2010.04.17. 대한심장학회 춘계통합학술대회, 부산 벡스코

Molecular mechanisms of Cardiac Fibrosis

동아의대 김 영대

Cardiac Fibrosis

- Accumulation of extracellular matrix (ECM) in the myocardium
- Integral component of most cardiac pathological conditions.

Extracellular Matrix (ECM)

Structural proteins:

- Collagen I, III: fibrillar collagen
- Collagen IV, V: basement membrane
- Collagen V, VI: co-localized with collagen I, III

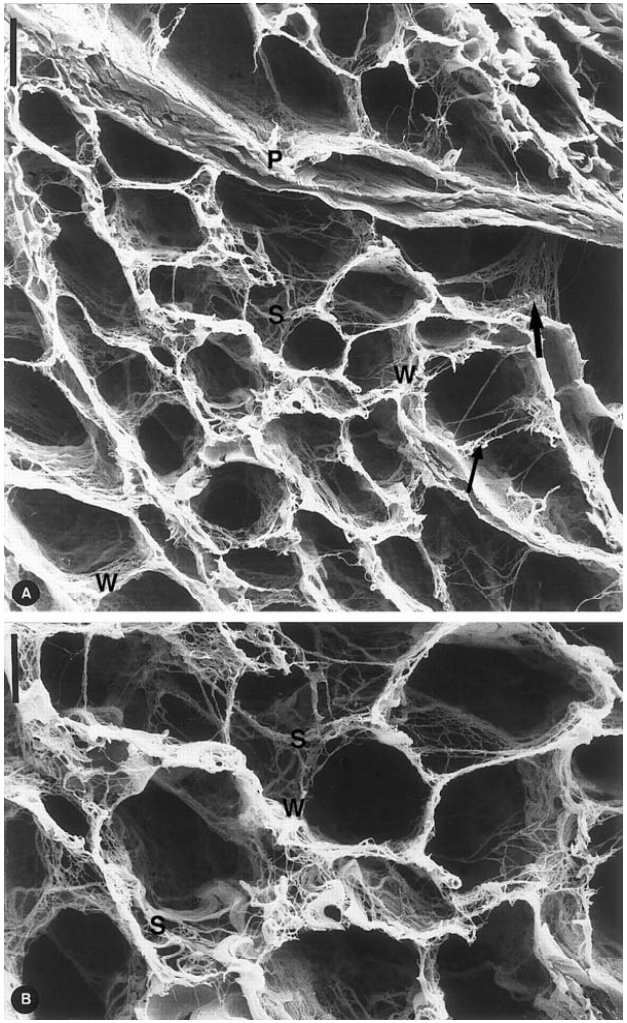
Elastic fibers:

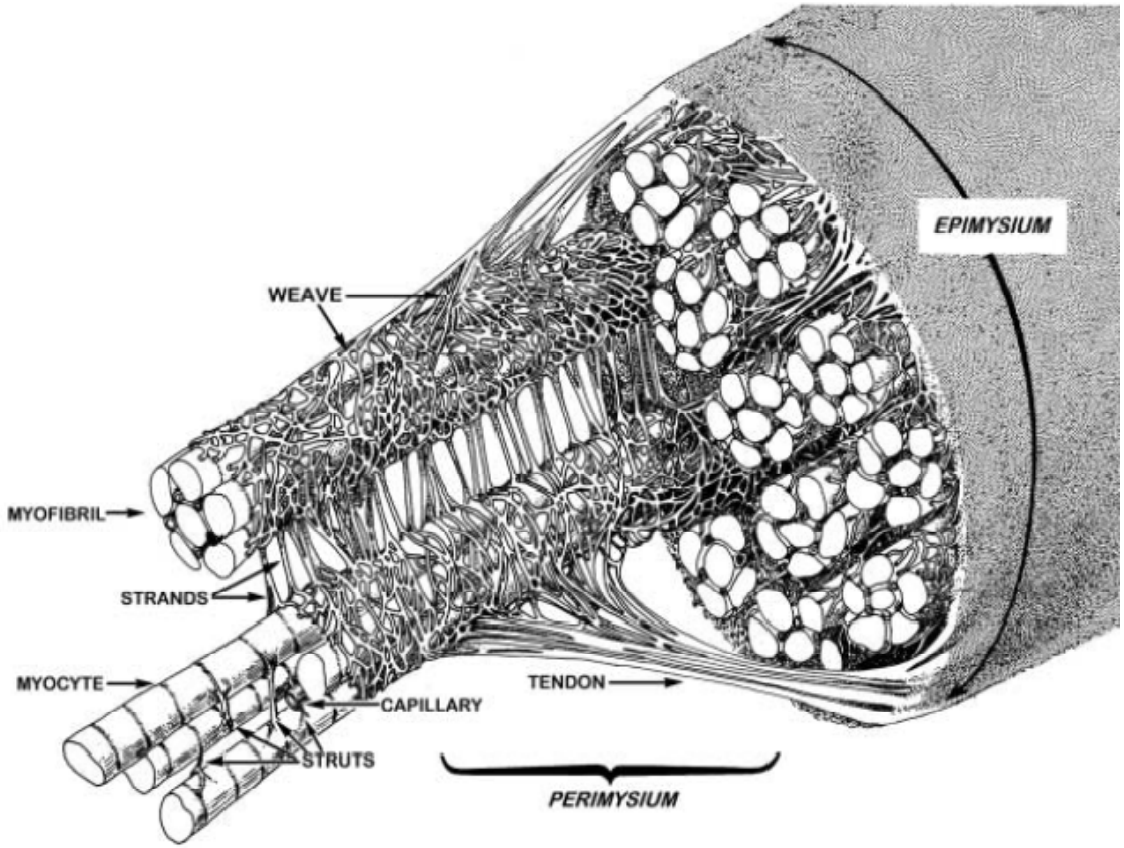
- Elastin, fibrillin

Adhesive proteins:

- Fibronectin
- Laminin
- Integrins

Fibrillar collagen network of the heart



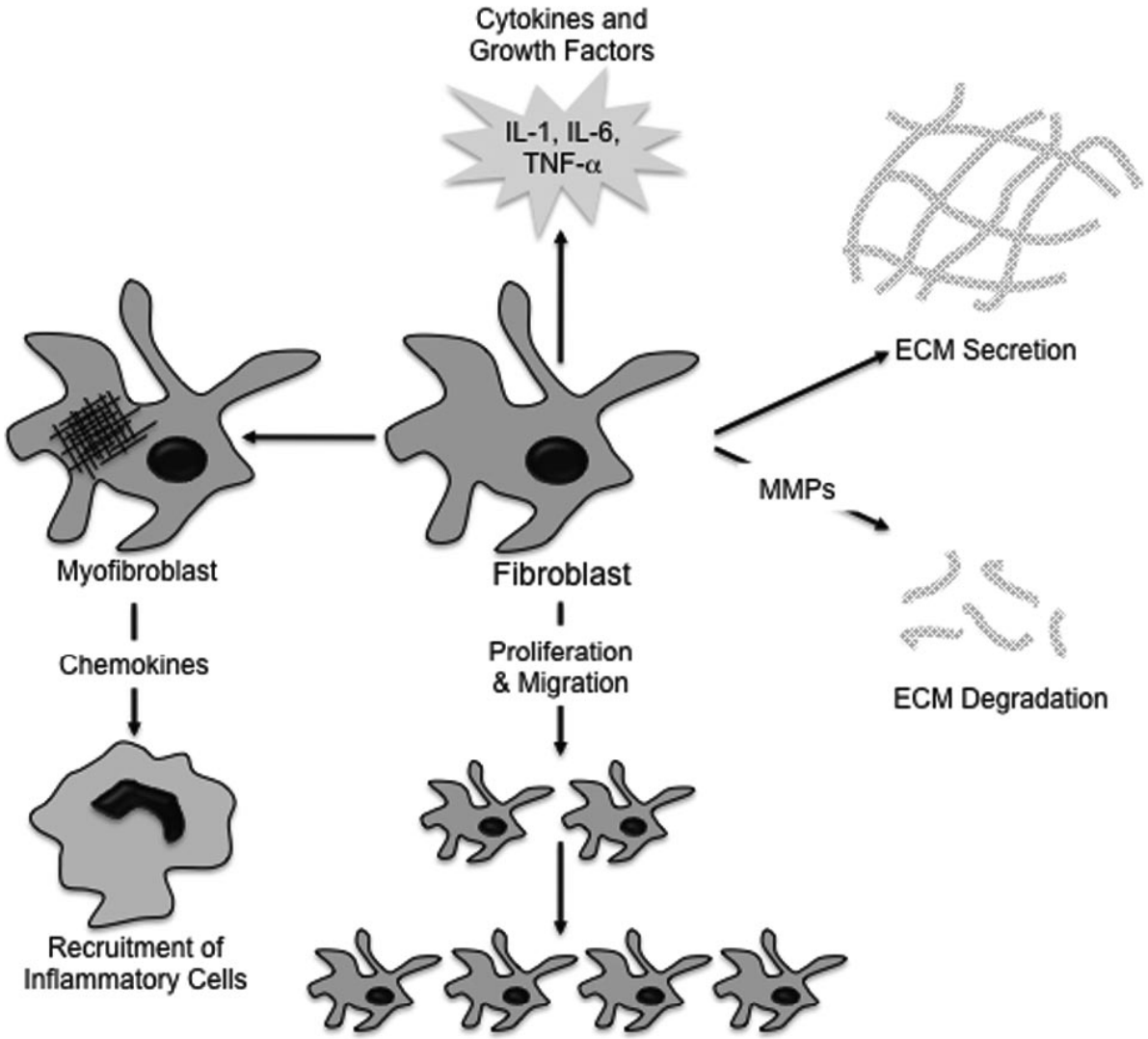


Rossi MA, et al. Circulation 1998;97:934-5.

Cardiac fibroblasts: Key regulators of ECM modulation

Cardiac fibroblast

Mast cell



Pharmacology & Therapeutics 123 (2009) 255–278

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate Editor: Barbara McDermott

Cardiac fibroblasts: At the heart of myocardial remodeling

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ARTICLE INFO

Keywords:
Heart
Fibroblast
Myofibroblast
Remodeling
Therapeutic agents

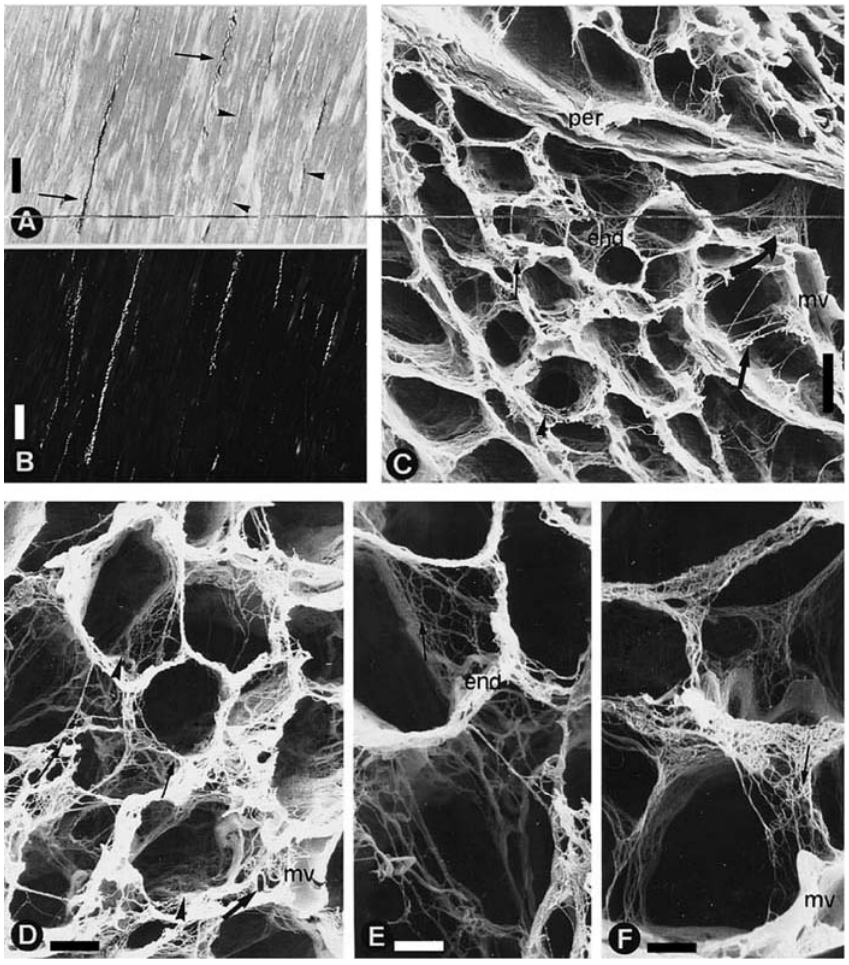
ABSTRACT

Cardiac fibroblasts are the most prevalent cell type in the heart and play a key role in regulating normal myocardial function and in the adverse myocardial remodeling that occurs with hypertension, myocardial infarction and heart failure. Many of the functional effects of cardiac fibroblasts are mediated through differentiation to a myofibroblast phenotype that expresses contractile proteins and exhibits increased migratory, proliferative and secretory properties. Cardiac myofibroblasts respond to proinflammatory cytokines (e.g. TNFα, IL-1, IL-6, TGF-β), vasoactive peptides (e.g. angiotensin II, endothelin-1, natriuretic peptides) and hormones (e.g. noradrenaline), the levels of which are increased in the remodeling heart. Their function is also modulated by mechanical stretch and changes in oxygen availability (e.g. ischaemia–

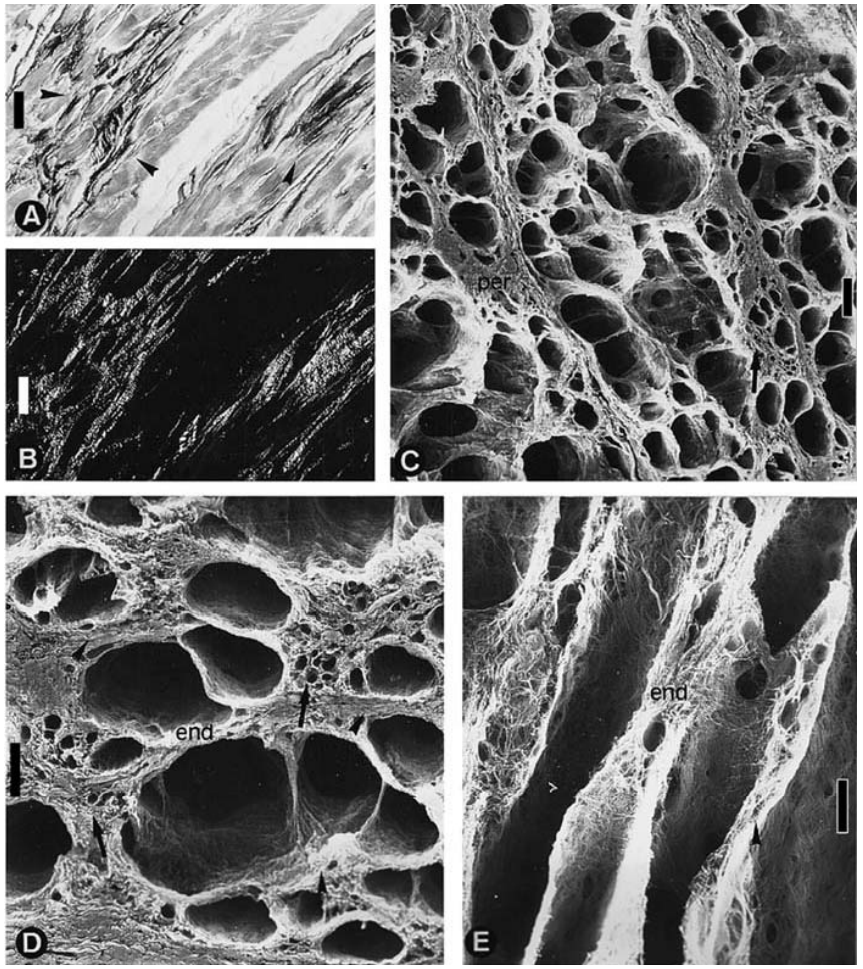
Souders CA, et al. Circ Res 2009;105:1164-76. Porter KE, et al. Pharmacol Therapeut 2009;123:255-78.

Connective tissue matrix in LV hypertrophy

due to hypertension in human



Control heart (250-350 g)



Hypertrophied heart (701-900 g)

J Hypertens, Volume 16(7).July 1998.1031–1041

Cardiac Fibrosis contributes to..

- Increased stiffness, diastolic dysfunction
- Reduced coronary reservoir
- Atrial and ventricular arrhythmia, sudden death
- Decreased contractility
- Chamber dilatation and systolic failure

Contents

Molecular Mechanisms of Cardiac Fibrosis

- Mechanical stress
- Neurohormonal

    Angiotensin II/TGF-beta /Endothelin 1

    Aldosterone (Mineralocorticoid receptor)

Origin of Cardiac Fibroblast

Contents

Molecular Mechanisms of Cardiac Fibrosis

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- Neurohormonal
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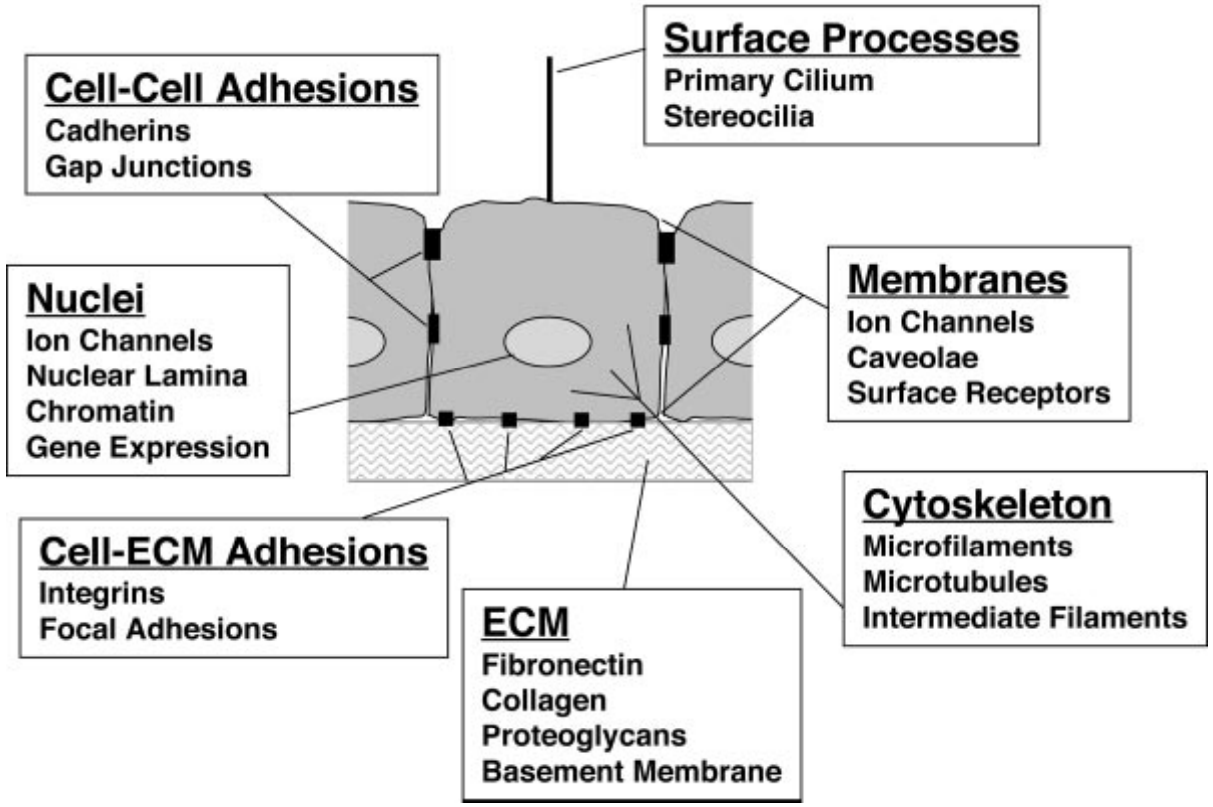
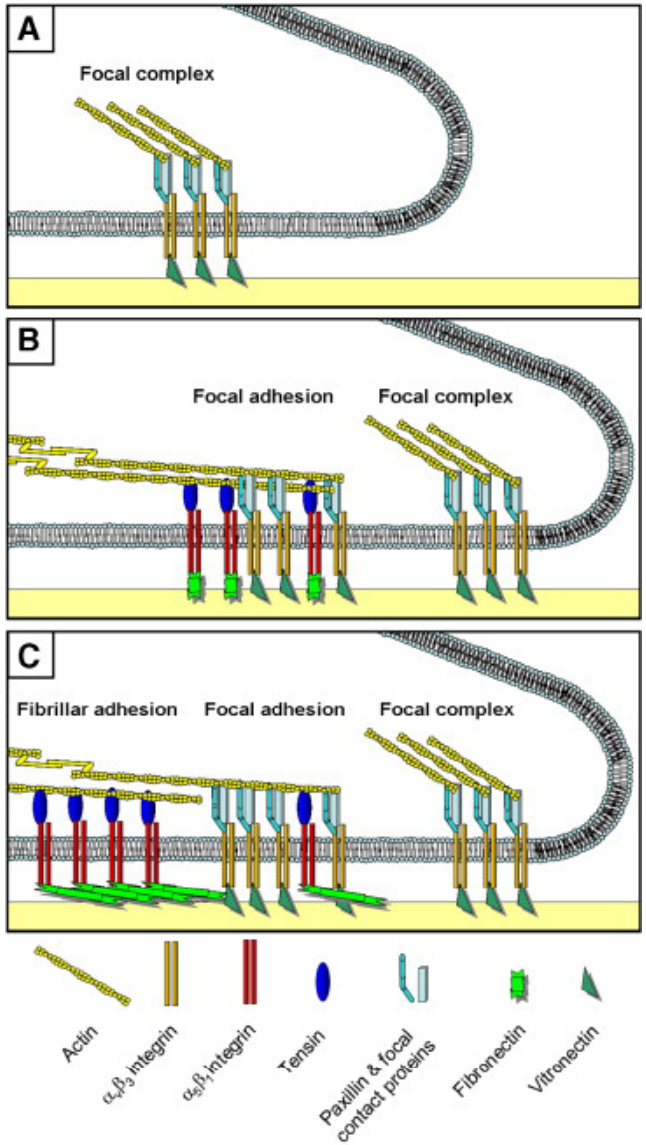
  - Aldosterone (Mineralocorticoid receptor)

