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Paracrine Mechanisms in Adult Stem Cell Signaling and Therapy

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Introduction(1)

- 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]

1 Beltrami et al, N Engl J Med 2001;344:1750-1757
2 Beltrami et al, Cell 2003;114:763-776

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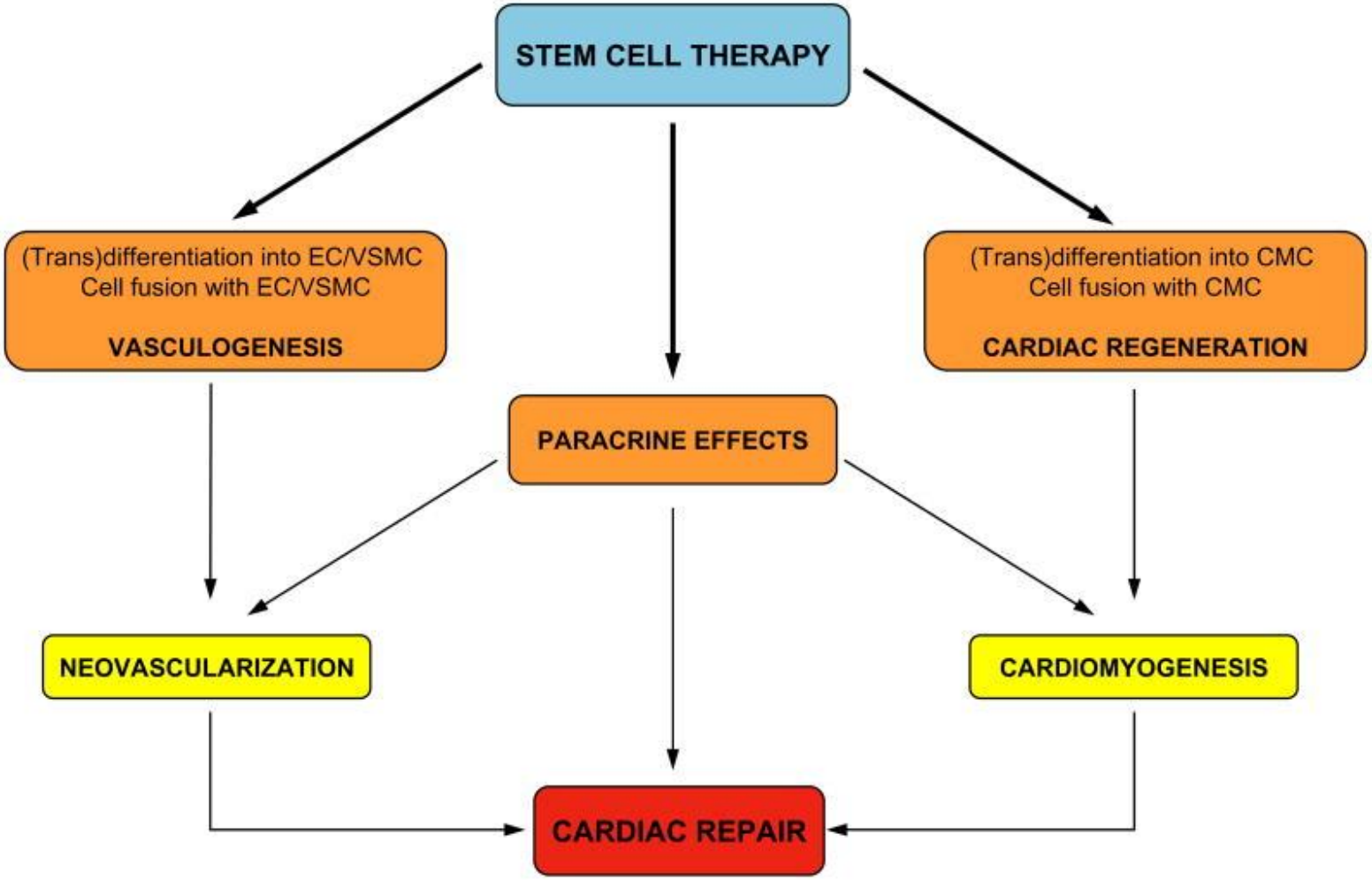
Stem Cell Therapy



