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Minireview

Improving regenerating potential of the heart after myocardial infarction: Factor-based approach

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ABSTRACT

The emerging evidence that the heart has the potential to regenerate, albeit not ideally, has stimulated considerable interest in the field of cardiac regenerative medicine. Several lines of research demonstrated that factor-based therapy is feasible and effective, whether it is used independently or as an adjunct to cell therapy. The ultimate goal of the factor-based approach is to improve the regenerating potential of the heart as a means to treat patients with cardiovascular disease. This article reviews recent approaches involving factor-based therapy for cardiac repair and regeneration including some of the advantages of this type of therapy as well as some of the hurdles that must be overcome before this therapeutic approach becomes a standard part of clinical medicine.

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Introduction

The adult mammalian heart was long considered as a post-mitotic organ without the ability to regenerate. Over the past decades, a growing number of experimental studies have provided substantial evidence for the concept of cardiac regeneration, supporting a new paradigm that the heart is capable of repair and regrowth (Laugwitz

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et al. 2005; Beltrami et al. 2003; Table 1). However, evidence also suggests that endogenous cardiac regenerative potential normally functions at a low level and, under normal circumstances, does not play a major role as a response to acute injury (Bergmann et al. 2009). This notion that the ability of the heart to repair and regenerate is endogenously inadequate has facilitated enormous therapeutic efforts to overcome the biological limitation as a strategy for treating patients with ischemic heart disease. Particularly, given that myocardial infarction is the most common cause of mortality and morbidity in developed countries, improving the regenerative response to cardiac injury beyond its limit could be of tremendous therapeutic importance.

Various therapeutic strategies have been developed to improve the regenerating potential of the heart. Much of the research emphasis has

Table 1
Experimental studies supporting the efficacy of factor-based therapy.

Factors	Species	Concentration	Volume	Timing of application	Route	Delivery media	Outcome	Outcome timing	Comments
IGF, HGF Rota et al. (2008)	Rat	HGF, 50–200 ng/mL IGF, 200 ng/mL	10 μL 10 μL	20 days after infarction	Intramyocardial	PBS	↓Remodeling, improved Cardiac function	20 days after treatment	Resident cardiac progenitor cells
IGF, HGF Linke et al. (2005)	Dog	HGF, 150 ng/mL IGF, 200 ng/mL	80 μL×4	4 h after occlusion	Intramyocardial	PBS	Tissue regeneration ↑Cardiac function	28 days after treatment	Resident cardiac progenitor cells
G-CSF Harada et al. (2005)	Mice	10–100 μg/kg/d		Immediately after occlusion	Subcutaneous	Saline	↑Cardiomyocyte survival ↓Remodeling	Up to 4 weeks	Direct effect of G-CSF on cardiomyocyte survival
Thymosin-β4 Bock-Marquette et al. (2004)	Mice	ic, 400 ng ip, 150 μg	ic, 10 μL ip, 300 μL	Immediately after occlusion	Intramyocardial, ip	Collagen PBS	↑Myocyte survival ↑Cardiac function	Up to 4 weeks	ic, ip, and ic + ip comparison
FGF-2, PDGF-BB Lu et al. (2007)	Pig	FGF-2, 5 μg PDGF-BB, 10 μg		Immediately after occlusion	Pallet was attached to infarcted heart	Sucrose aluminum sulfate coated with hydron polymer	↑Myocardial collateral growth	6 and 14 weeks after treatment	Synergistic effects with combined approach
SDF-1α Zhao et al. (2009)	Rat			Immediately after occlusion	Intramyocardial	Mesenchymal stem cells expressing SDF-1α	↑Survival and homing and regeneration of transplanted cells ↑Blood vessel density	21 days after treatment	Overexpression Heterotopic heart transplantation
SDF-1α Abbott et al. (2004)	Mice			Immediately after occlusion	Intramyocardial	Adenoviral gene delivery	↑Bone marrow-derived cells	Up to 7 days after treatment	Injury was required to have the effect
VEGF-2 Kawamoto et al. (2004)	Pig	VEGF-2 800 μg G-CSF, 5 mg/kg/day SCF, 20 mg/kg/day	VEGF, 3 mL	Immediately after occlusion, SCF + G-CSF were treated for 7 days	Intramyocardial (VEGF-2) + subcutaneous (SCF + G-CSF)	Plasmid human VEGF-2 in PBS	↑Incorporation of bone marrow-derived cells into neovasculature, capillary density, and cardiac function	4 weeks after gene therapy	VEGF-2 gene therapy combined with SCF + G-CSF treatment Rat was also tested
IGF-1 Davis et al. (2006)	Rat	10 ng/ml	80 μL	Immediately after occlusion	Intramyocardial	Biotinylated peptide nanofibers	↑Systolic function	Up to 28 days after treatment	Use of biotinylated peptide nanofibers
SDF-1 Pasha et al. (2008)	Rat	MSC incubated in SDF-1 medium (0.05 μg/mL)	MSC in 20 μL	Immediately after occlusion	Intramyocardial		↑MSC survival and engraftment ↑Vascular density and myocardial function	4 weeks after treatment	MSC preconditioning with SDF-1
SDF-1 Segers et al. (2007)	Rat	30 nmol/L (1% in 295 mmol/L sucrose solution)	80 μL	Immediately after occlusion	Intramyocardial	Nanopeptide	↑Stem cell recruitment ↑Cardiac function	4 weeks after treatment	Engineered to protease resistant
FGF-2 Wang et al. (2009a,b)	Pig	~26 μg		~6 h after occlusion	Intramyocardial	PLGA scaffold	↑Neovascularization ↑Blood perfusion and cardiac function	Up to 6 weeks after treatment	Use of degradable PLGA
G-CSF + CSF Sesti et al. (2005)	Rat	G-CSF, 100 μg/kg CSF, 25 μg/kg Daily for 4 days		2 h after occlusion	Subcutaneously	Sterile water	↓Systolic and diastolic volumes under dobutamine stress	8 weeks after treatment	No histological evidence of cardiac regeneration
PDGF-AB Edelberg et al. (2002)	Rat	100 ng	50 μL	Immediately after occlusion	Intramyocardial	PBS	↑Angiogenesis ↓Myocardial infarct	2 weeks after treatment	Effects of aging use of parathyroid hormone
PTH Zaruba et al. (2008)	Mice	80 μg/kg/day Up to 14 days		Immediately after occlusion	Subcutaneously		↑Function, remodeling, and neovascularization ↑$CD45^+$ and 34^+ cells	6 and 30 days after treatment	Use of biologically active fragment Use of parathyroid hormone

PBS, phosphate-buffered saline; SCF, stem cell factor; G-CSF, granulocyte-colony stimulating factor; LPGA, poly D, L-lactic-coglycolic acid; MSC, mesenchymal stem cells; PTH, parathyroid hormone; ic, intramyocardial; ip, intraperitoneal.