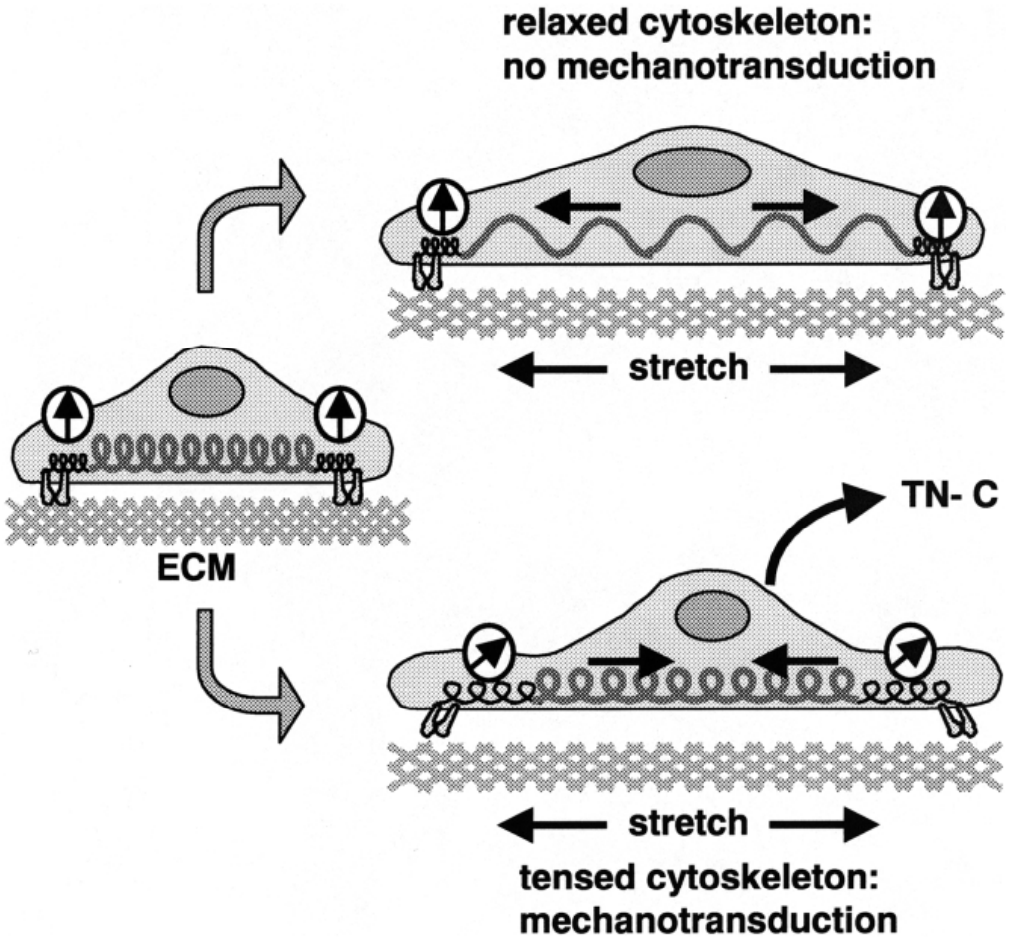
Mediators of Mechanotransduction



Inger DE. FASEB J 2006;20:811-827.

How do fibroblasts translate mechanical signals into change in ECM production?



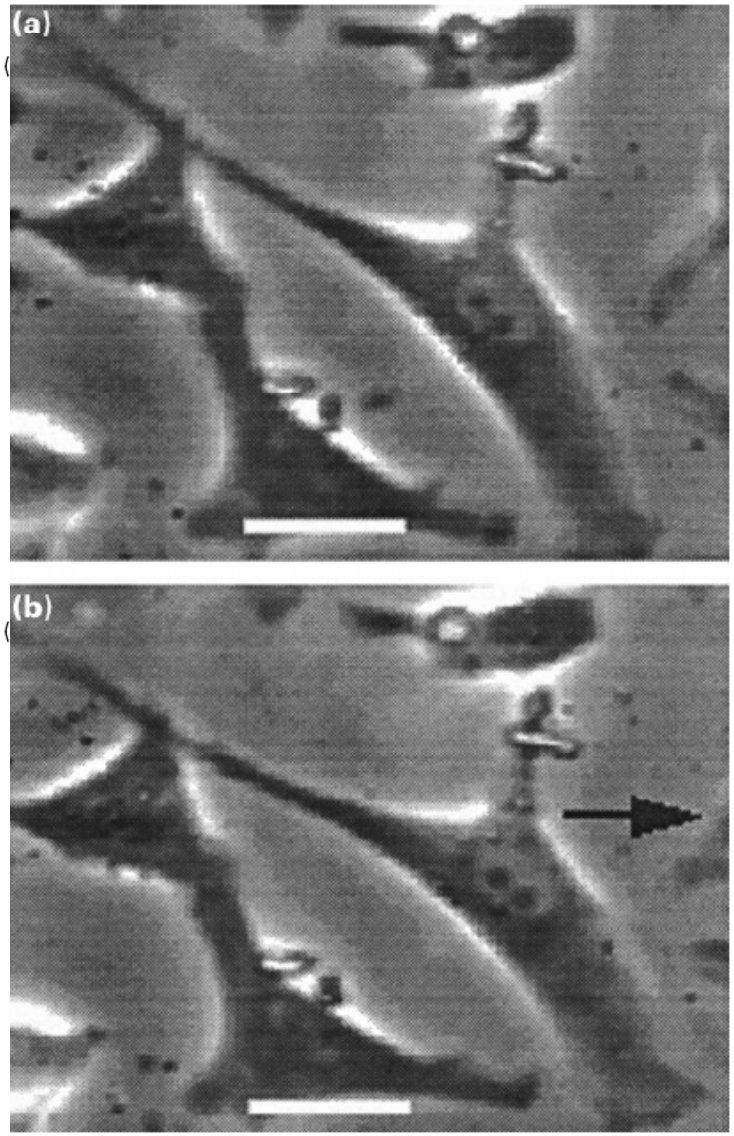


TN-C : Tenascin-C

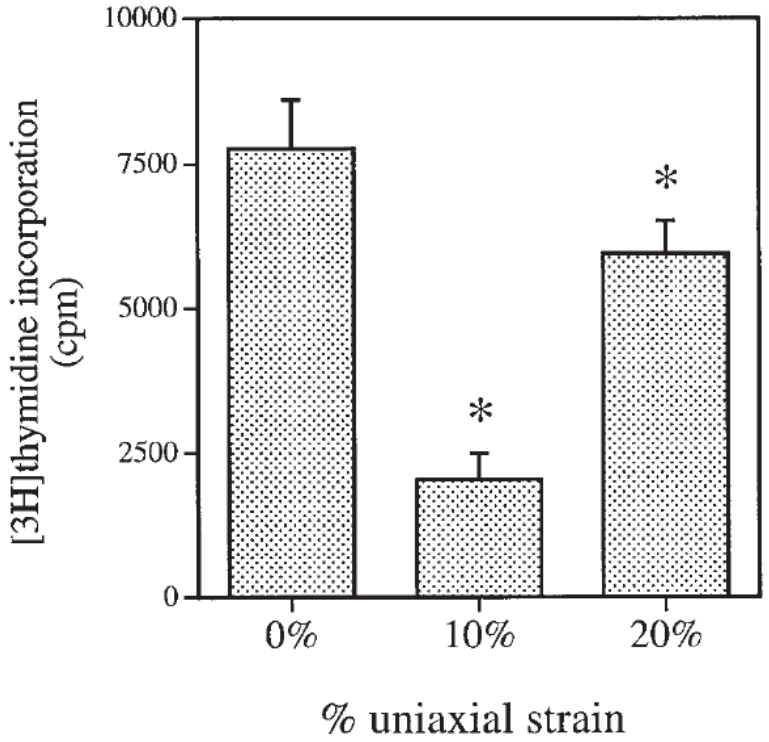
Chiquet M, et al. Biochim Biophysic Acta 2009;1793:911-20

Chiquet M et al. Matrix Biol 2003;22:73-80.

Responses of Cardiac Fibroblasts to Mechanical Strain

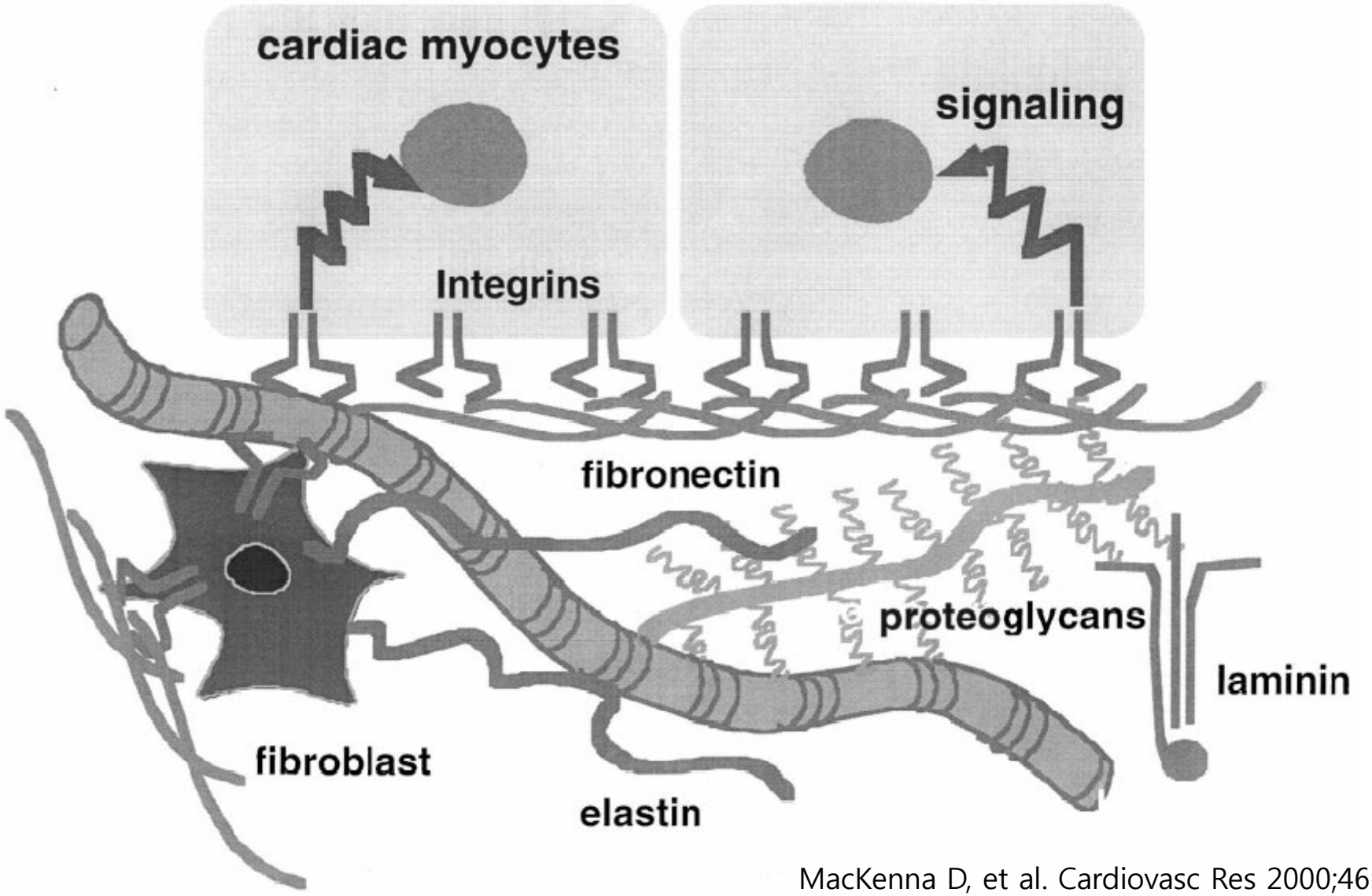


Detection of TGFβ activity

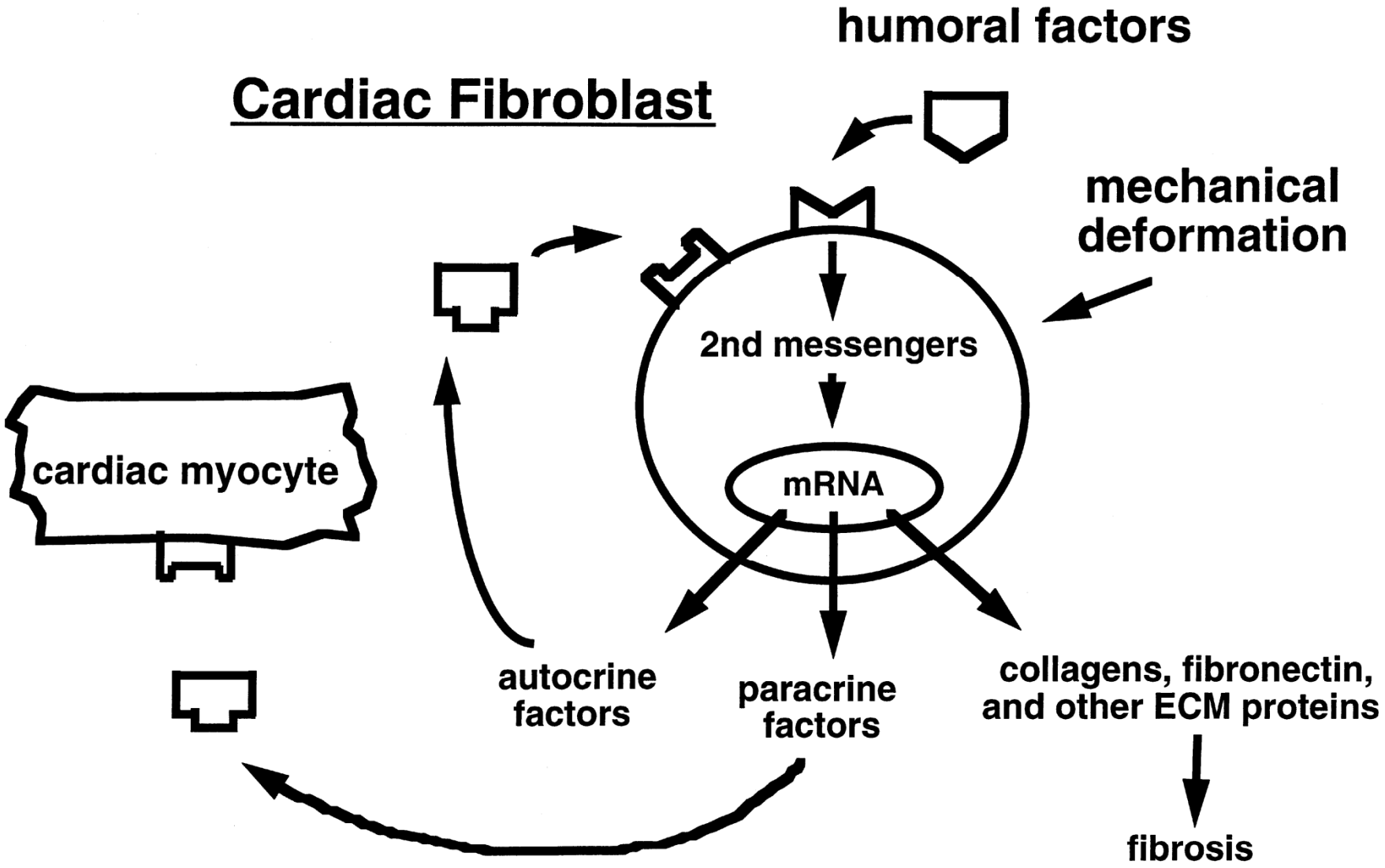


Lee A, et al. J Mol Cell Cardiol 1999;31:1833-43.

MYOCARDIAL ENVIRONMENT



MacKenna D, et al. Cardiovasc Res 2000;46:257.

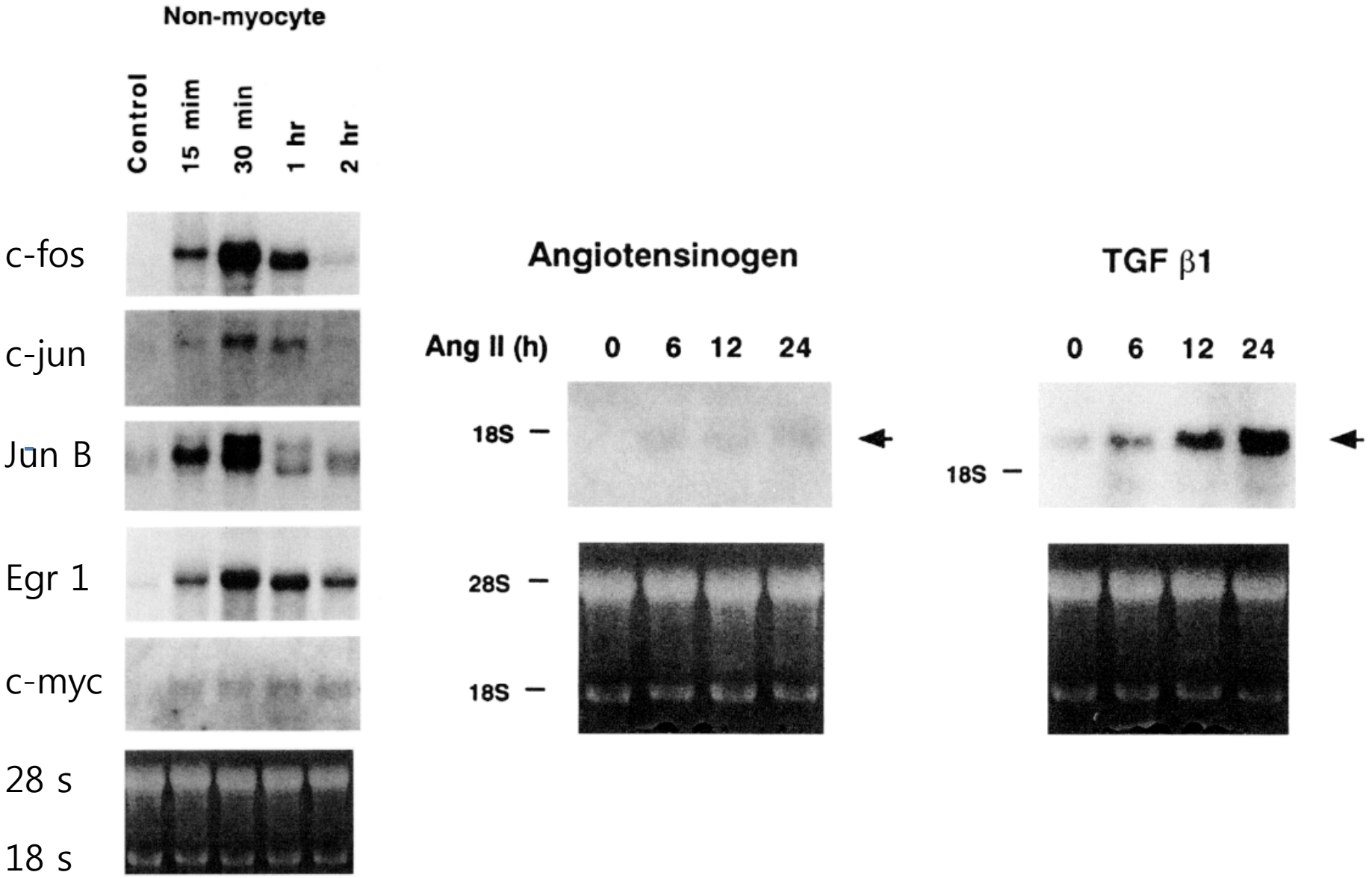


MacKenna D, et al. Cardiovasc Res 2000;46:257.