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

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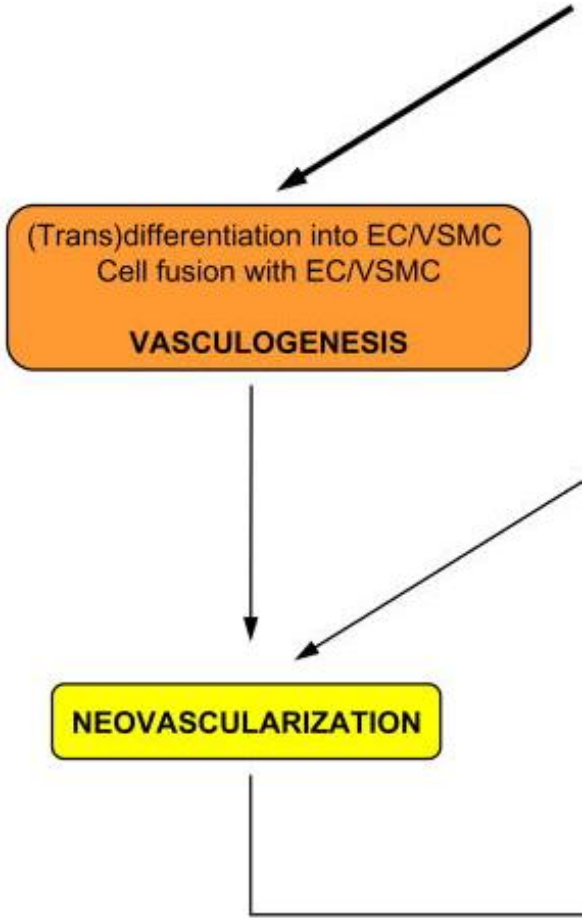
Stem Cell Therapy



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

Messina et al, Circ Res 2004;95:911-921

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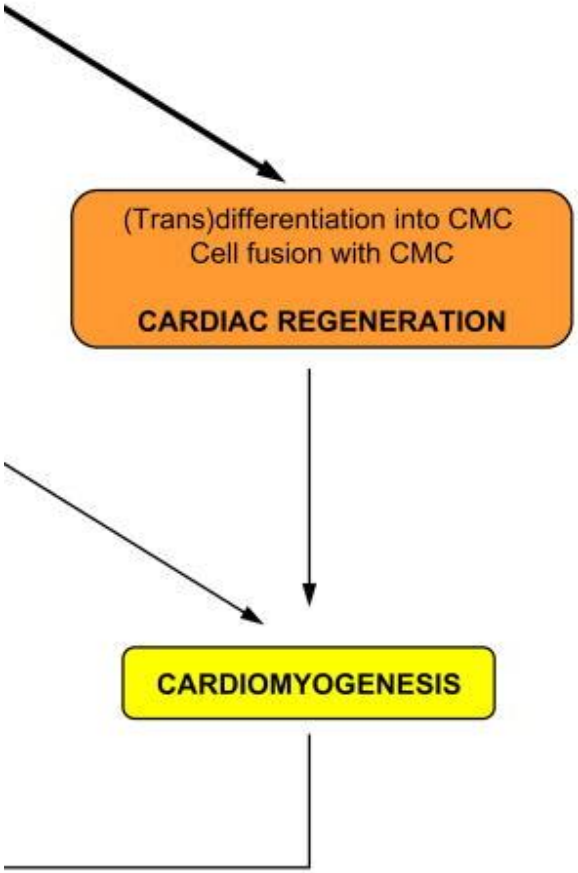
Stem Cell Therapy

