foundation (PK)

NIH HL- 091983 (RK)

NIH HL-105597 (RK)

Dr.Raj Kishore and Lab members

Dr.Douglas Losordo and Lab members

Dr.Gangjian Qin and Lab members

Members of FCVRI