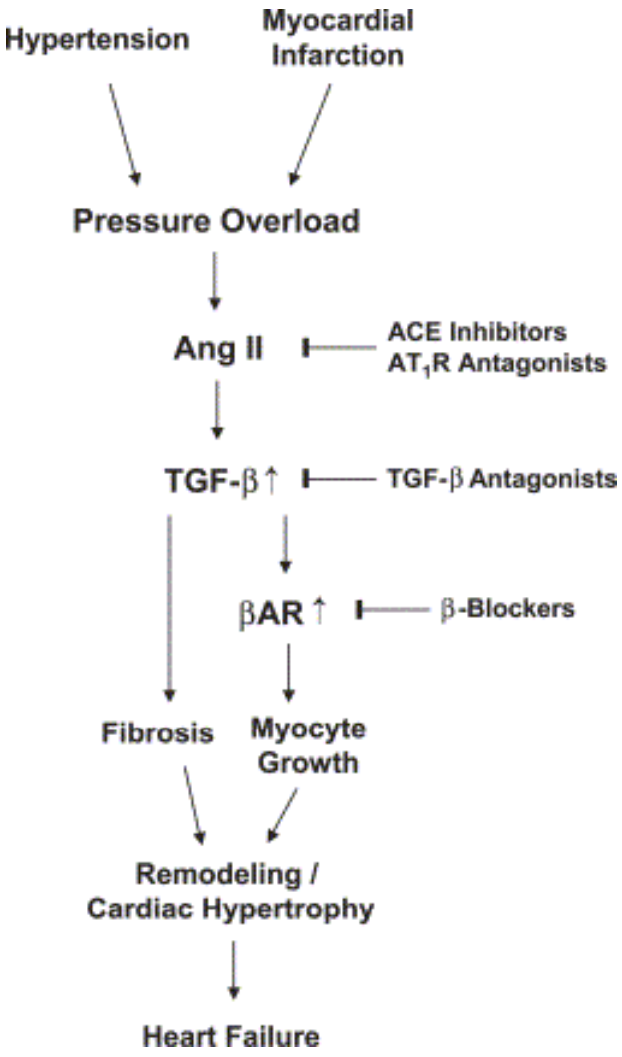
Molecular Mechanisms of Cardiac Fibrosis

- Mechanical stress
- Neurohormonal
  - Angiotensin II/TGF-beta /Endothelin 1
  - Aldosterone (Mineralocorticoid receptor)

Molecular Phenotype of cardiac cell in response to angiotensin II

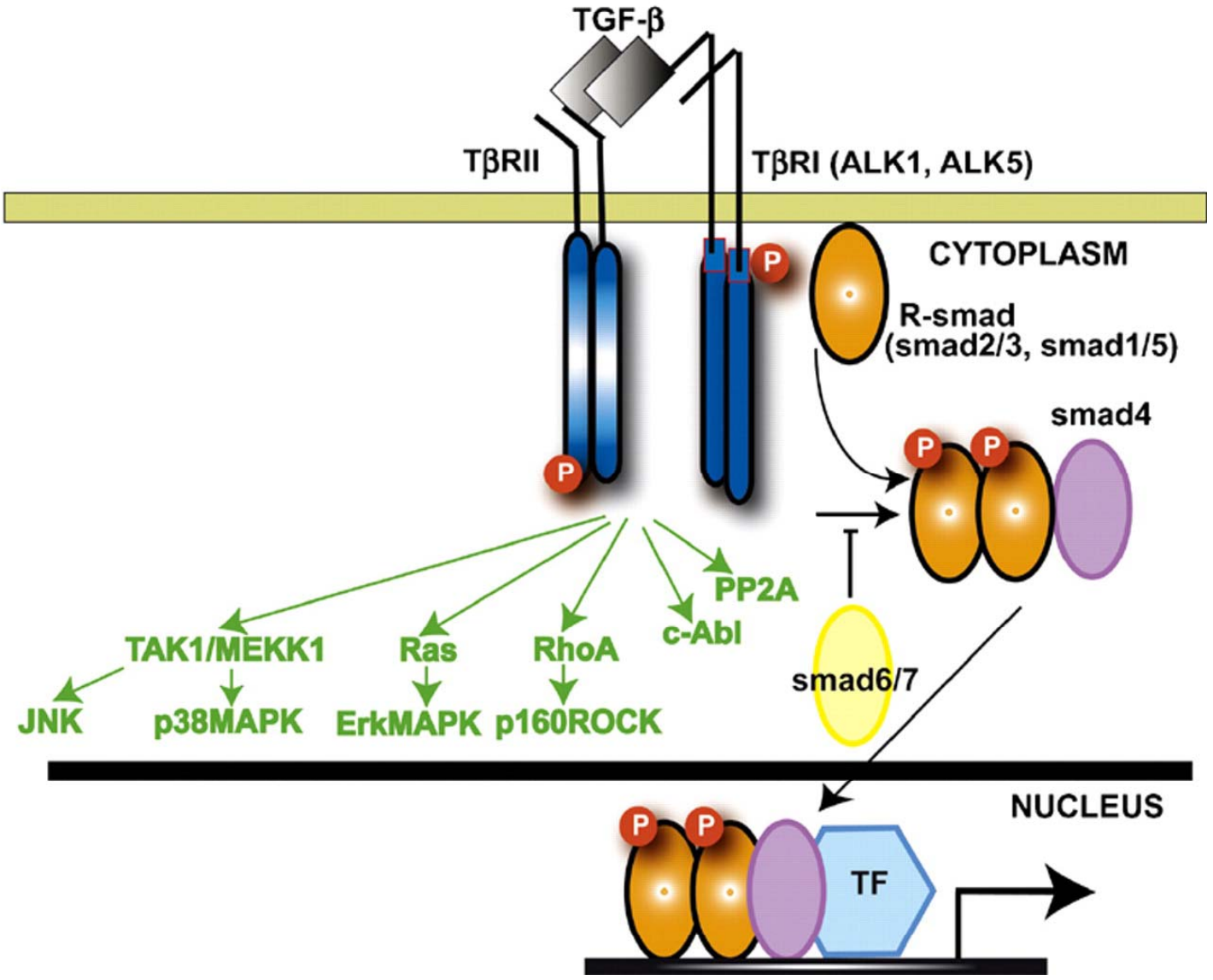


Sadoshima J, et al. Circ Res 1993;73:413



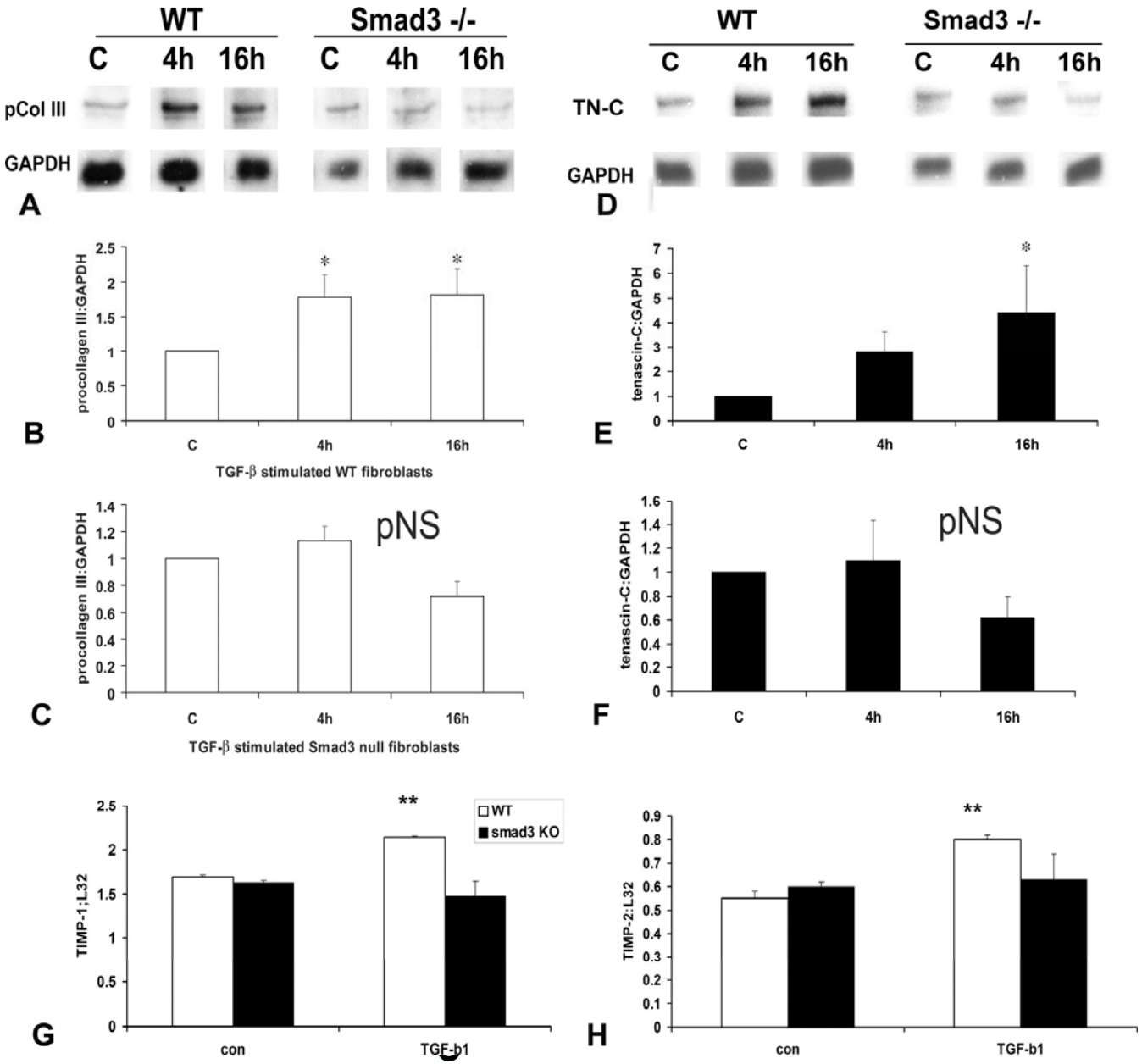
Rosenkranz S. Cardiovasc Res 2004;63:423.

TGF-β signaling pathways



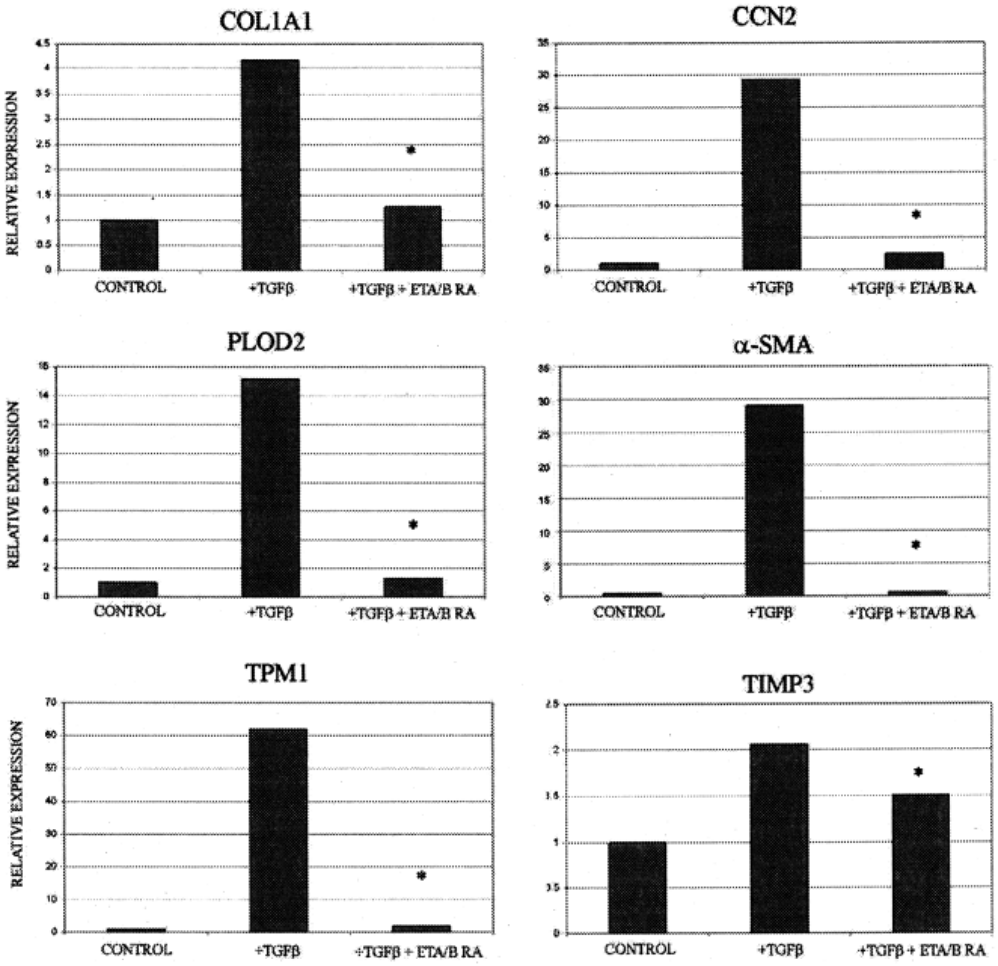
Murphy-Ullrich JE. Cytokine Growth Factor Rev 2000;11:59-69. Bujak M, et al. Cardiovasc Res 2007;72:184-95.

Essential Role of Smad3 in Infarct Healing and Cardiac Remodeling

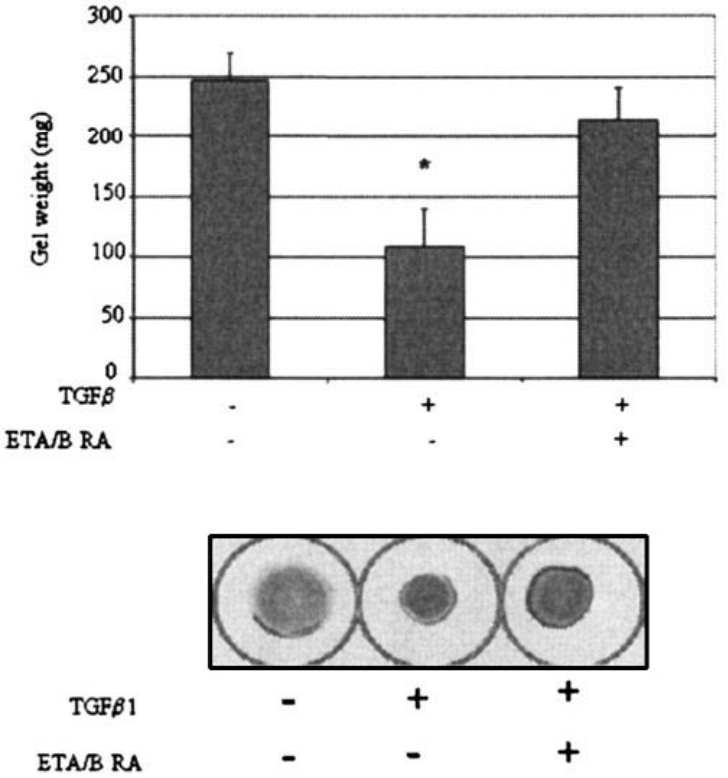


Bujak M, et al. Circulation 2007;116:2127-38.

Endothelin is a downstream mediator of profibrotic response of TGF-β in human lung fibroblasts



TGFβ induced collagen gel contraction



ETA/B RA; endothelinA/B receptor antagonist

Shi-wen X, et al. Arthritis Rheum 2007;56:4189-94.

TGF-β induces the ET-1 promoter

in a Smad-independent JNK/AP-1 pathway.

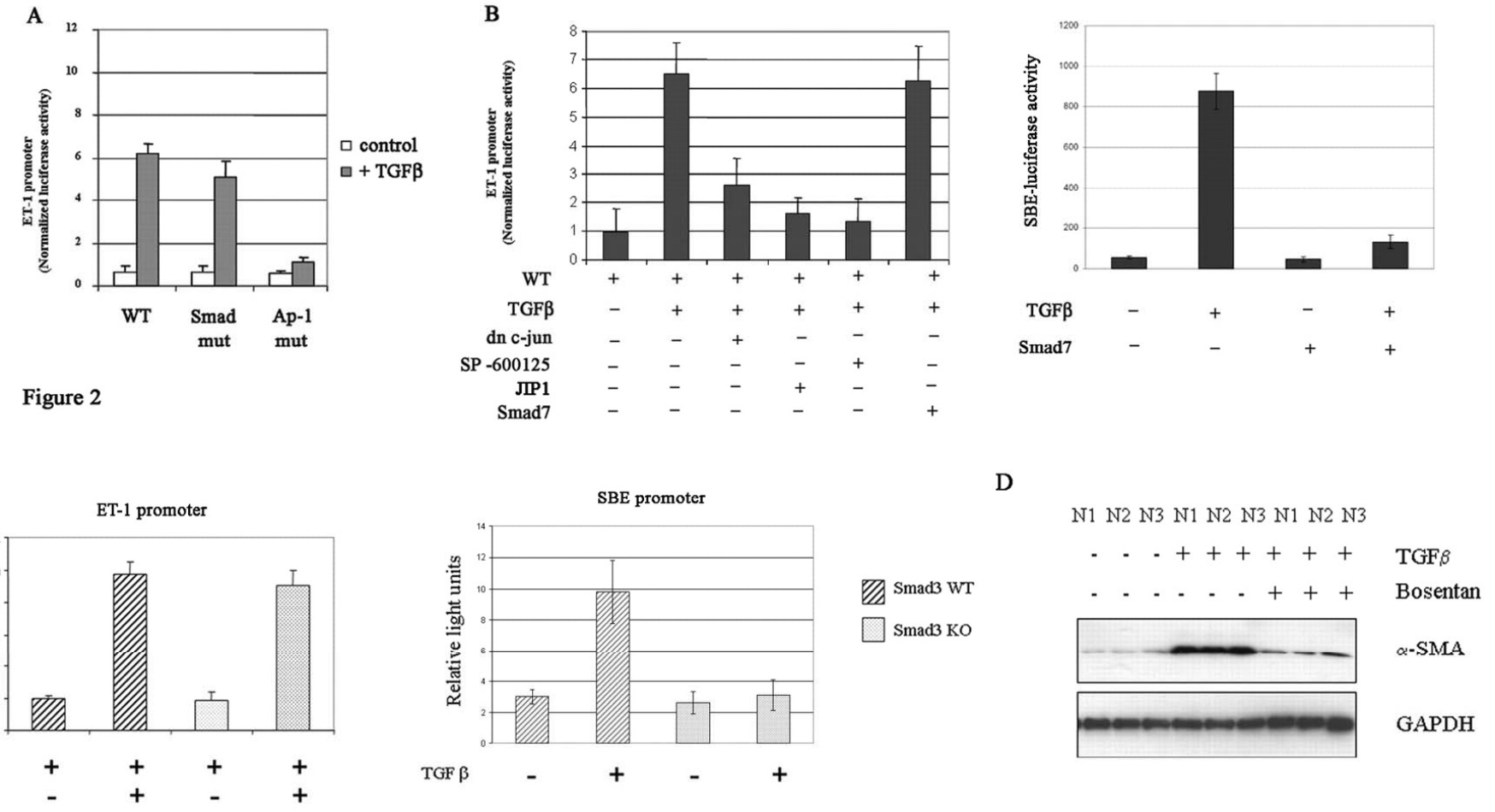
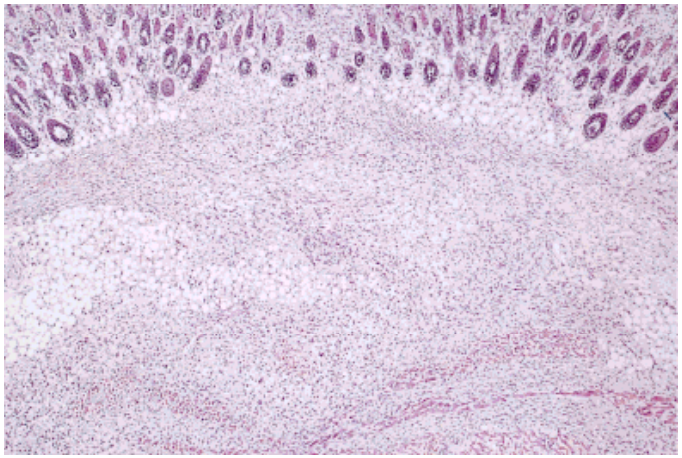


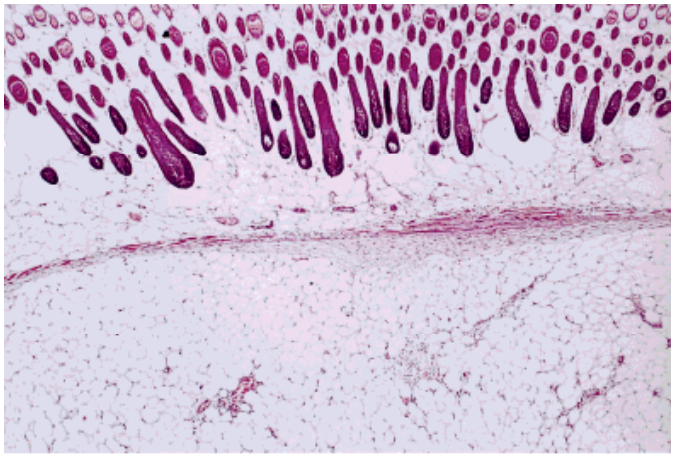
Figure 2

Shi-wen X, et al. Mol Cell Biol 2006;26:5518-27.