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



1 Orlic et al, Nature 2001;410:701-705

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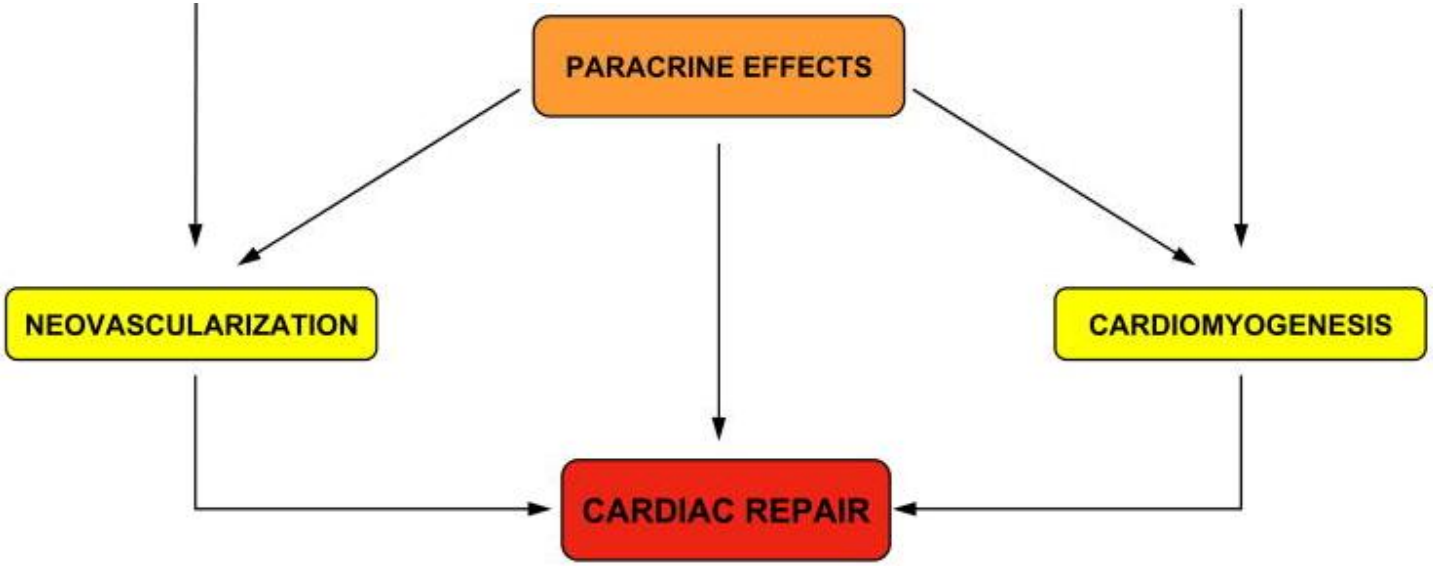
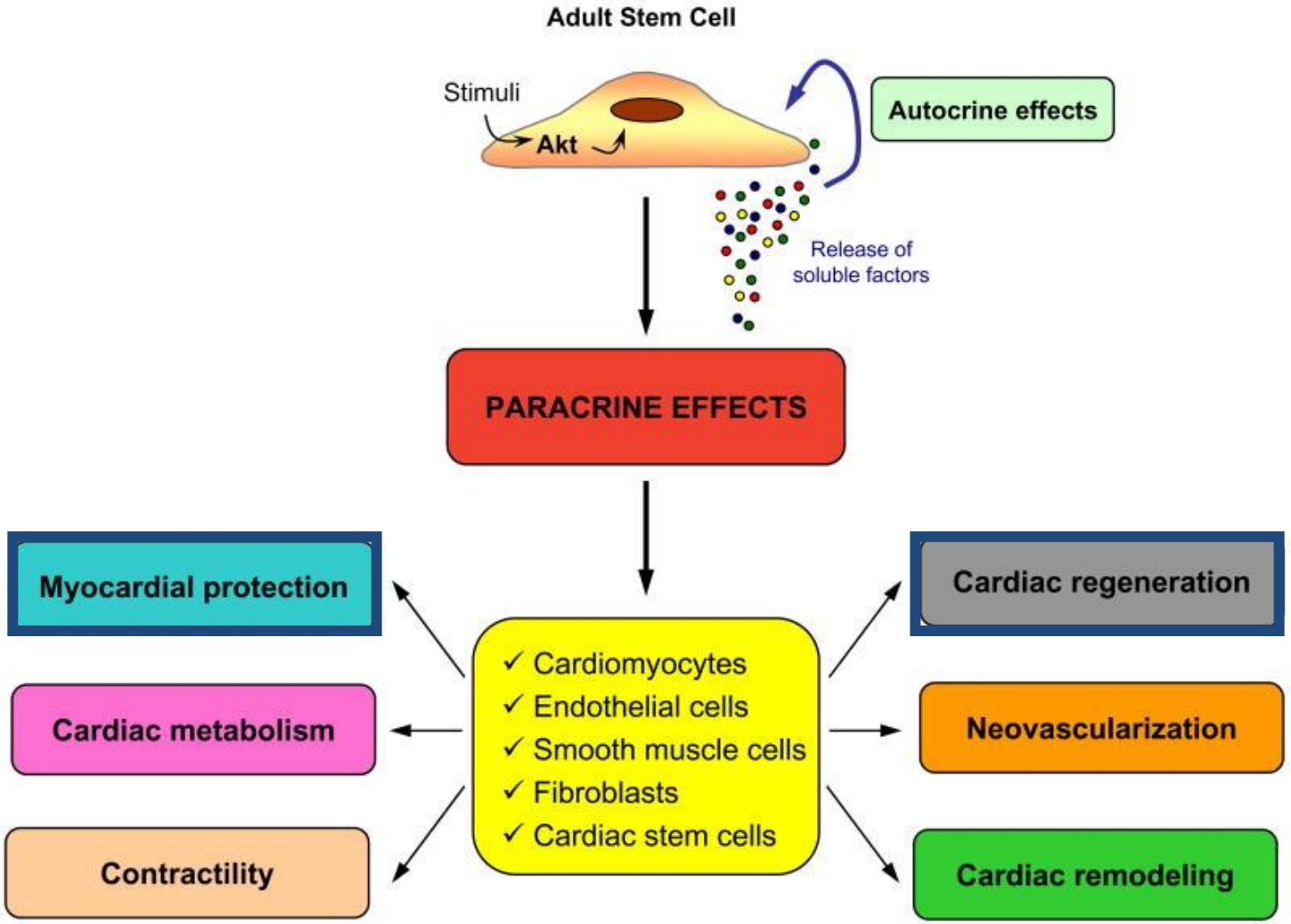
Stem Cell Therapy

