Paracrine Mechanisms in Adult Stem Cell Signaling and Therapy

Massimiliano G necchi, Zhiping Zhang, Aiguo Ni, Victor J. Dzau

Circulation Research 2008 Nov 21;103(11):1204-19
After AMI all of the cardiac tissue served by the infarction related artery undergoes necrosis or apoptosis

The endogenous regenerative capacity of the heart is not able to replenish a significant loss of tissue such as after AMI\(^1\)

Therapeutic myocardial regeneration might be achieved by using adult stem cells (ASC)\(^2\)

2 Beltrami et al, Cell 2003;114:763-776
Stem Cell Therapy

STEM CELL THERAPY

(Trans)differentiation into EC/VSMC
Cell fusion with EC/VSMC
VASCULOGENESIS

(Trans)differentiation into CMC
Cell fusion with CMC
CARDIAC REGENERATION

PARACRINE EFFECTS

NEOVASCULARIZATION

CARDIOMYOGENESIS

CARDIAC REPAIR

Gnecchi et al, Circ. Res. 2008: 103:1204-1219
Cardiac stem cells (CSC) – when injected into infarcted murine hearts – are able to differentiate into endothelial cells (EC) and vascular smooth muscle cells (VSMC)

1 Leri et al, Physiol Rev. 2005;85:1373-1416
Bone marrow derived stem cells injected into mouse hearts after AMI were able to engraft, transdifferentiate into cardiac cells and regenerate 60% of the infarcted area with newly formed cardiomyocytes.
It has been shown that the number of newly generated cardiomyocytes is too low to explain significant functional improvement\(^1\)

The functional benefits might be related to secretion of soluble factors, acting in a paracrine fashion\(^1\)

---

1 Gnegchi et al, Circ. Res. 2008: 103:1204-1219
Paracrine Effects

Adult Stem Cell

Stimuli

Akt

Autocrine effects

Release of soluble factors

PARACRINE EFFECTS

Myocardial protection

Cardiac metabolism

Contractility

Cardiac regeneration

Neovascularization

Cardiac remodeling

- Cardiomyocytes
- Endothelial cells
- Smooth muscle cells
- Fibroblasts
- Cardiac stem cells

Gnczchi et al, Circ. Res. 2008: 103:1204-1219
Conditioned medium was collected from MSCs after 12 h of exposure either to normoxia or hypoxia.

Synthesis:
- GFP-MSC
- MSC overexpressing Akt1

Graph:
- Baseline
- CTR-M
- GFP N-M
- Akt N-M
- GFP H-M
- Akt H-M

* * *

Gnecchi et al, Circ. Res. 2008;103:1204-1219
Myocardial Protection

G necchi et al, Circ. Res. 2008: 103:1204-1219
Myocardial Protection

Evaluation of some candidate genes encoding for molecules known to be released by MSC by **quantitative RT-PCR**

↓

Significant upregulation of (in Akt-MSC):

**VEGF, HGF, IGF-1, Thymosin beta-4**
Paracrine Effects

Adult Stem Cell

Stimuli

Akt

Autocrine effects

Release of soluble factors

PARACRINE EFFECTS

Myocardial protection

Cardiac metabolism

Contractility

Cardiac regeneration

Neovascularization

Cardiac remodeling

- Cardiomyocytes
- Endothelial cells
- Smooth muscle cells
- Fibroblasts
- Cardiac stem cells

Gnecchi et al, Circ. Res. 2008: 103:1204-1219
ASCs, when injected into the injured myocardium, are able to:

- Proliferate and transdifferentiate into cardiomyocytes\(^1\)
- Fuse with native cardiomyocytes and regenerate the lost myocardium\(^1\)
- Activate resident cardiac stem cells and stimulate cardiomyocytic replication via \textit{paracrine action} \(^1\)
Cardiac Regeneration

Intramyocardial administration of VEGF and IGF-1 at the infarct border zone induces CSC migration, proliferation and differentiation\(^1\)

Conclusion

- Transplantation of stem cells for their paracrine effects still represents a reasonable strategy – multiple factors might be functioning together.

- If specific paracrine cell-derived factors will be identified protein based therapy might be more easily translated into clinical benefits than cell based therapy.
Future in Stem Cell Therapy for the Heart

- Choice of cell type to administer: the cardiomyogenic potentiality of each ASC is not explored yet

- Extensive loss of the cells once transplanted in combination with the extreme rareness of specific stem cell populations

- Idea of improving cell survival by overexpressing protective genes: e.g. combination of genetic modification and preconditioning with different cytokines

- Cell administration immediately after infarction or after the inflammatory process has subsided?
Future in Stem Cell Therapy for the Heart

- Age of the patient and presence of disease status adversely influences characteristics of ASCs – using allogenic cells from young and healthy donors? Cell rejection? MSC display an immunoprivileged phenotype!

- Introduction of standard operating procedures and nomenclature among different laboratories will be mandatory to optimize our understanding of stem cell biology

1 Dzau et al, Hypertension. 2005;46:7–18
Thank you for your attention!