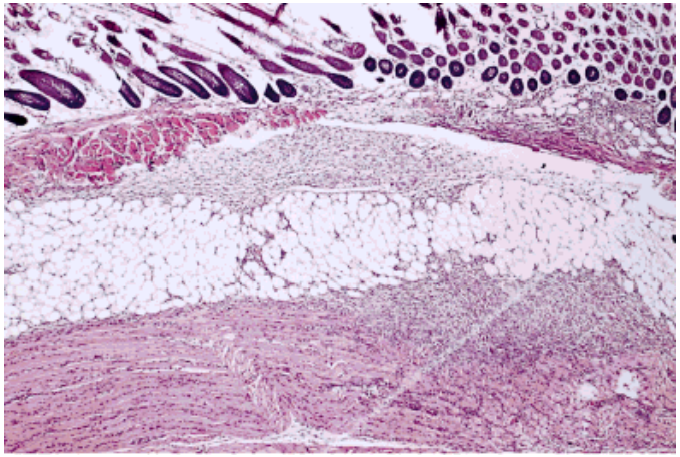
Role and Interaction of Connective Tissue Growth Factor with TGF-β in Persistent Fibrosis: A mouse model



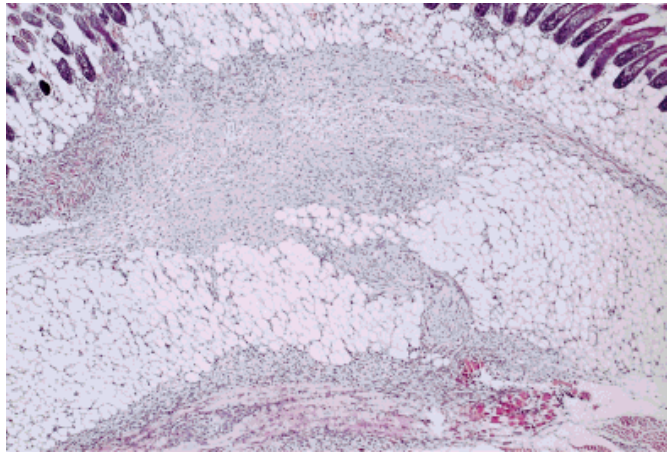
TGF-β (day 1-3) Day 3



TGF-β (day 1-7) Day 7



TGF-β+CTGF (day 1-7) Day 11

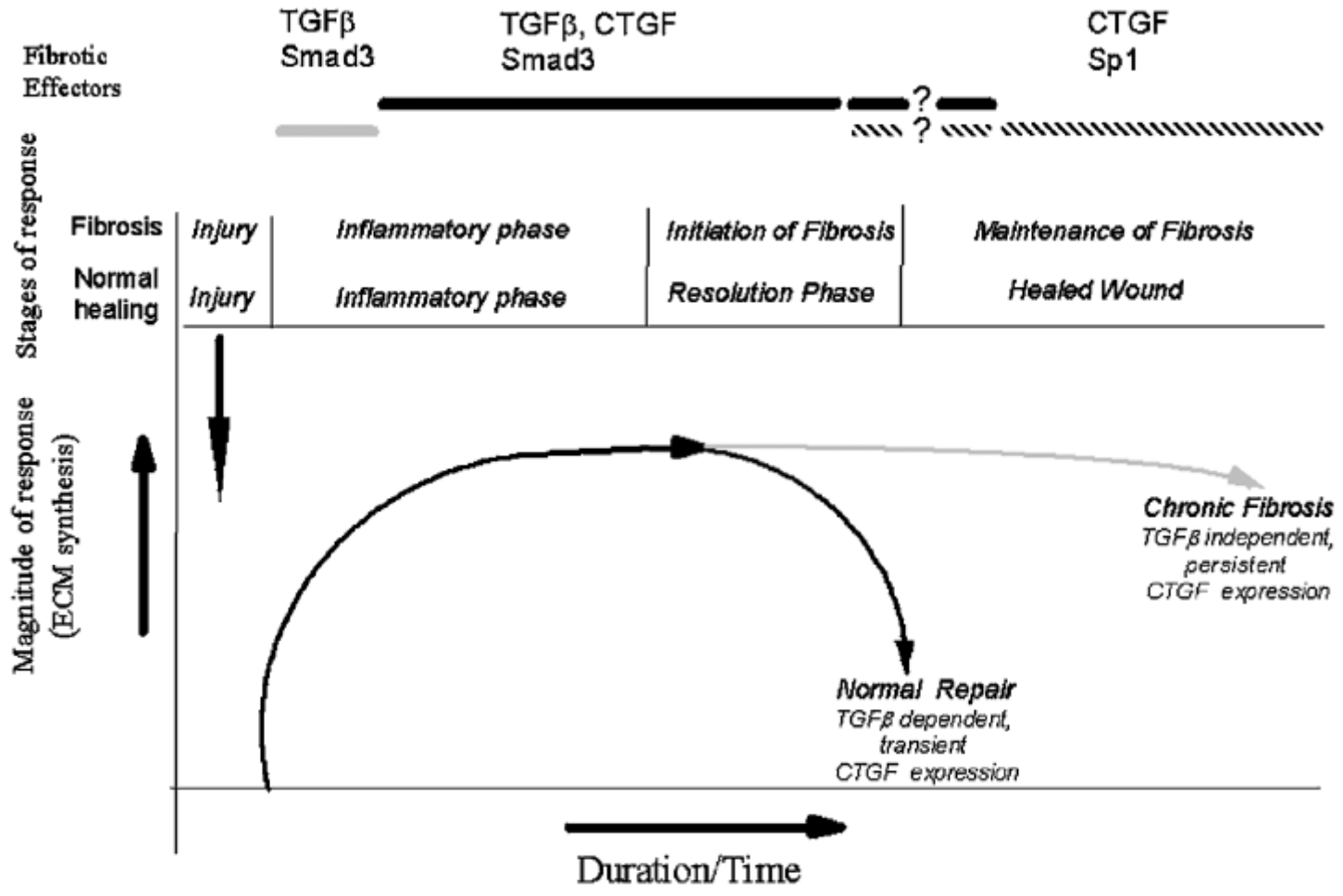


TGF-β (day 1-3) CTGF (day 4-7) Day 8

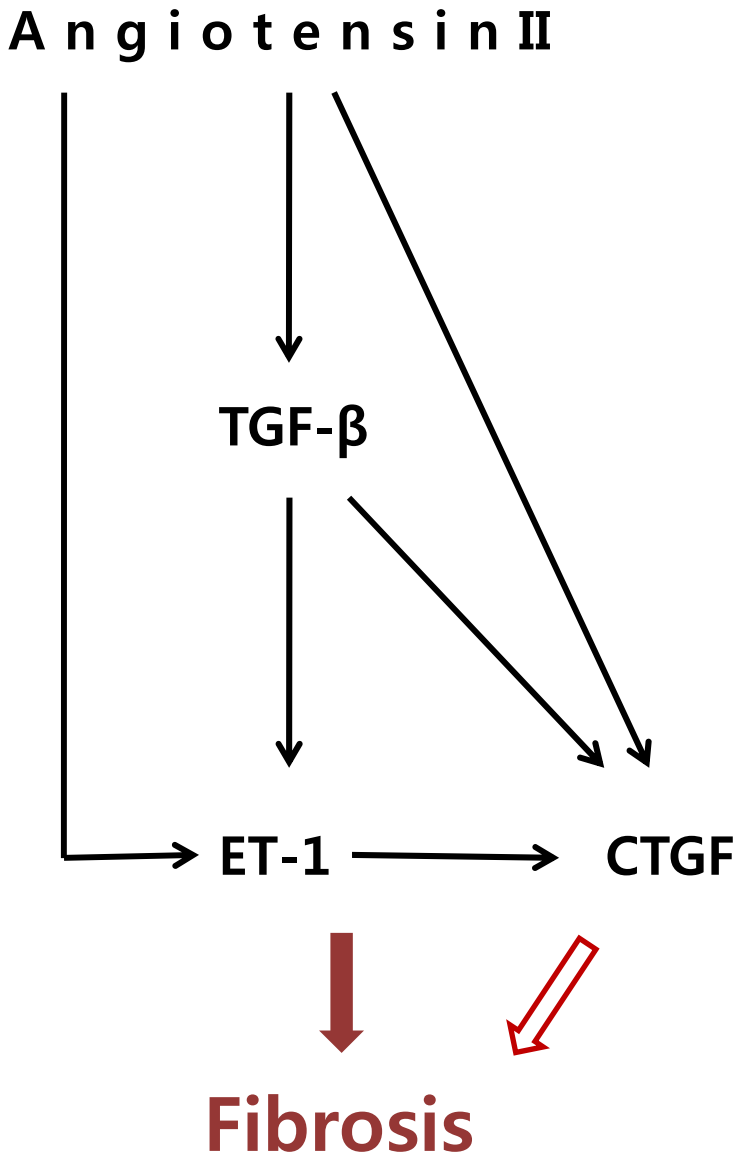
Injection into neck subcutaneous tissueof newborn BALB/c mouse

Mori T, et al. J Cell Physiol 1999;181:153-9.

Model of sustained, chronic fibrosis

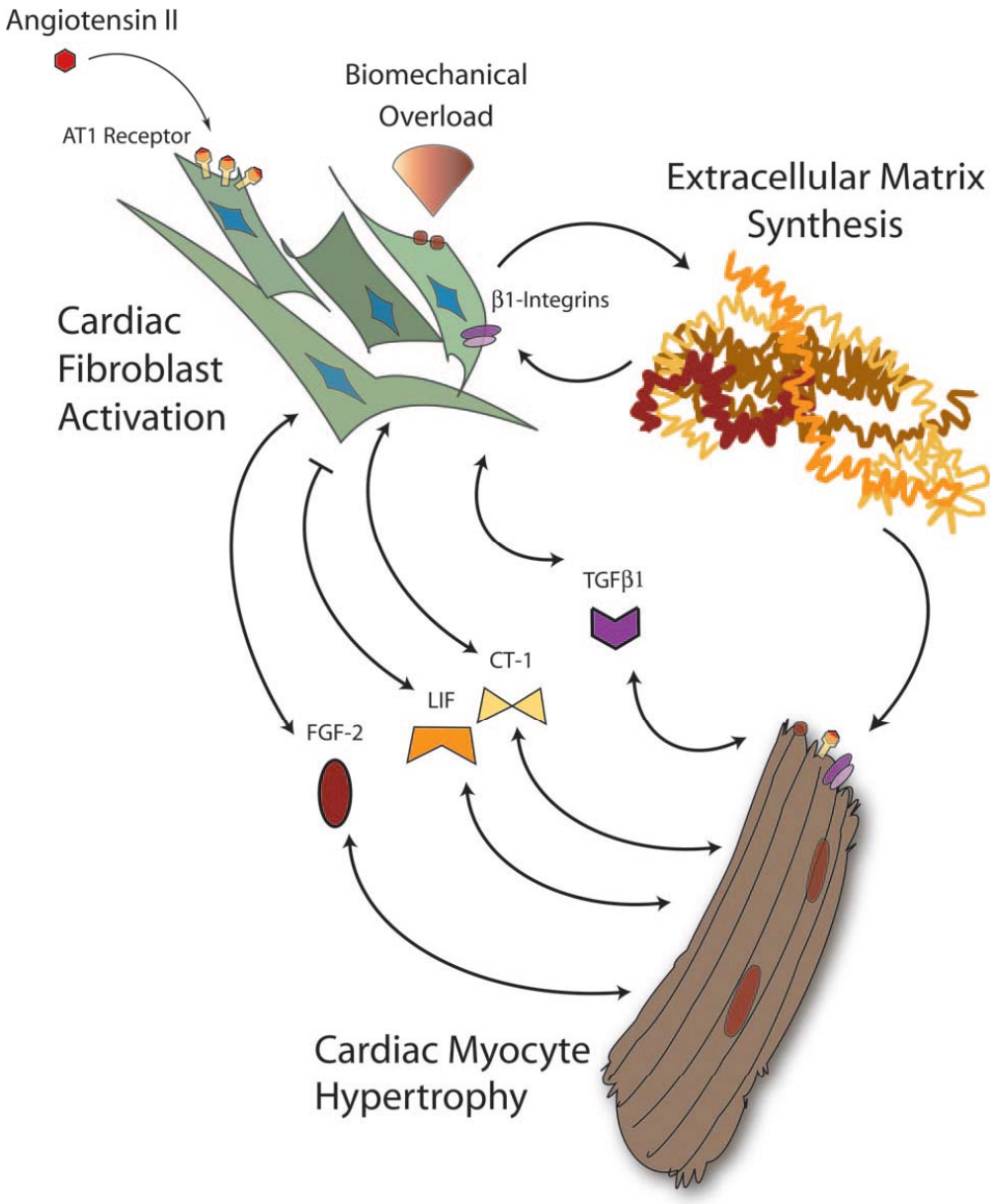


Leask A, et al. J Invest Dermatol 2002;122:1-6.



Leask A. Cardiovasc Res 2007;7f4:207-12.

Cross-talk between fibroblast and cardiomyocyte



Kakka R, et al. Circ Res 2010;106:47-57.

Molecular Mechanisms of Cardiac Fibrosis

- Mechanical stress
- Neurohormonal
  - Angiotensin II/TGF-beta /Endothelin 1
  - Aldosterone (Mineralocorticoid receptor)

Aldosterone :

Genomic pathways

Mineralocorticoid Receptor (MR):

A member of steroid/thyroid/retinoids superfamily of ligand-activated transcription factor

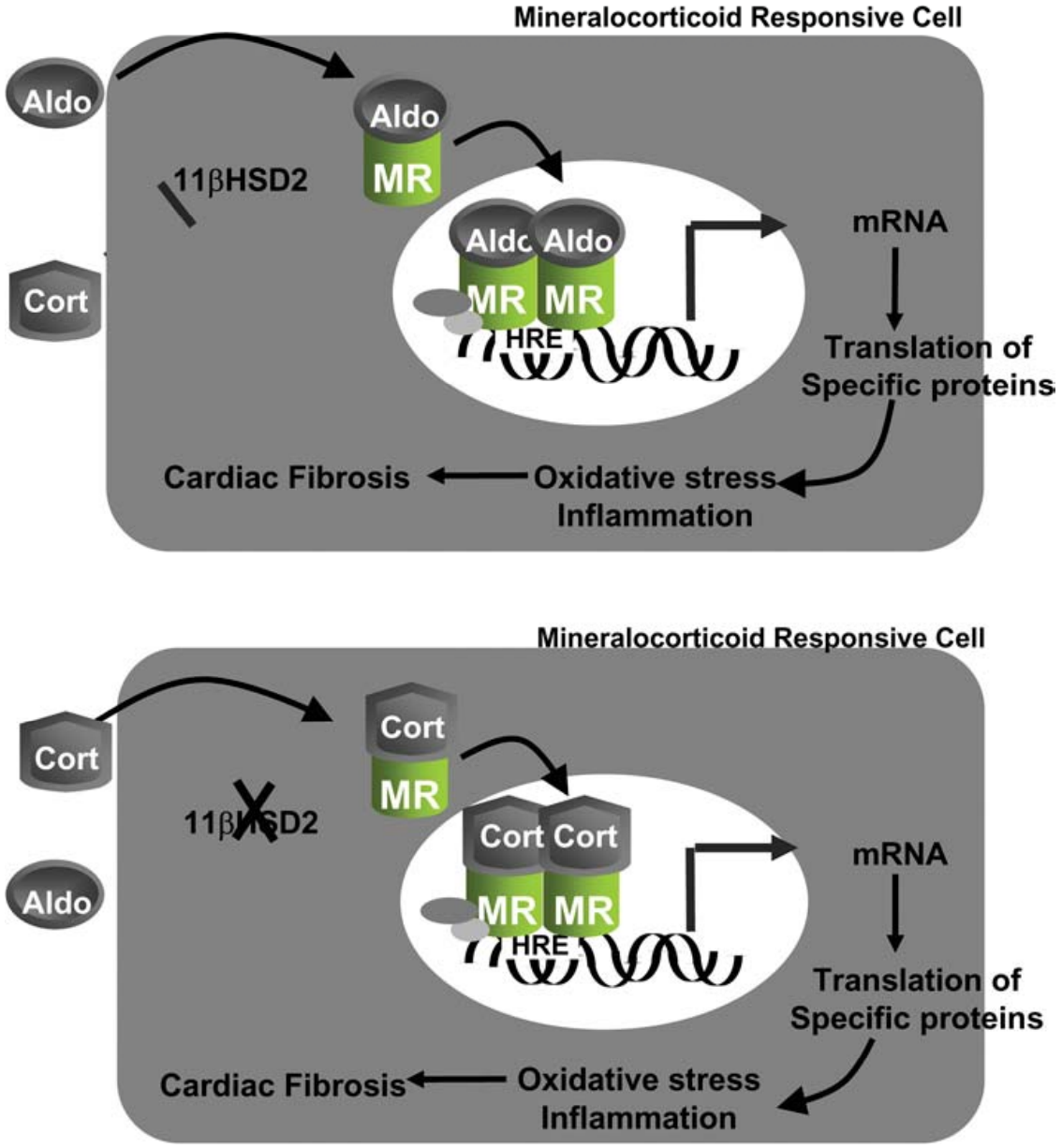
Epithelial tissue & Non-epithelial tissue (heart, brain, vessel wall)

Rapid 'non-genomic pathways

PKC_{ξ}-dependent mechanism (heart)