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

Paracrine Effects



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

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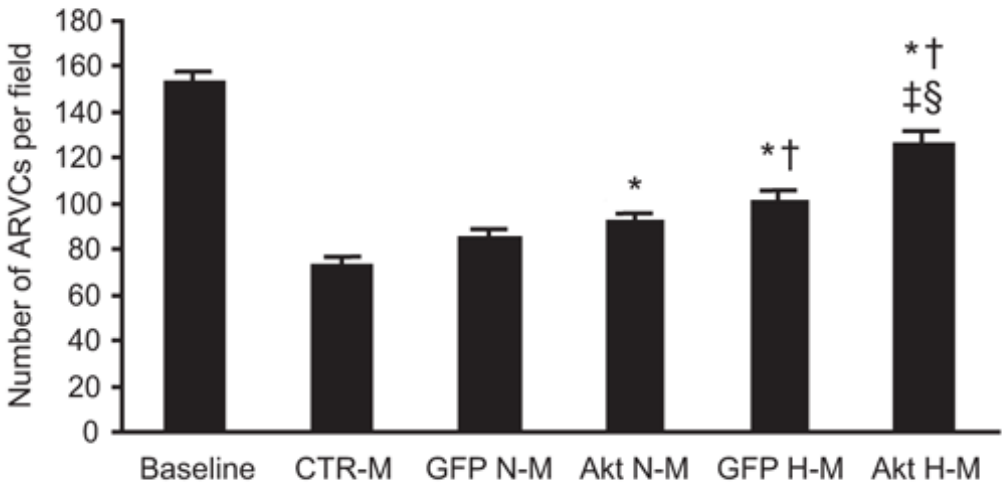
Myocardial Protection

Conditioned medium was collected from MSCs after 12 h of exposure either to normoxia or hypoxia

↓ ↓

GFP-MSC MSC overexpressing Akt1

↓ ↓



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

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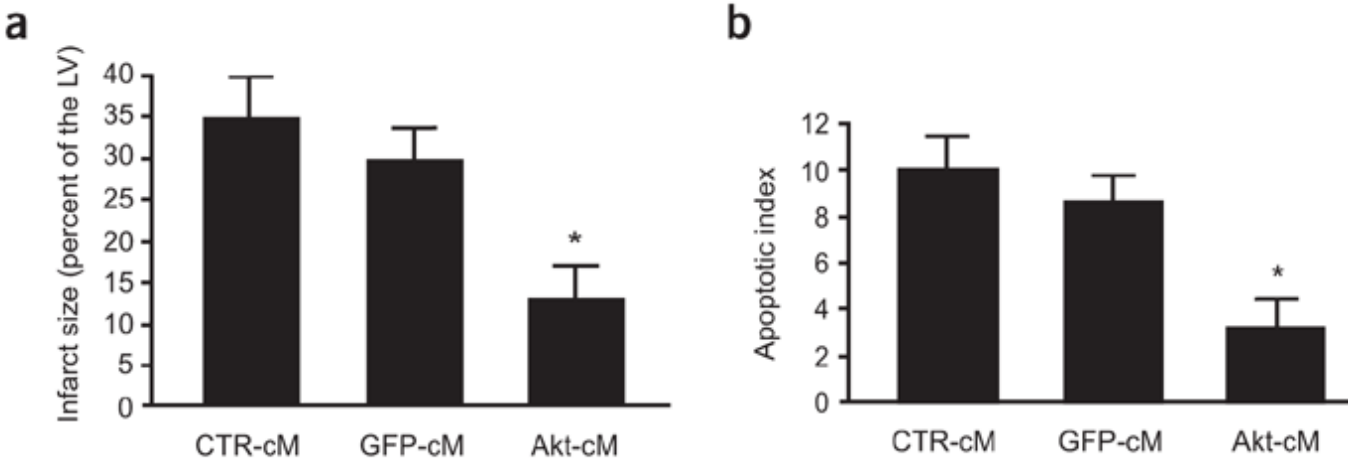
Myocardial Protection