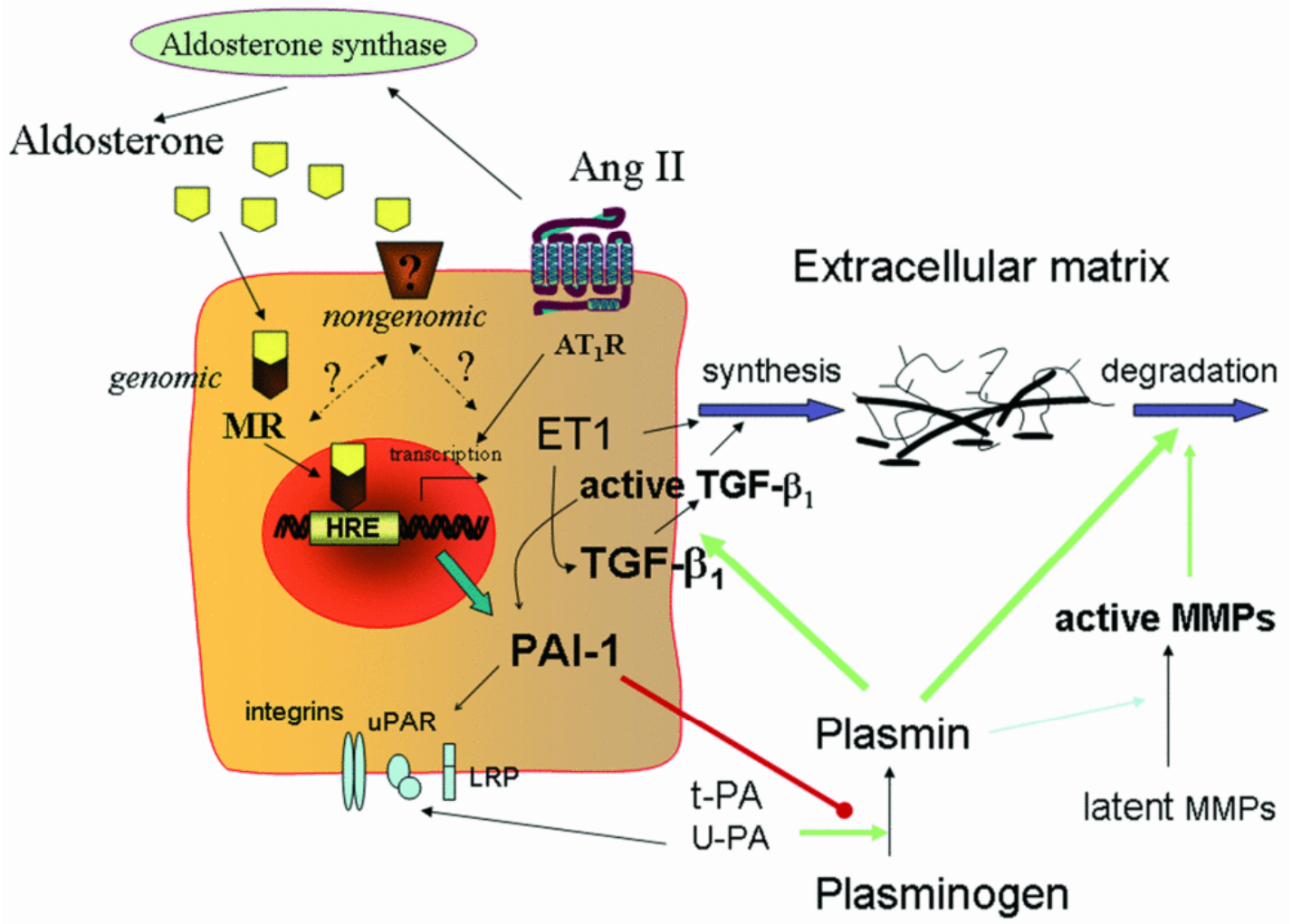
$Ins(1,4,5)P_3$, diacylglyceriol, PKC- ↑ $[Ca^{2+}]$ (VSMCs and endothelial cells)

Genomic pathways



11β-HSD1; 11β-hydroxysteroid dehydrogenase

Possible mechanisms involved in profibrotic effect of aldosterone

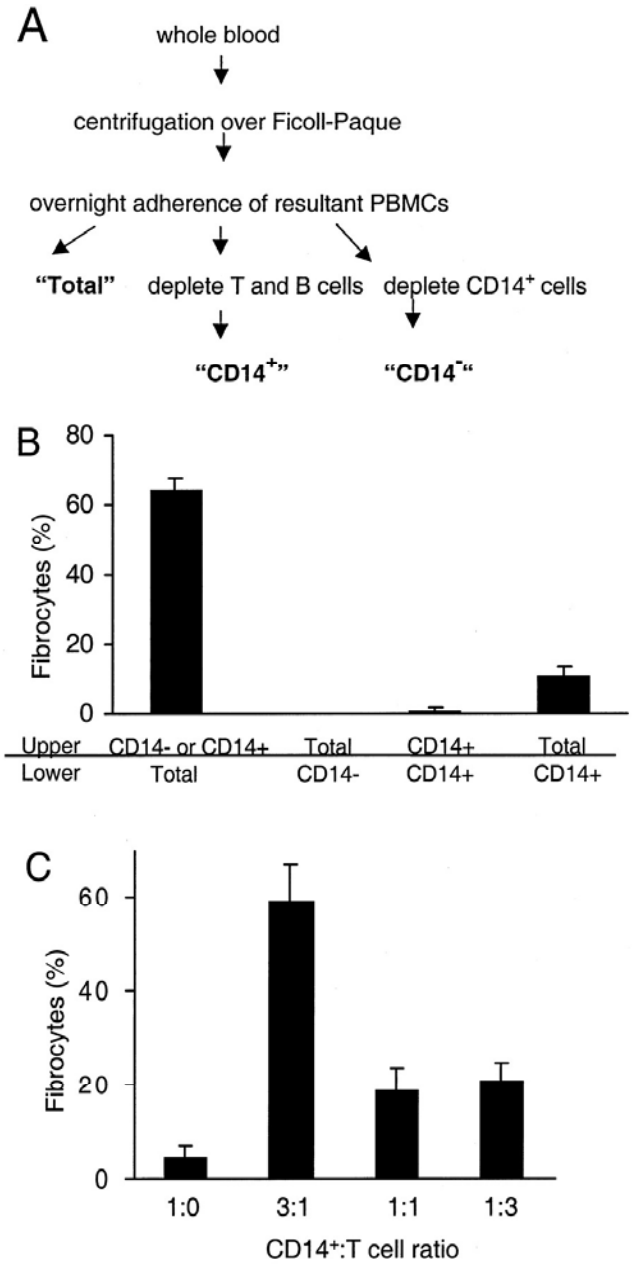


Marney AM, et al. Clin Sci 2007;113:267.

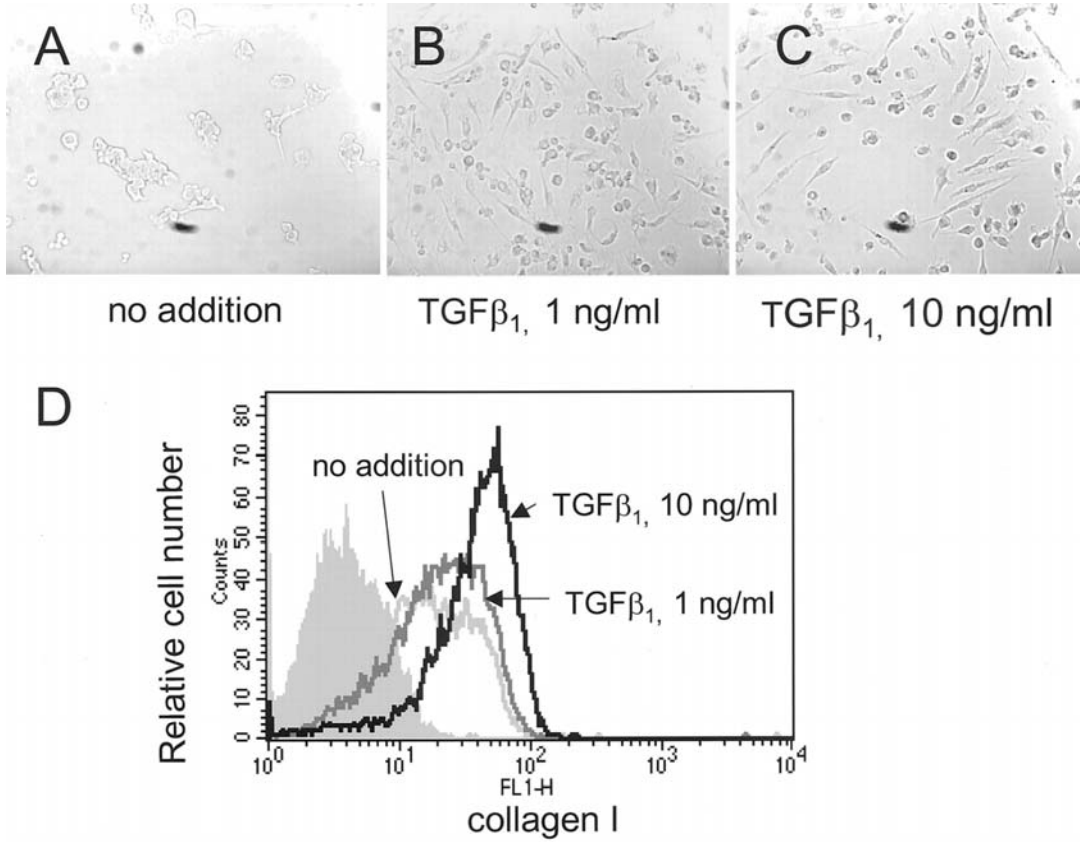
Origin of Cardiac Fibroblast

1. Local residential fibroblast
2. Bone marrow-derived fibrocyte
3. Epithelial-to-mesenchymal transition

Peripheral blood fibrocytes: differentiation & migration to wound healing



TGF-β promotes the differentiation of the fibrocytes

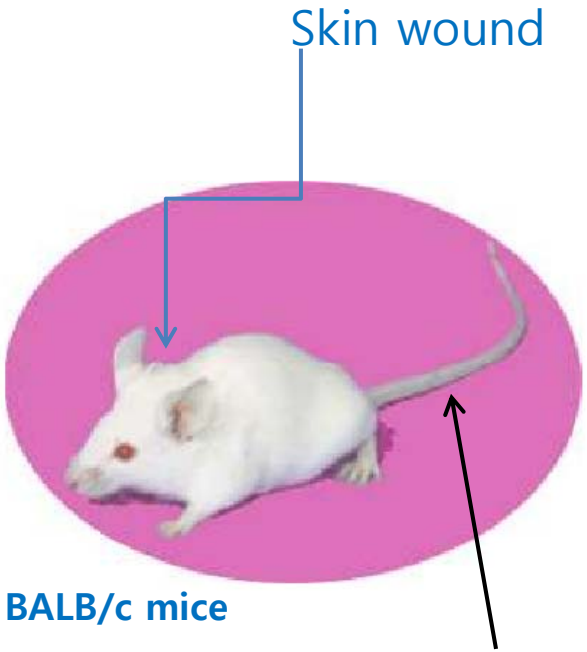


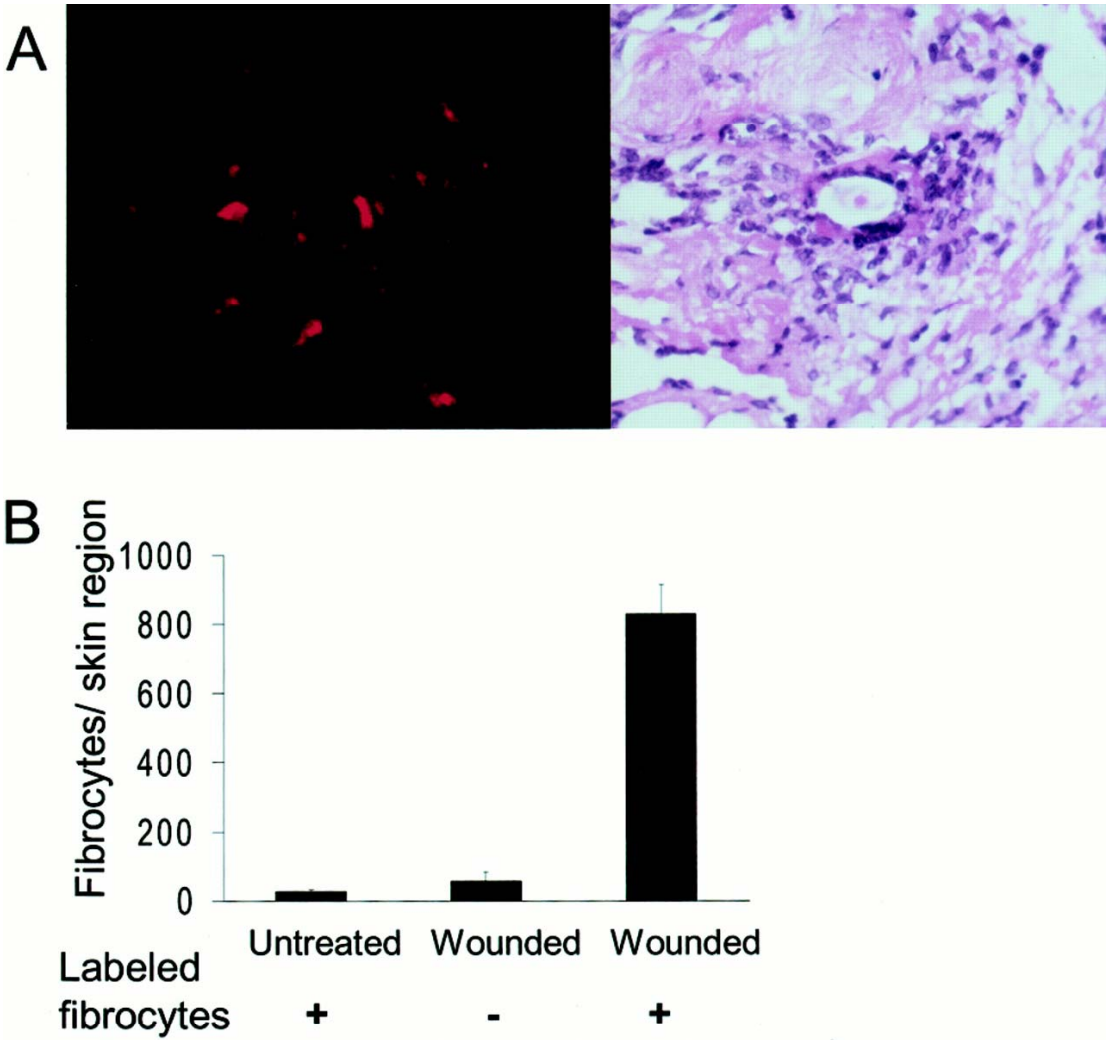
Fibrocyte: surface phenotype

(ColI+/CD11b+/CD13+/CD34+/CD45RO+/MHCclassII+/CD86+)

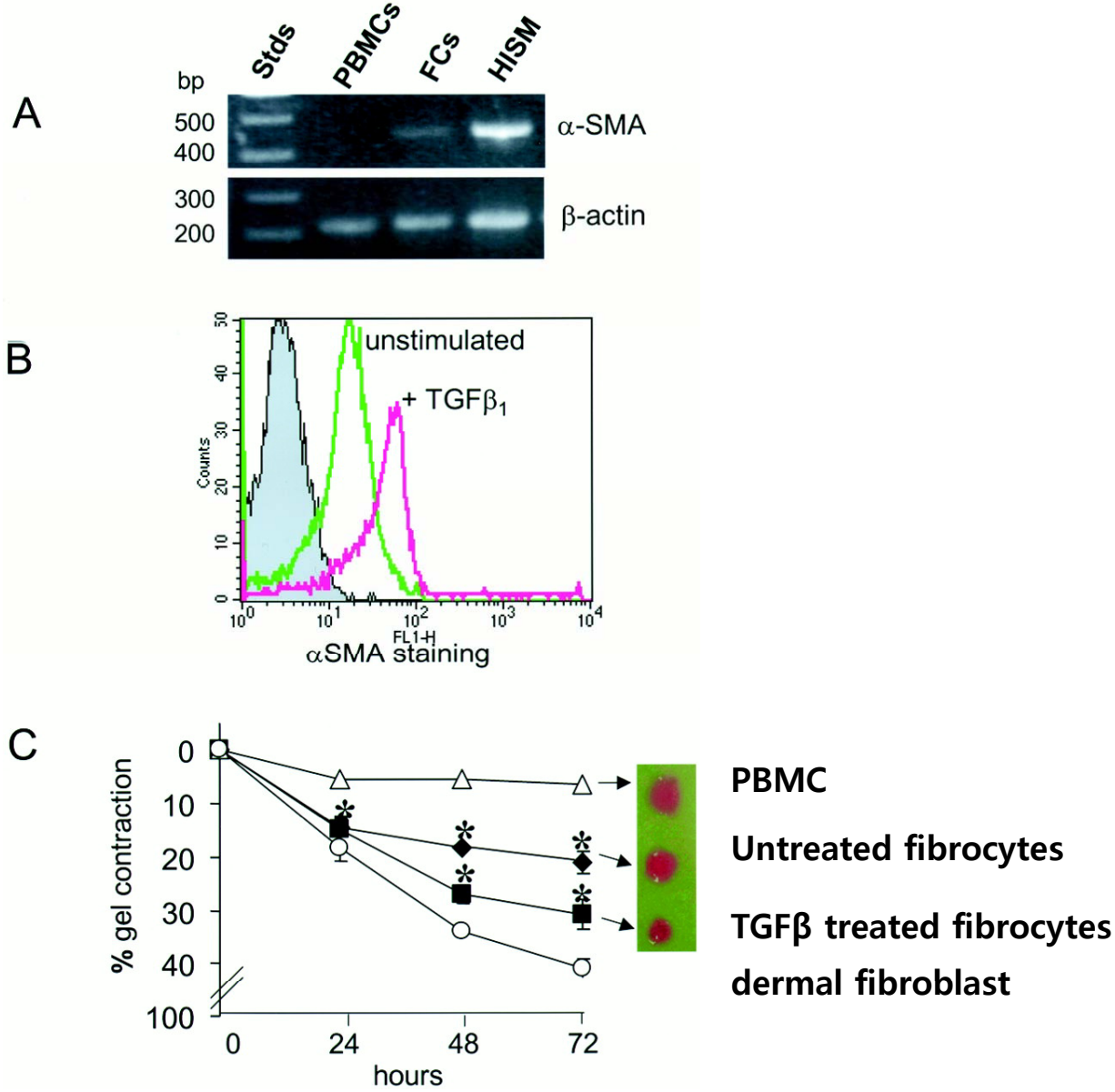
Abe R, et al. J Immunol 2001;166:7556-62.

Fibrocytes migrate to wound sites in vivo



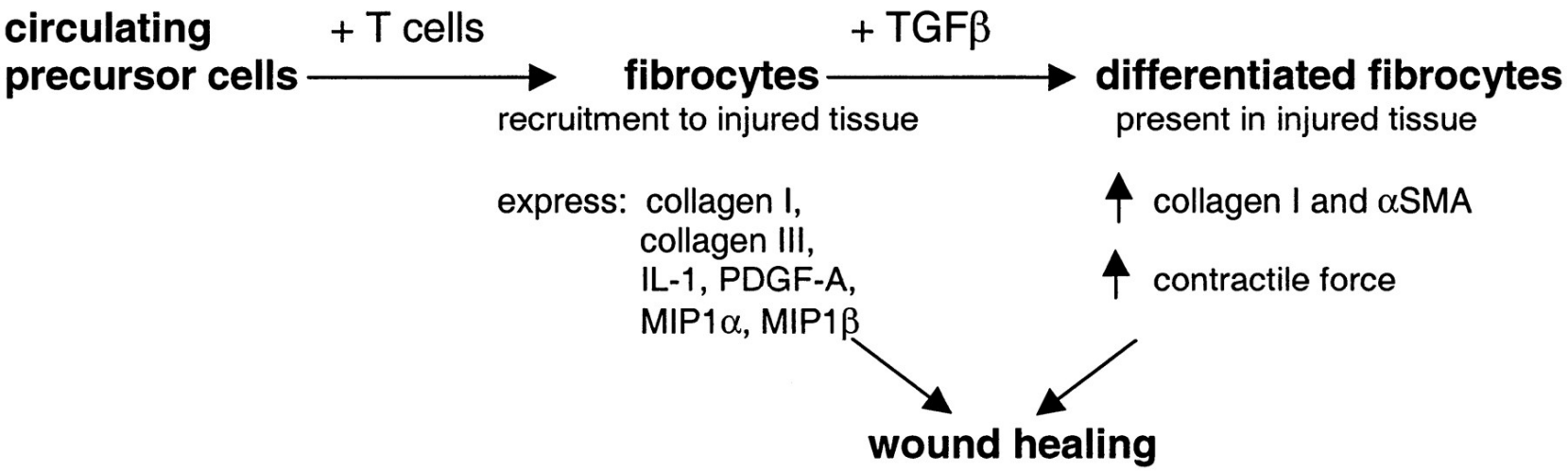


Fibrocytes express SMA and contract collagen gels



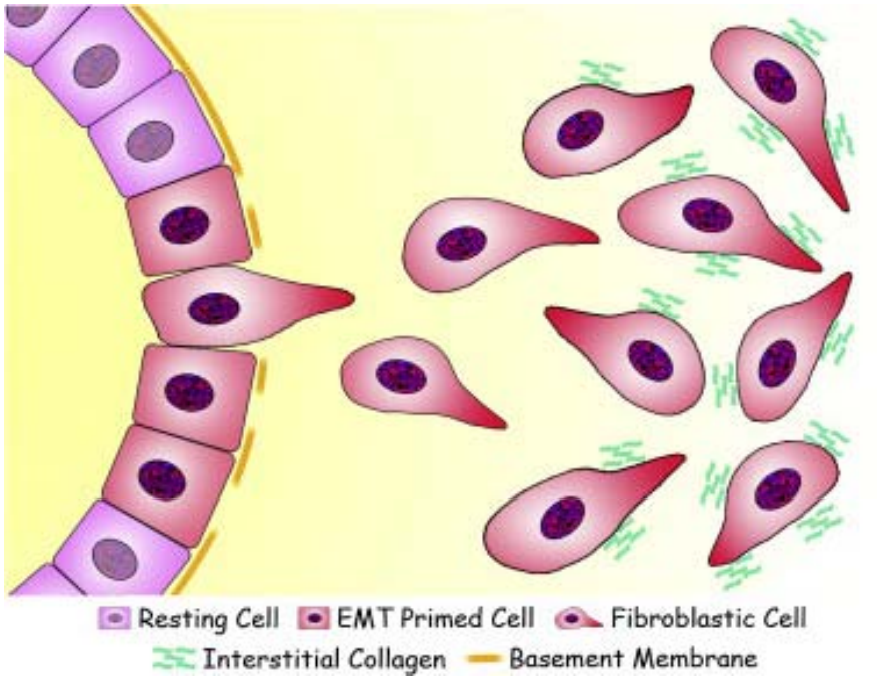
Abe R, et al. J Immunol 2001;166:7556-62.

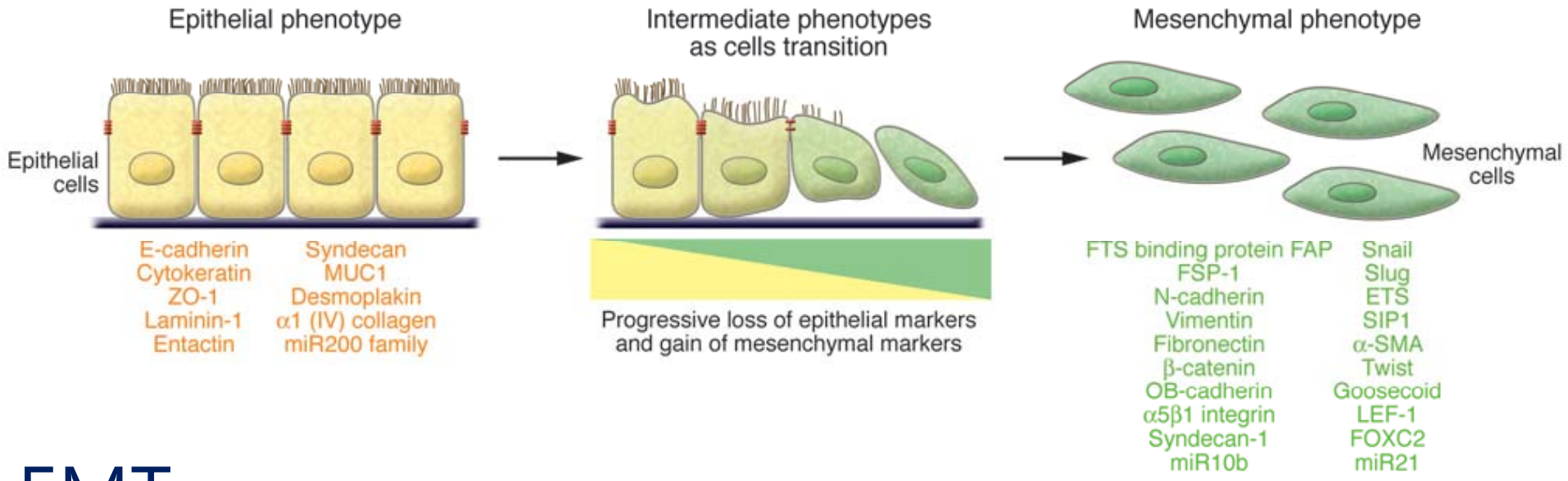
Peripheral blood fibrocytes: differentiation & migration to wound healing



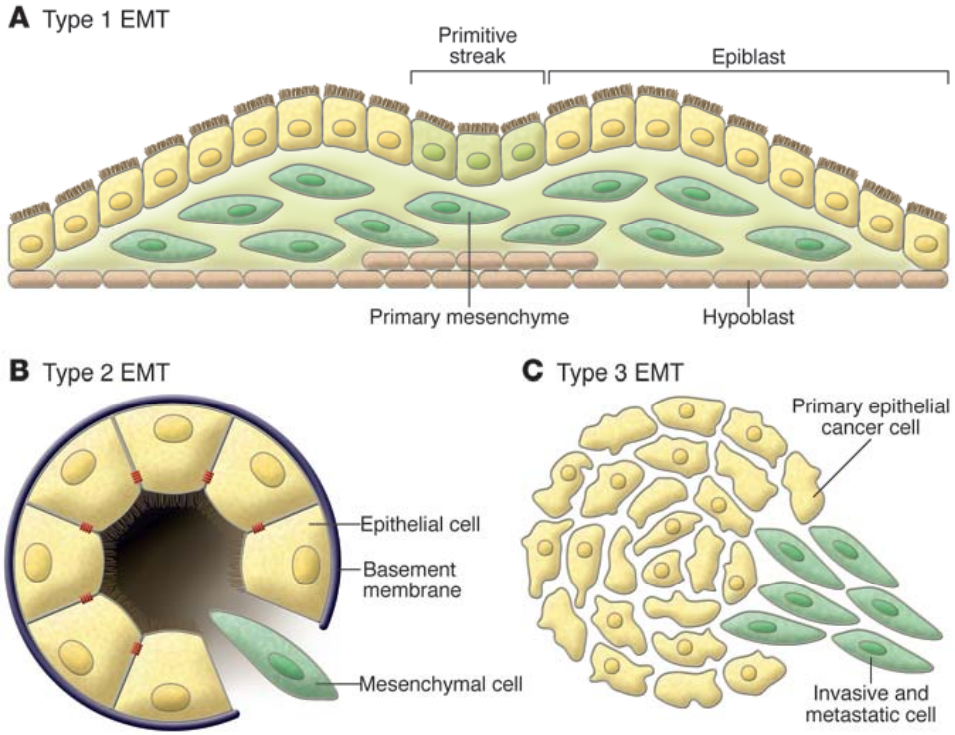
Abe R, et al. J Immunol 2001;166:7556-62.

Epithelial-to-Mesenchymal Transition (EMT)



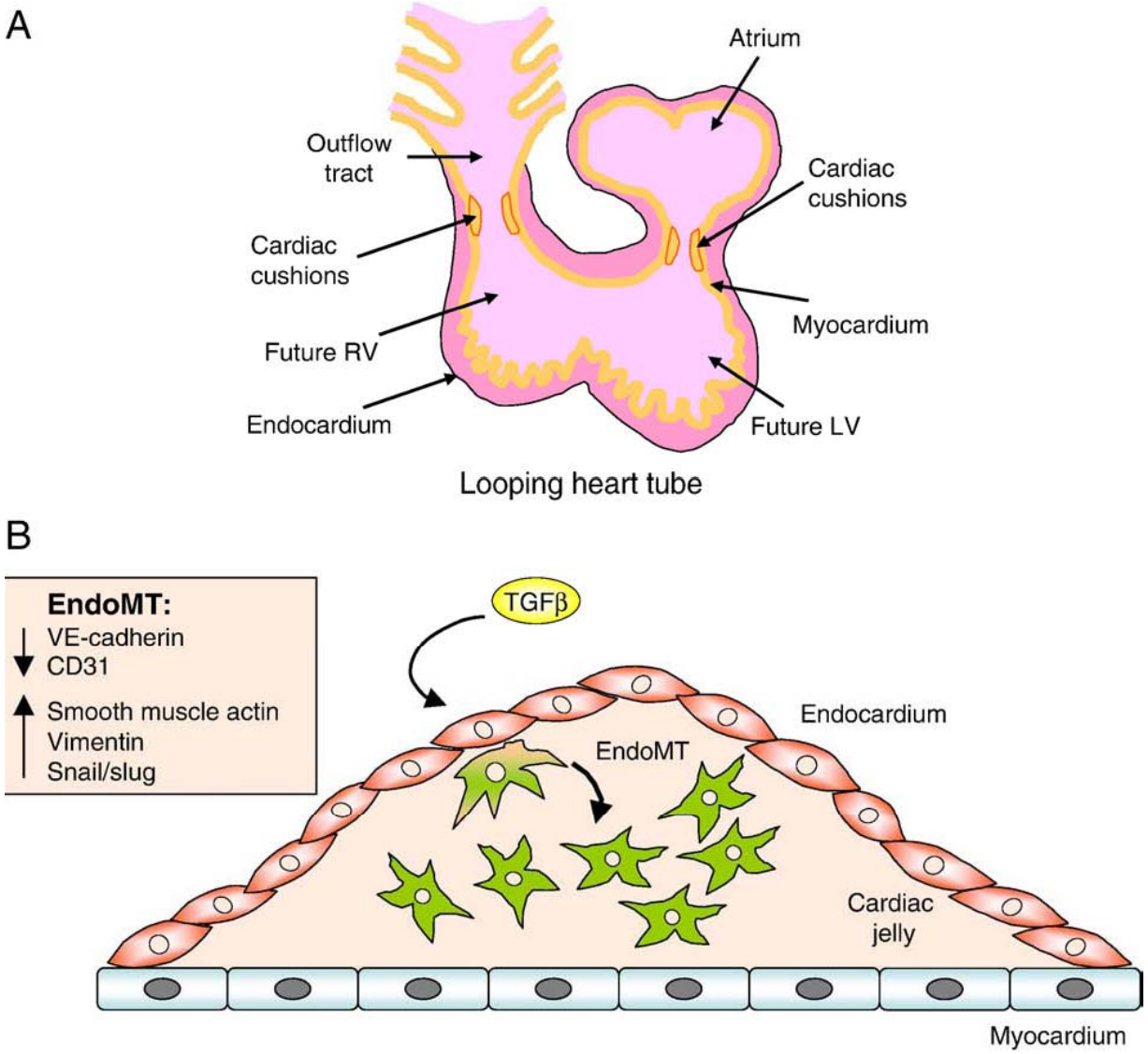


EMT



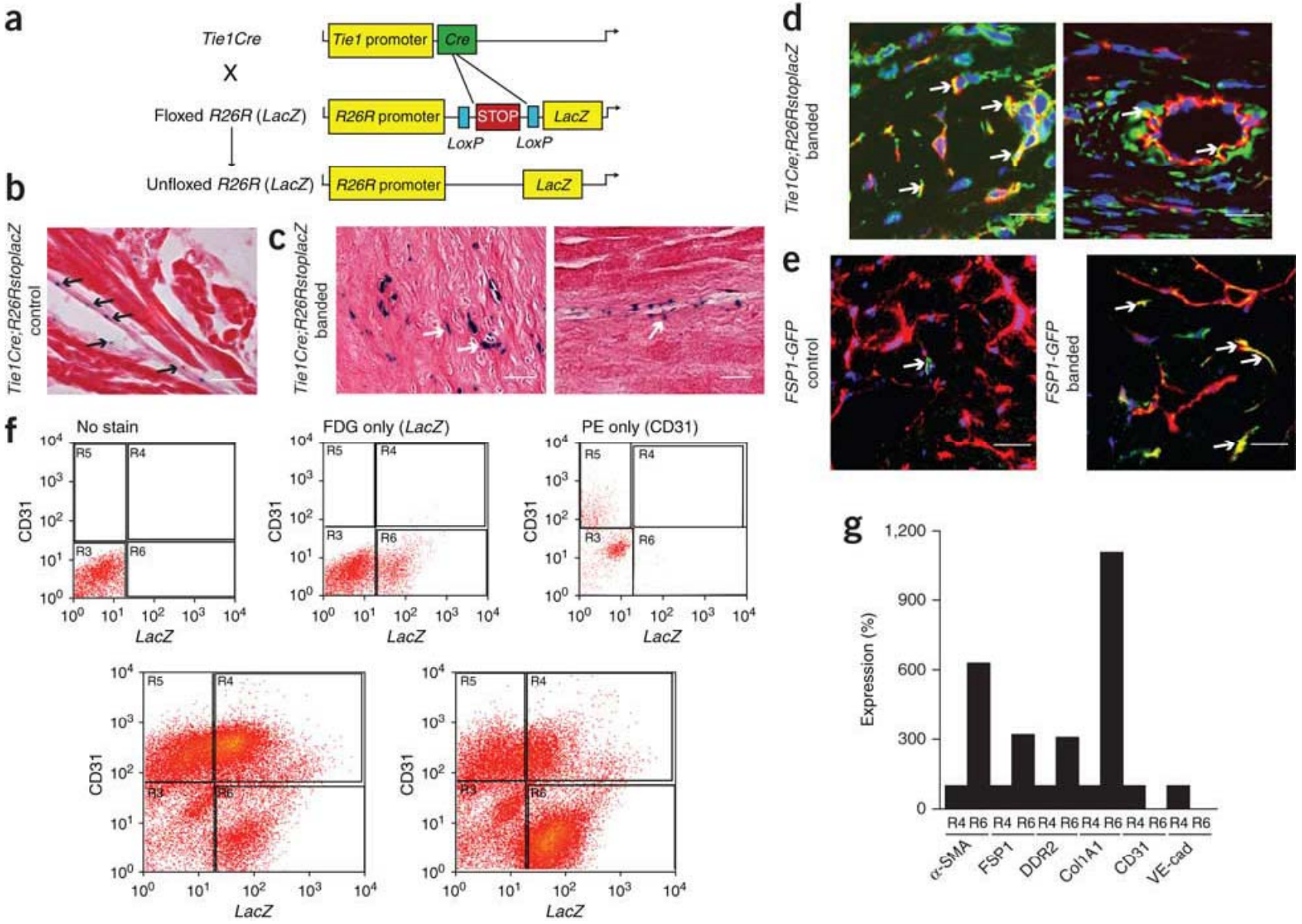
Kalluri R, et al.
J Clin Invest 2009;119:1420-8.

TGF β- induced Endothelial-to-Mesenchymal Transition



Coumans MJ, et al. Trends Cardiovasc Med 2008;18:293-8.

EndMT occurs during cardiac fibrosis



Zeisberg EM, et al. Nat Med 2007;13:952-62.

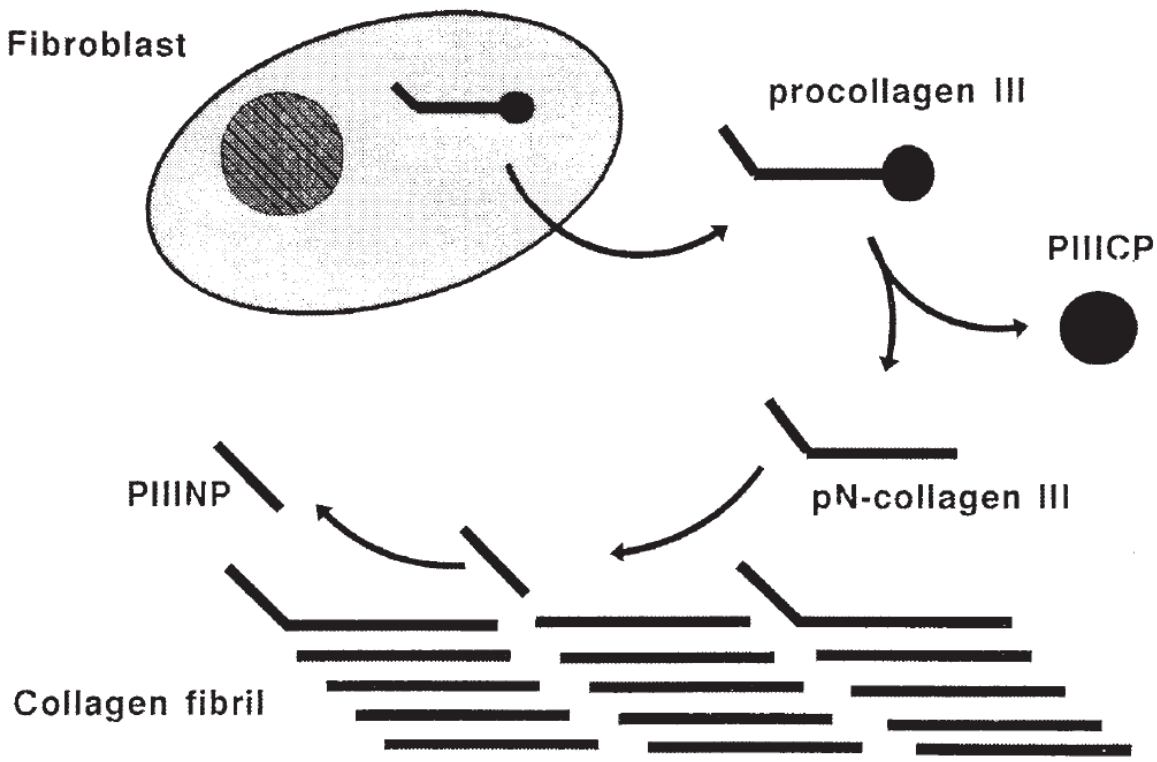
Conclusions

1. Two major stimuli of cardiac fibrosis are mechanical stress and neurohumoral activation.

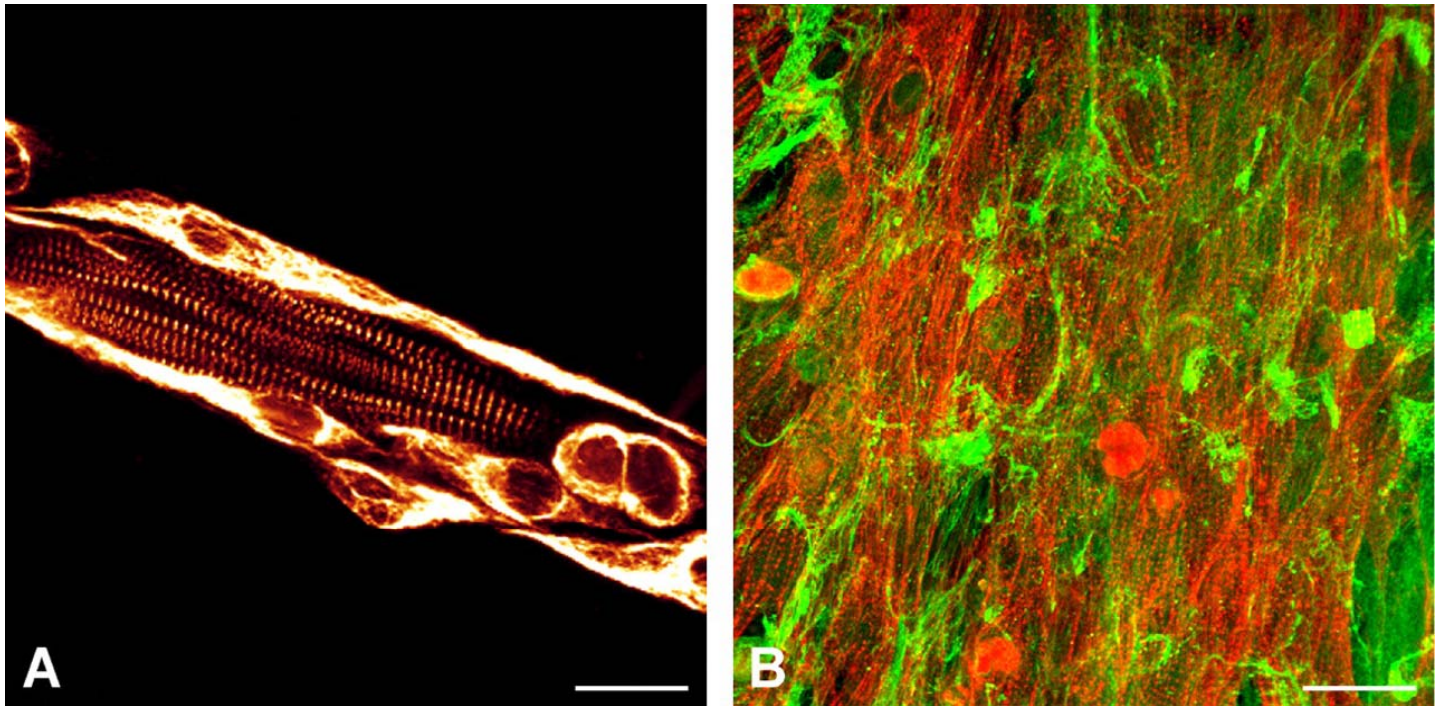
2. These stimuli trigger various signaling pathways, including ATII, TGFβ, and MR related pathways.