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

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Myocardial Protection

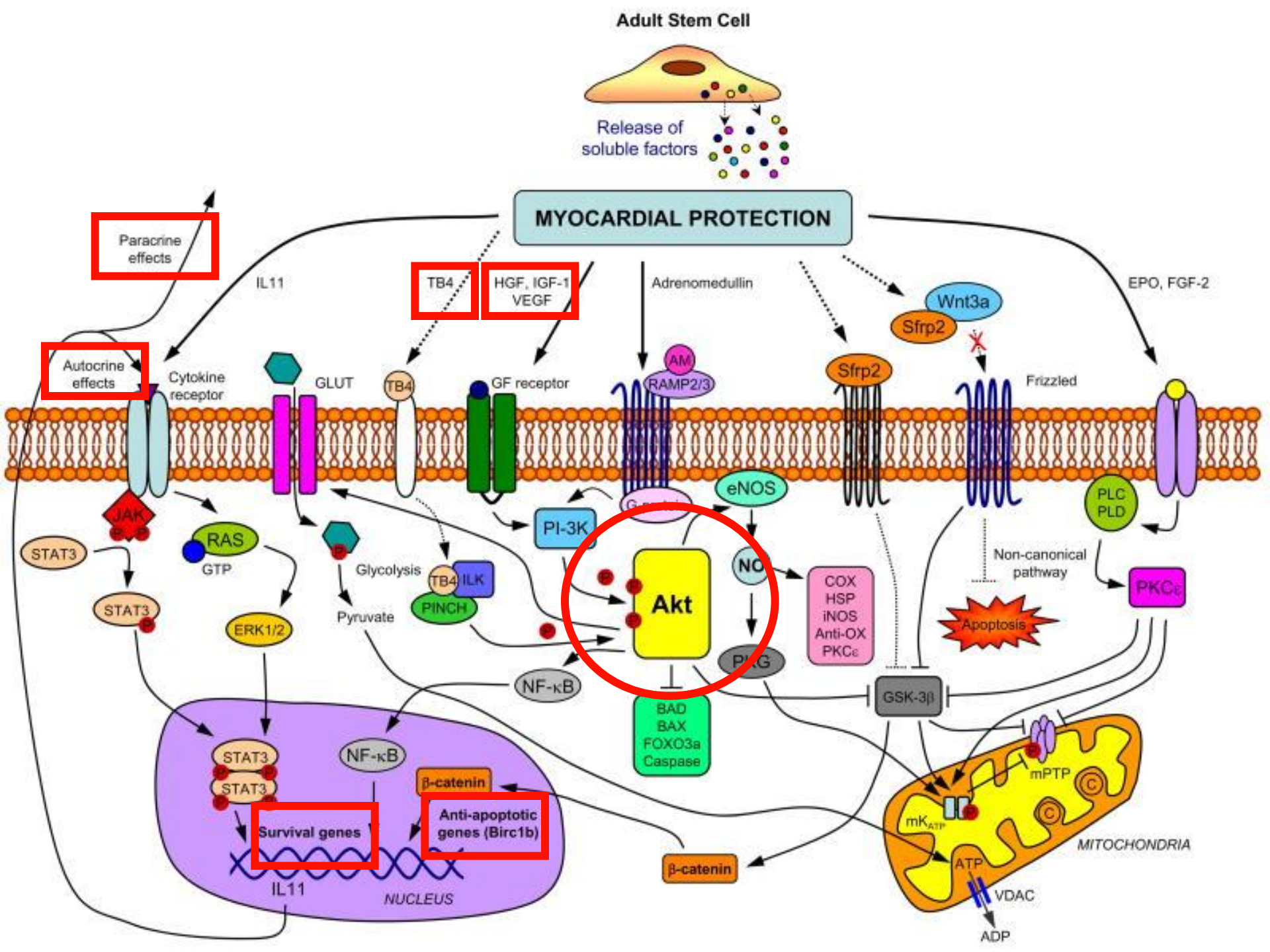
Evaluation of some cadidate genes encoding for molecules known to be released by MSC by **quanitative RT-PCR**