3. Cardiac fibroblasts are key player in ECM modulation, and they act in concert with other cells.

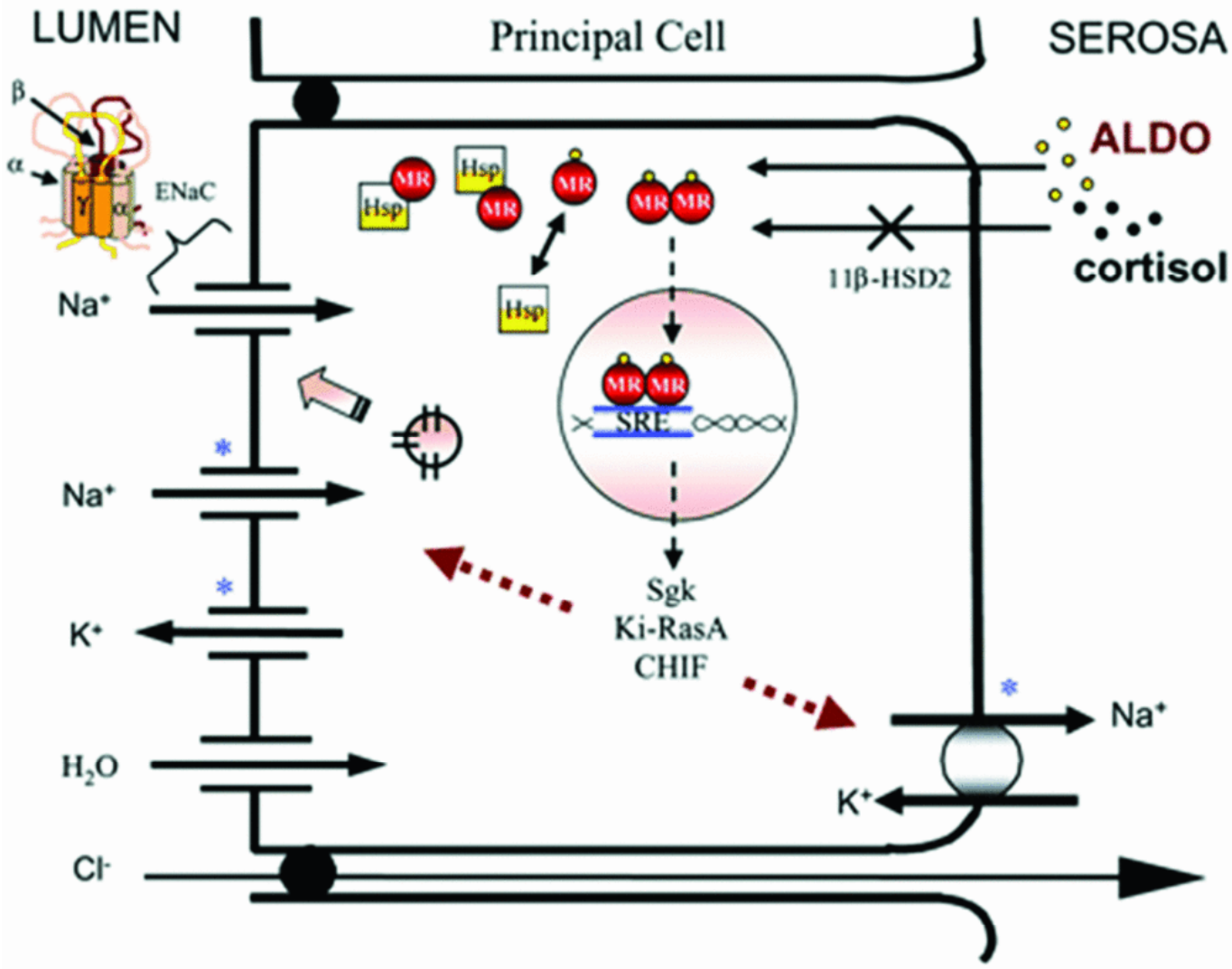
4. Fibroblasts are also recruited from BM-derived cells, and from Epithelial-to-Mesenchymal transition, in addition to from local resident fibroblasts.


Fibroblast
procollagen III
PIIICP
pN-collagen III
PIIINP
Collagen fibril

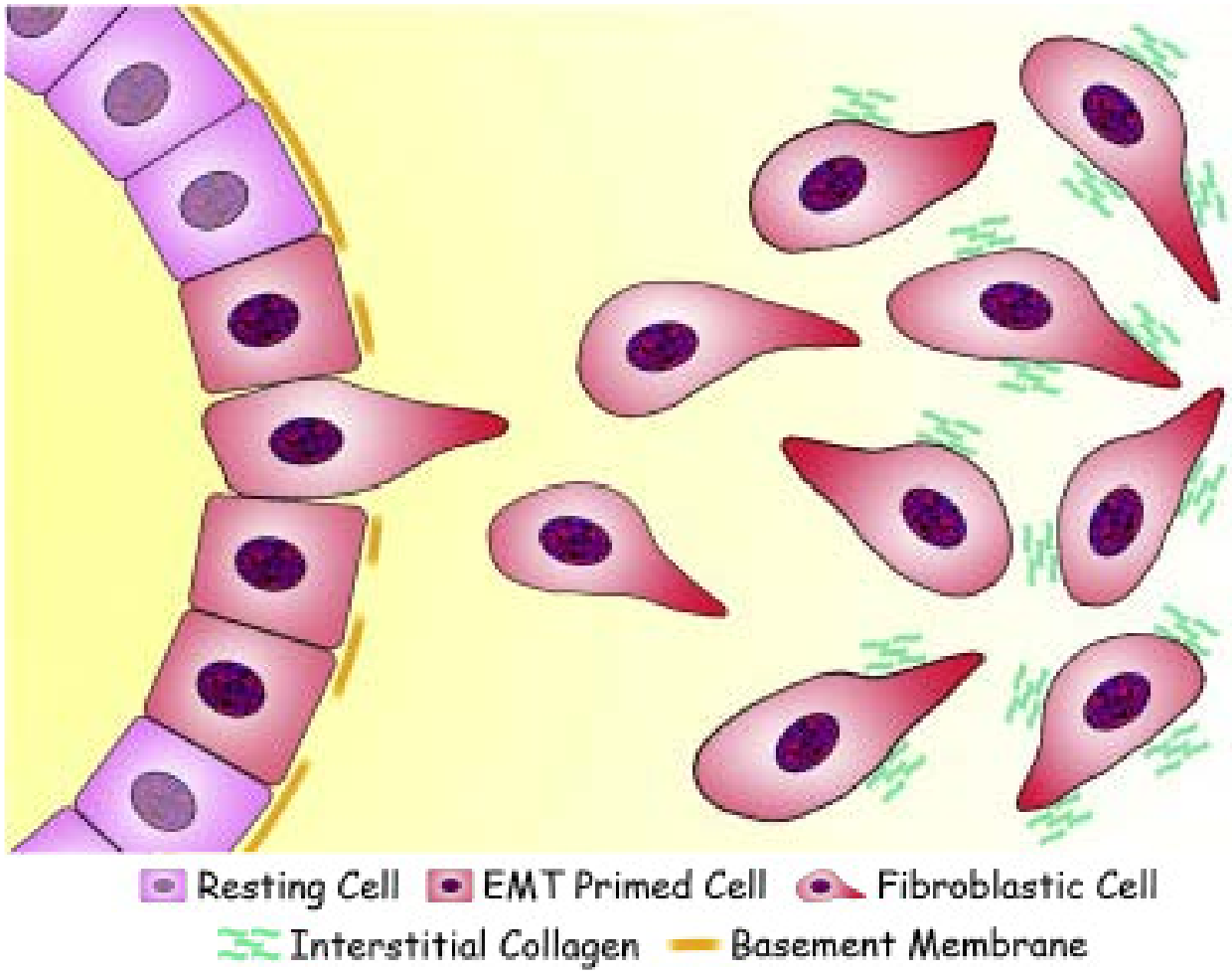
Cardiac Fibroblasts



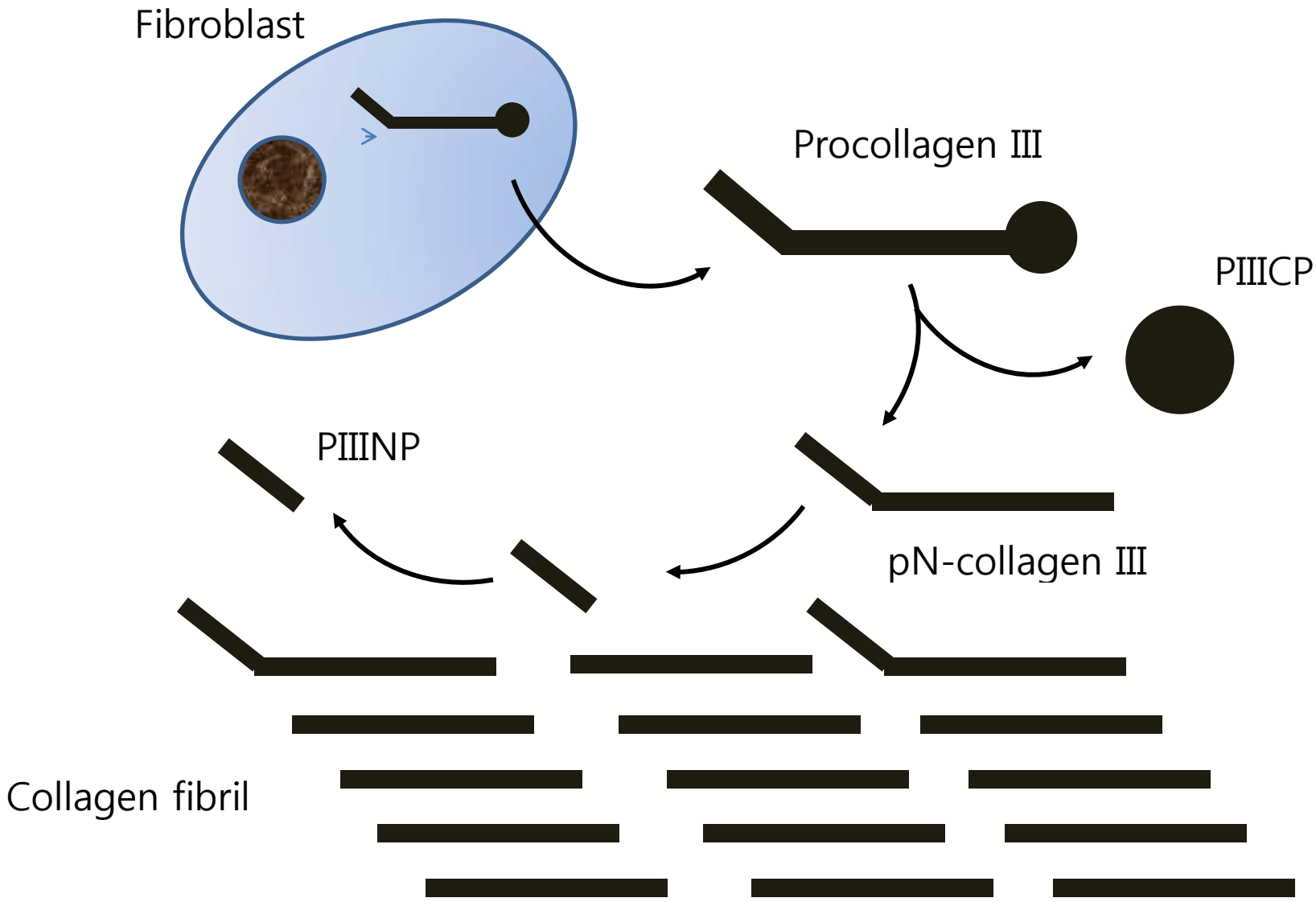
Camelliti P. Cardiovac Res 2005;65:40-51.

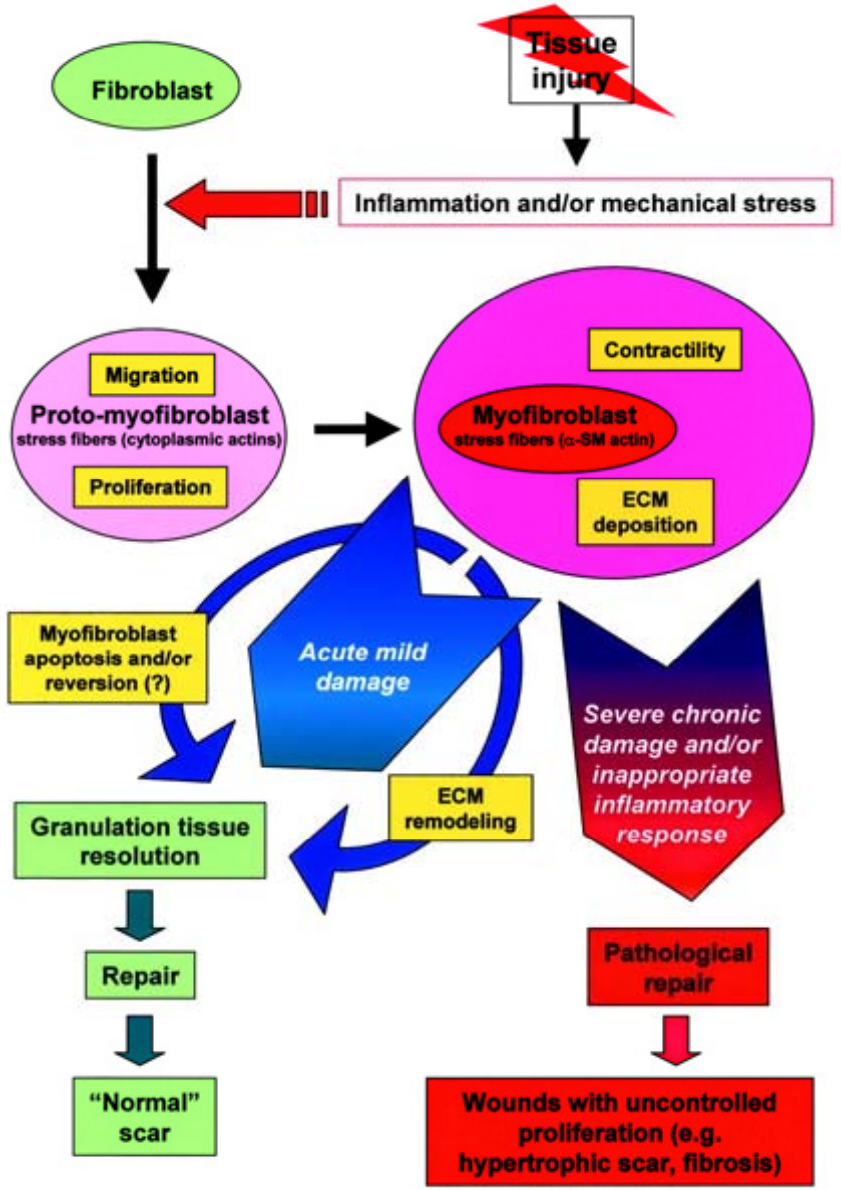


Marney AM, et al. Clin Sci 2007;113:267.

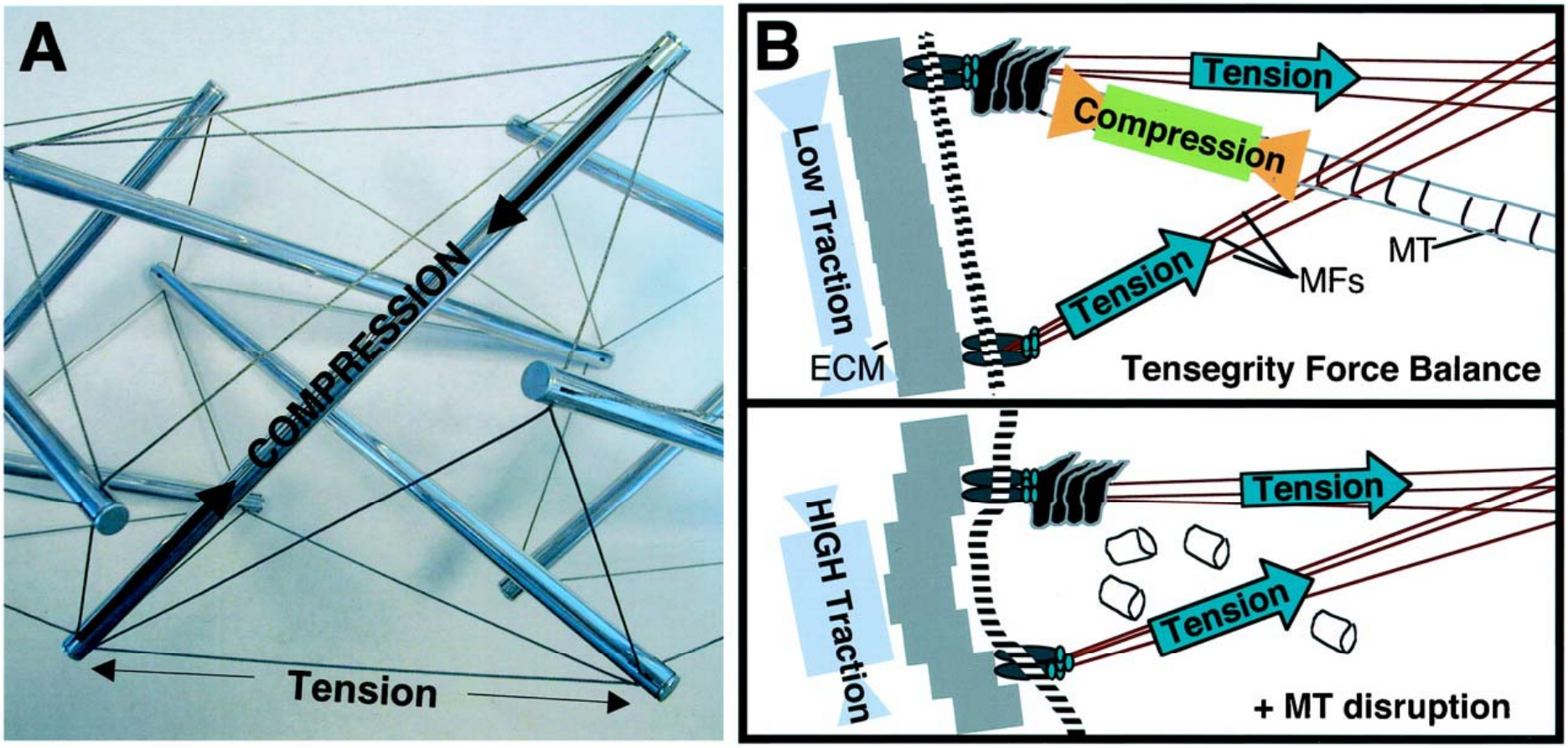


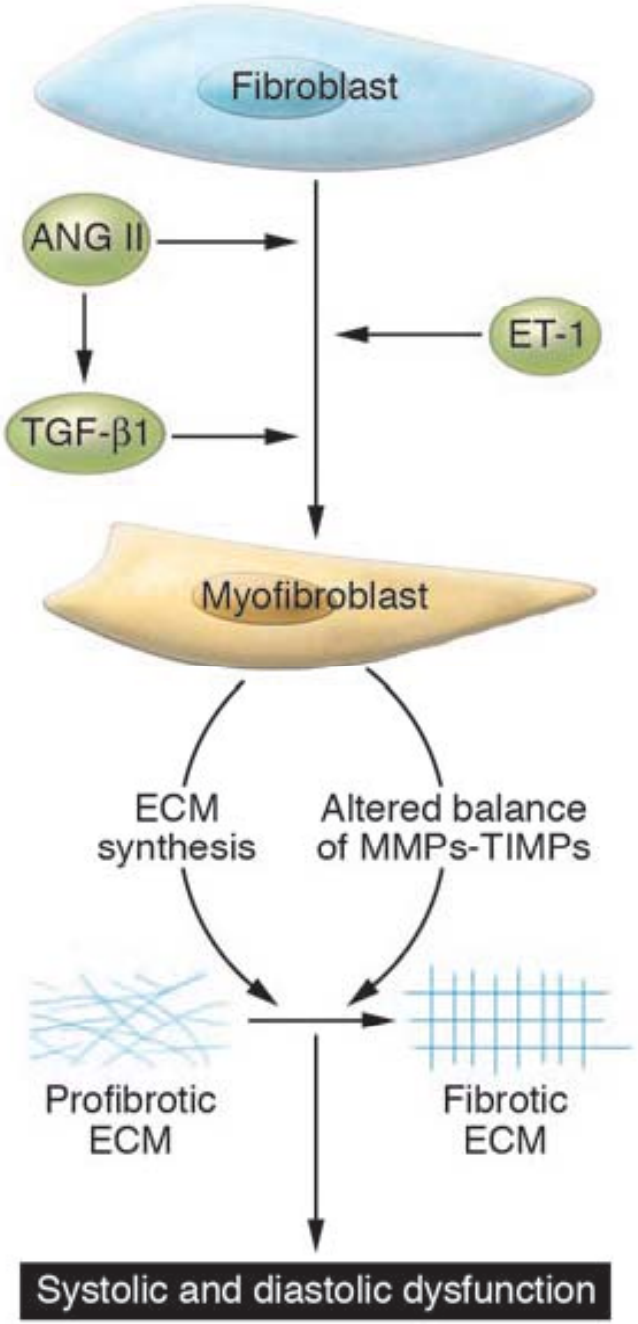
Human Pathology 2009; 40:1365-1376


Fibroblast
Procollagen III
PIIICP
PIIINP
pN-collagen III
Collagen fibril



Desmouliere A, et al. Lab Invest 2003;83:1689-707.