↓

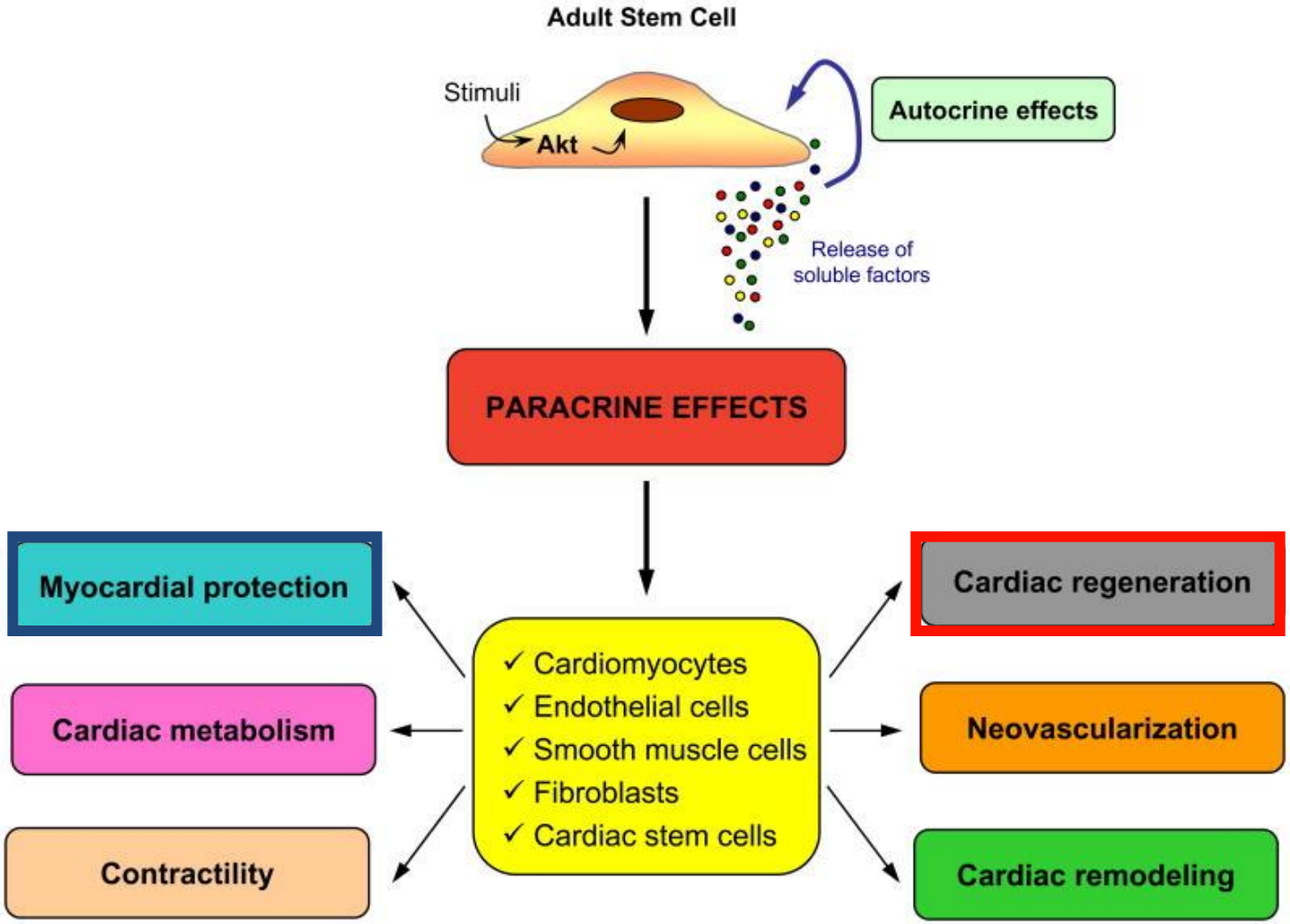
Significant upregulation of (in Akt-MSC):

VEGF, HGF, IGF-1, Thymosin beta-4

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


Adult Stem Cell
Release of soluble factors
MYOCARDIAL PROTECTION
Paracrine effects
Autocrine effects
IL11
TB4
HGF, IGF-1 VEGF
Adrenomedullin
Wnt3a
Sfrp2
EPO, FGF-2
Cytokine receptor
GLUT
TB4
GF receptor
AM
RAMP2/3
Sfrp2
Frizzled
JAK
STAT3
RAS
GTP
PI-3K
eNOS
PLC PLD
Glycolysis
TB4
ILK
PINCH
Akt
NO
COX HSP iNOS Anti-OX PKCε
Non-canonical pathway
PKCε
Apoptosis
ERK1/2
Pyruvate
NF-κB
PKG
GSK-3β
BAD BAX FOXO3a Caspase
STAT3
STAT3
NF-κB
β-catenin
Survival genes
Anti-apoptotic genes (Birc1b)
IL11
NUCLEUS
β-catenin
mPTP
mK$_{ATP}$
MITOCHONDRIA
ATP
VDAC
ADP

Paracrine Effects



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

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Cardiac Regeneration

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 **paracrine action**

1 Dimmeler et al, J Clin Invest 2005;115:572-583

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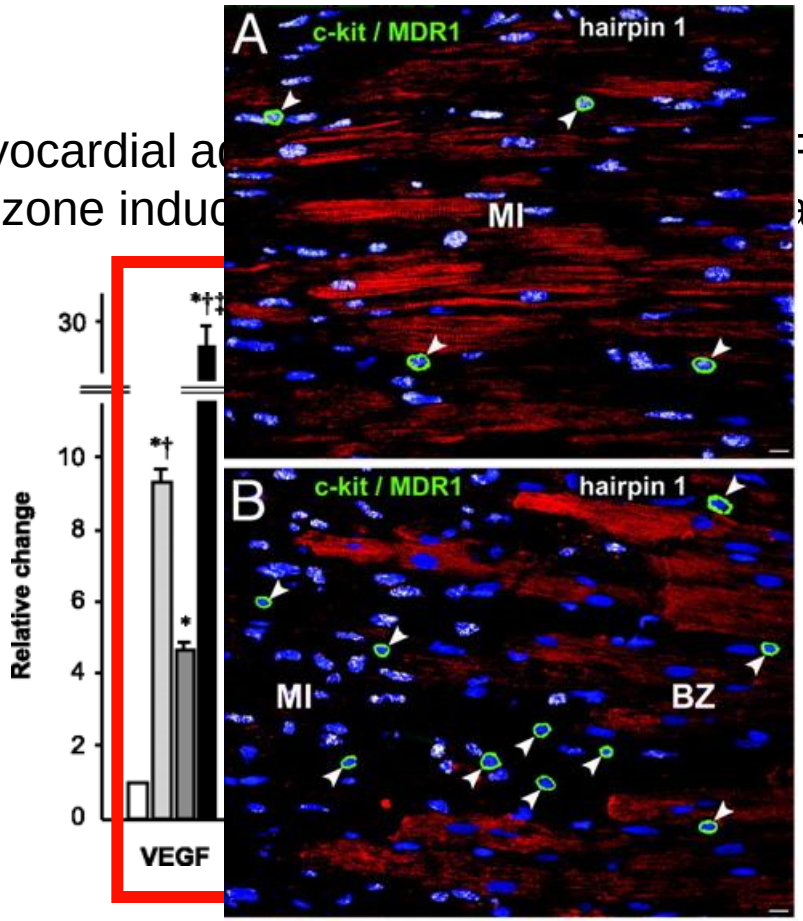
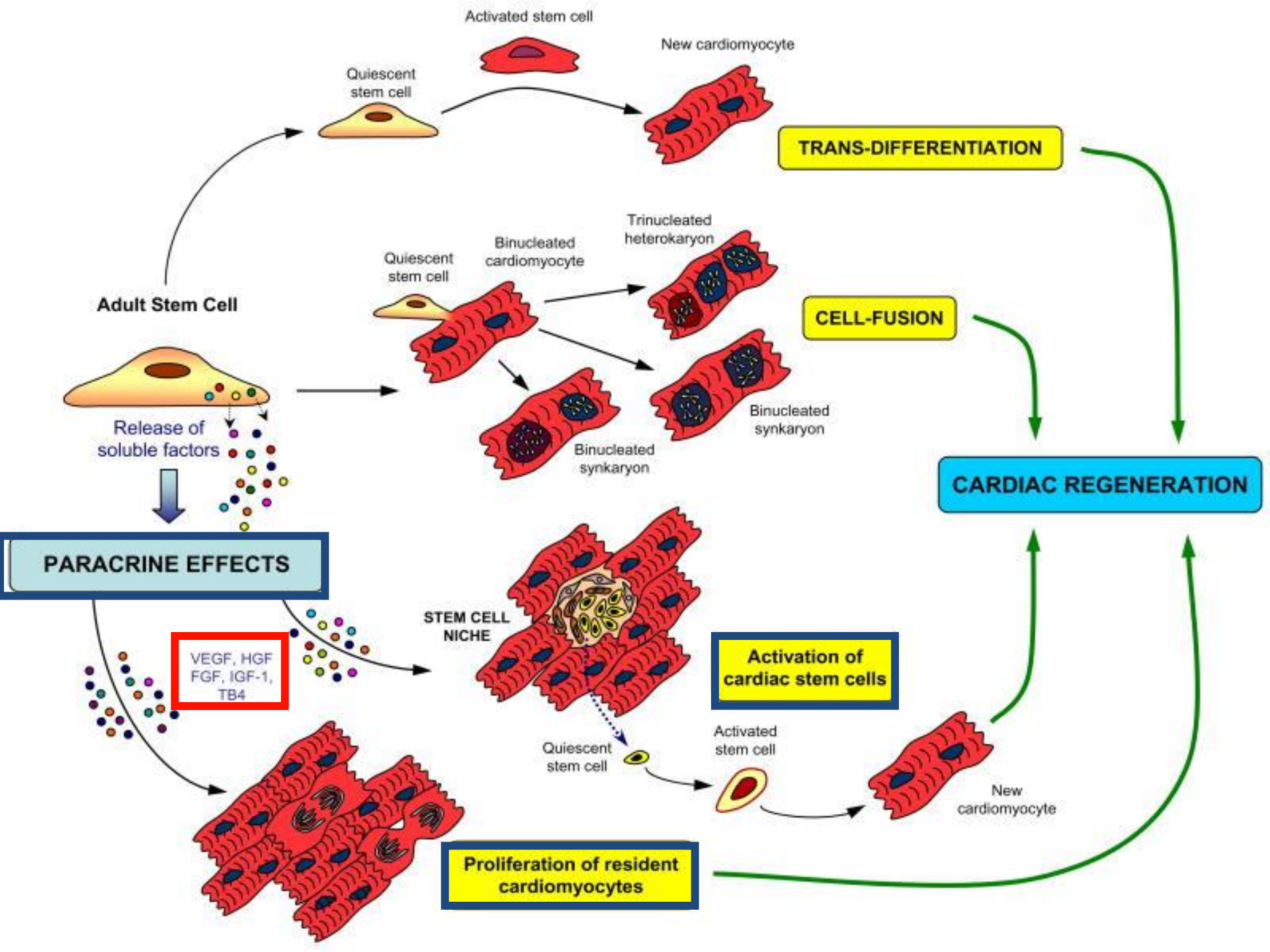
Cardiac Regeneration

Intramyocardial a[illegible] and IGF-1 at the infarct border zone induc[illegible]ation and differentiation[1]



1 Linke et al, Proc Natl Acad Sci U S A. 2005;102:8966–8971

2 Gnecchi et al, FASEB J. 2006;20:661– 669.


Activated stem cell
New cardiomyocyte
Quiescent stem cell
TRANS-DIFFERENTIATION
Trinucleated heterokaryon
Binucleated cardiomyocyte
Quiescent stem cell
Adult Stem Cell
CELL-FUSION
Binucleated synkaryon
Release of soluble factors
Binucleated synkaryon
CARDIAC REGENERATION
PARACRINE EFFECTS
STEM CELL NICHE
VEGF, HGF FGF, IGF-1, TB4
Activation of cardiac stem cells
Activated stem cell
Quiescent stem cell
New cardiomyocyte
Proliferation of resident cardiomyocytes

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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

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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?

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Future in Stem Cell Therapy for the Heart

- Age of the patient and presence of desease status adversely influences characteristics of ASCs – using allogenic cells from young and healthy donors? Cell rejection? MSC display an immunoprivileged phenotype![1]

- Introduction of standart 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

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Thank you for your attention!