A
COMPRESSION
Tension
B
Tension
Compression
Low Traction
ECM
Tension
MT
MFs
Tensegrity Force Balance
HIGH Traction
Tension
Tension
+ MT disruption

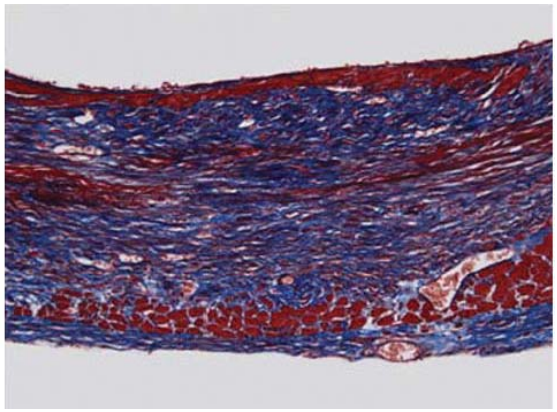


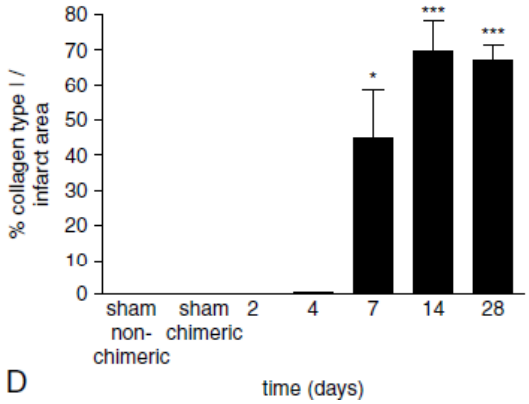
Berk BC, et al J Clin Invest 2007;117:568-575

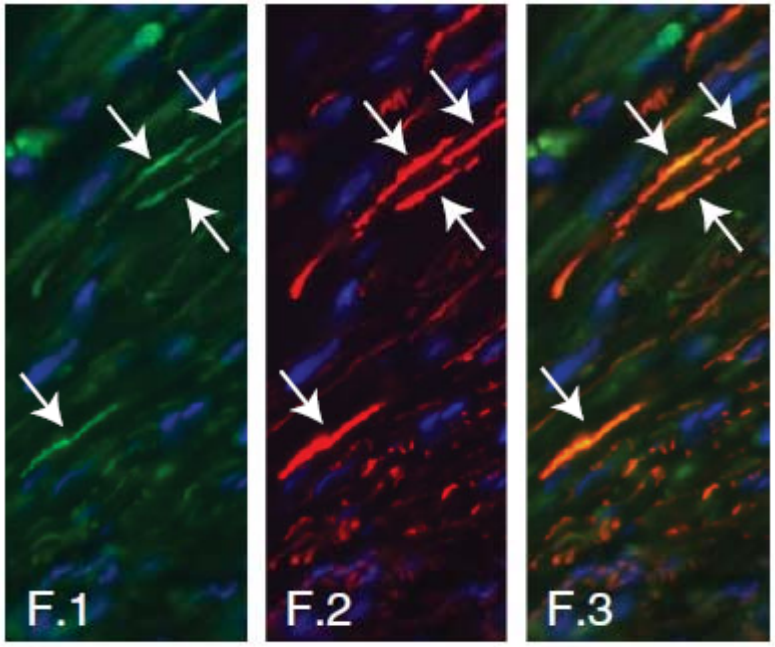
Pathways described for mediating MR signaling

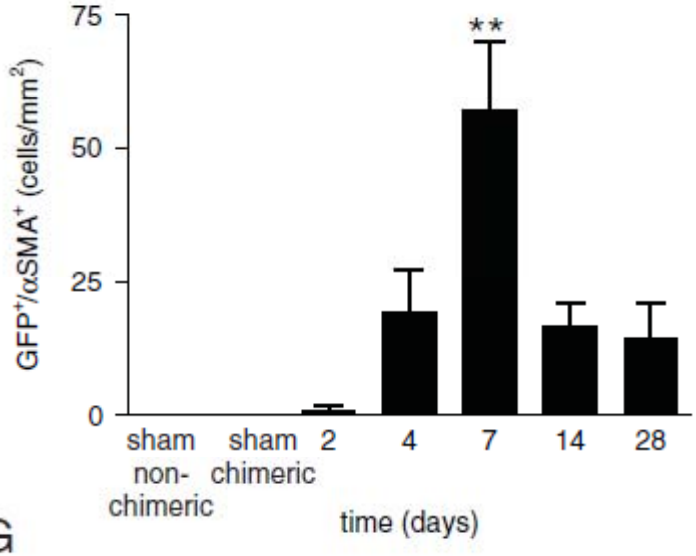
1. Angiotensin signaling
2. Endothelin1
3. Epidermal growth factor receptor (EGFR)
4. Oxidized LDL (Ox-LDL)
5. Lectin-like Ox-LDL receptor 1 (LOX1)
6. Rho-kinase
7. NADPH oxidase

Bone Marrow-derived myofibroblasts in scar formed after MI

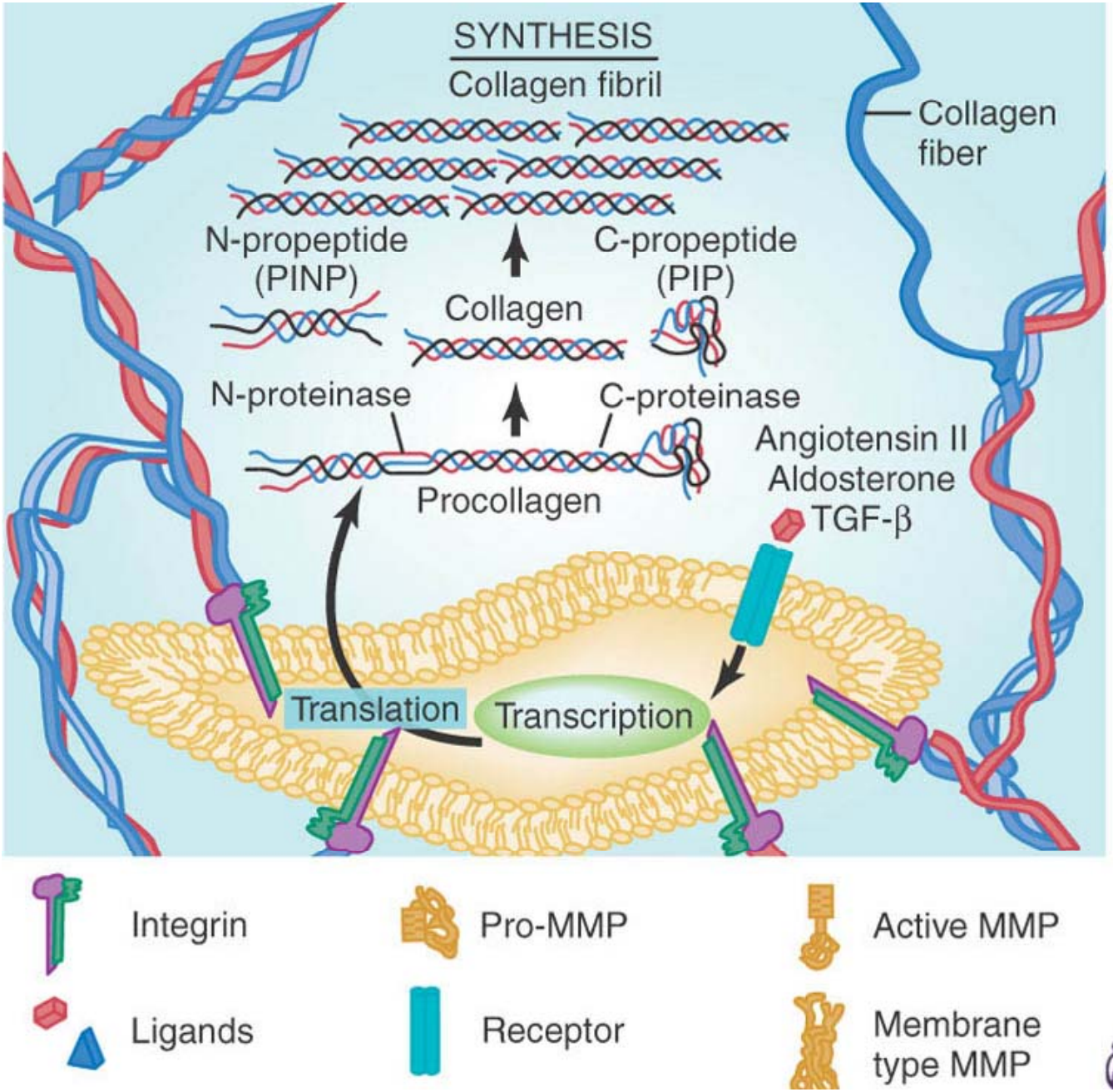


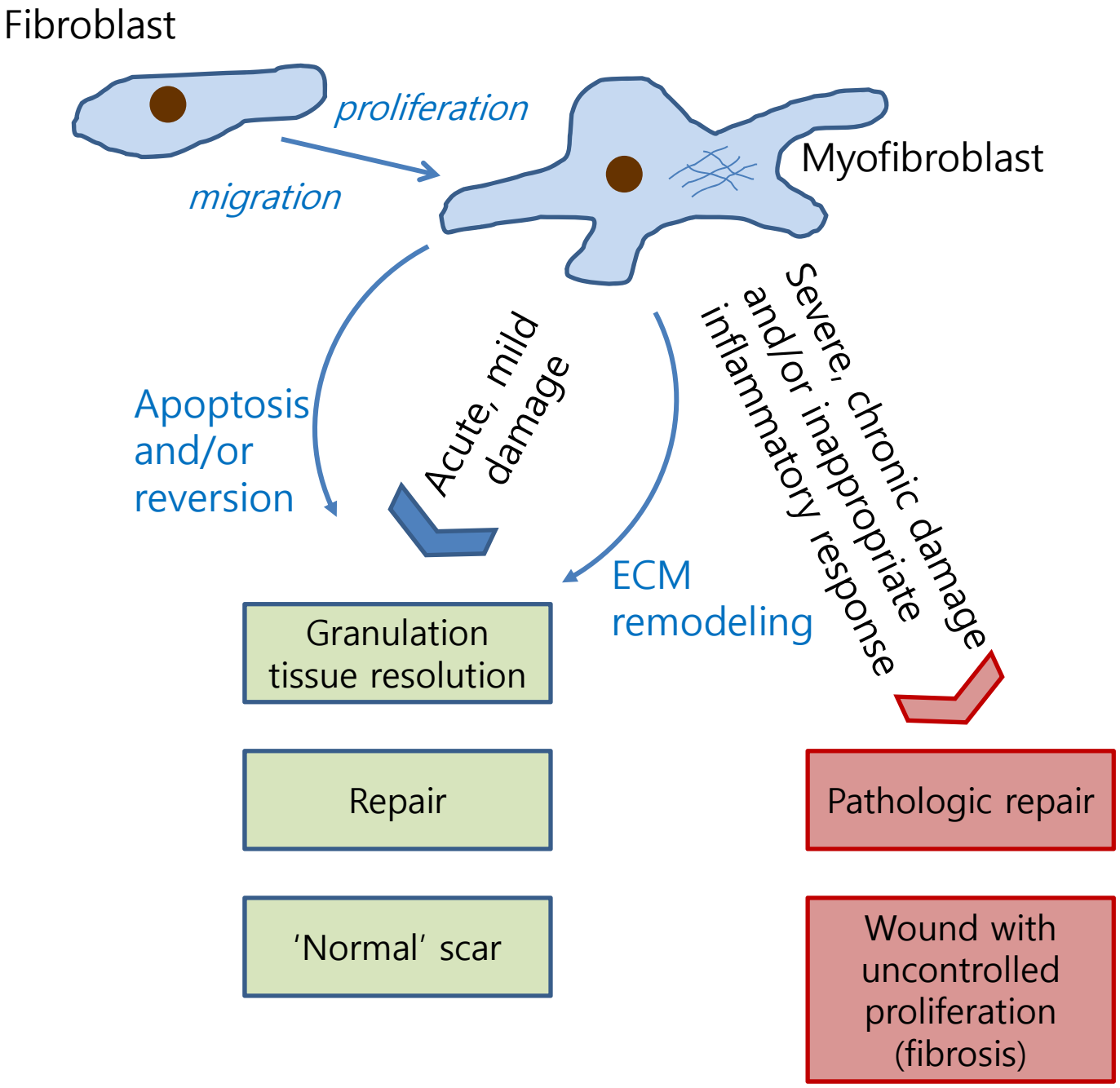






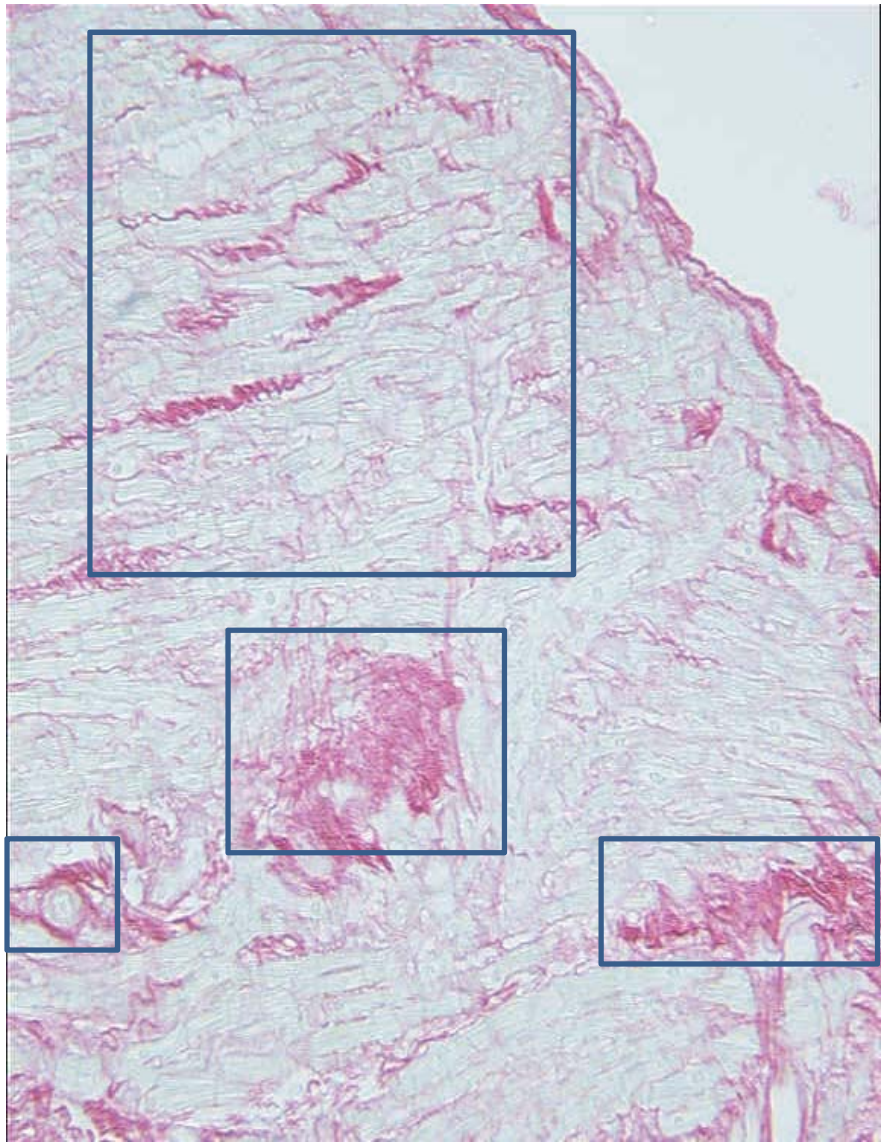
Van Amerongen MJ, et al. J Pathol 2008;214:377-86.


SYNTHESIS
Collagen fibril
Collagen fiber
N-propeptide (PINP)
C-propeptide (PIP)
Collagen
N-proteinase
C-proteinase
Procollagen
Angiotensin II
Aldosterone
TGF-β
Translation
Transcription
Integrin
Ligands
Pro-MMP
Receptor
Active MMP
Membrane type MMP



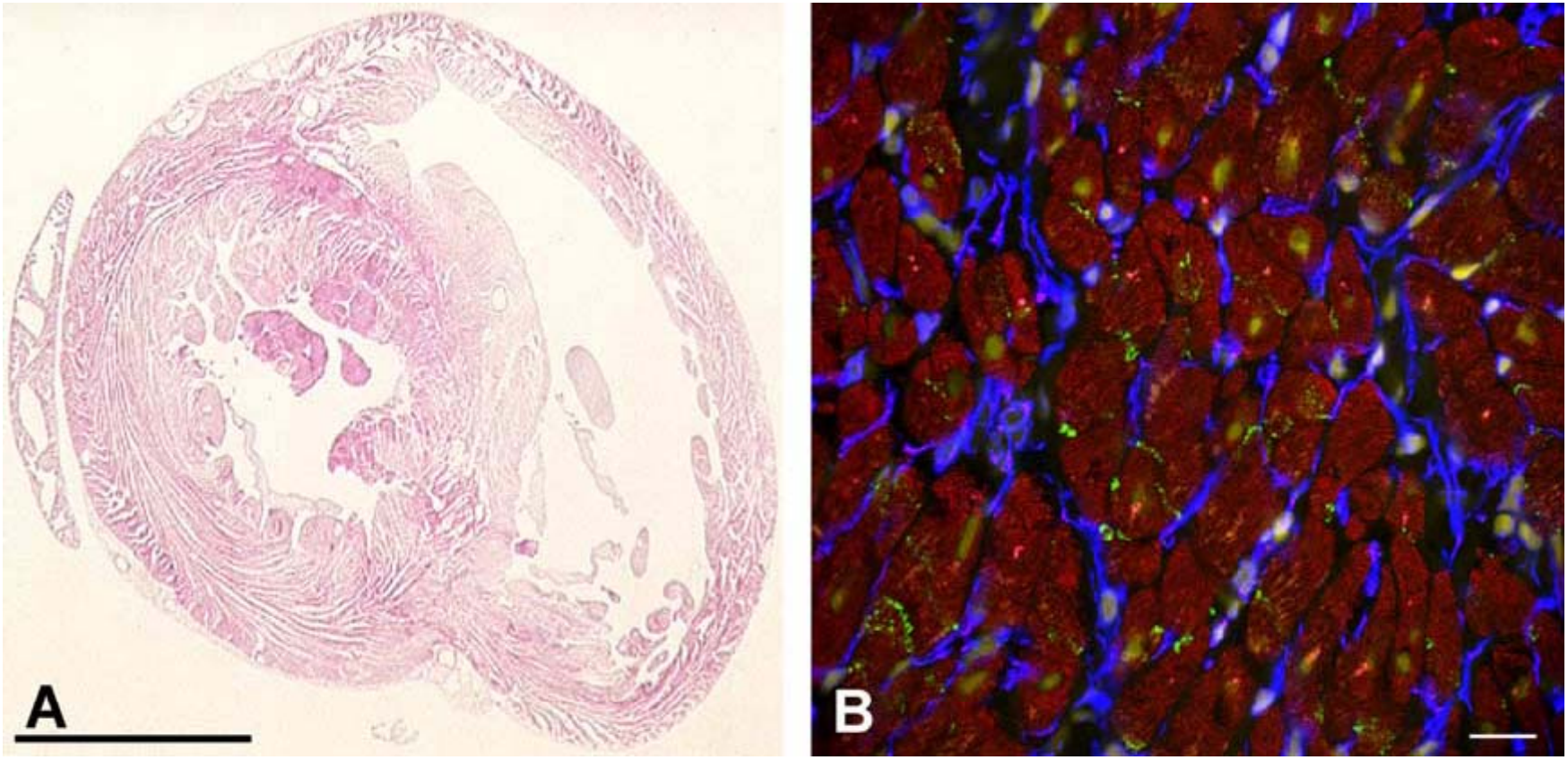
Desmouliere A, et al. Lab Invest 2003;83:1689-707.

Endomyocardium in a hypertensive patient; Picorsirius red staining



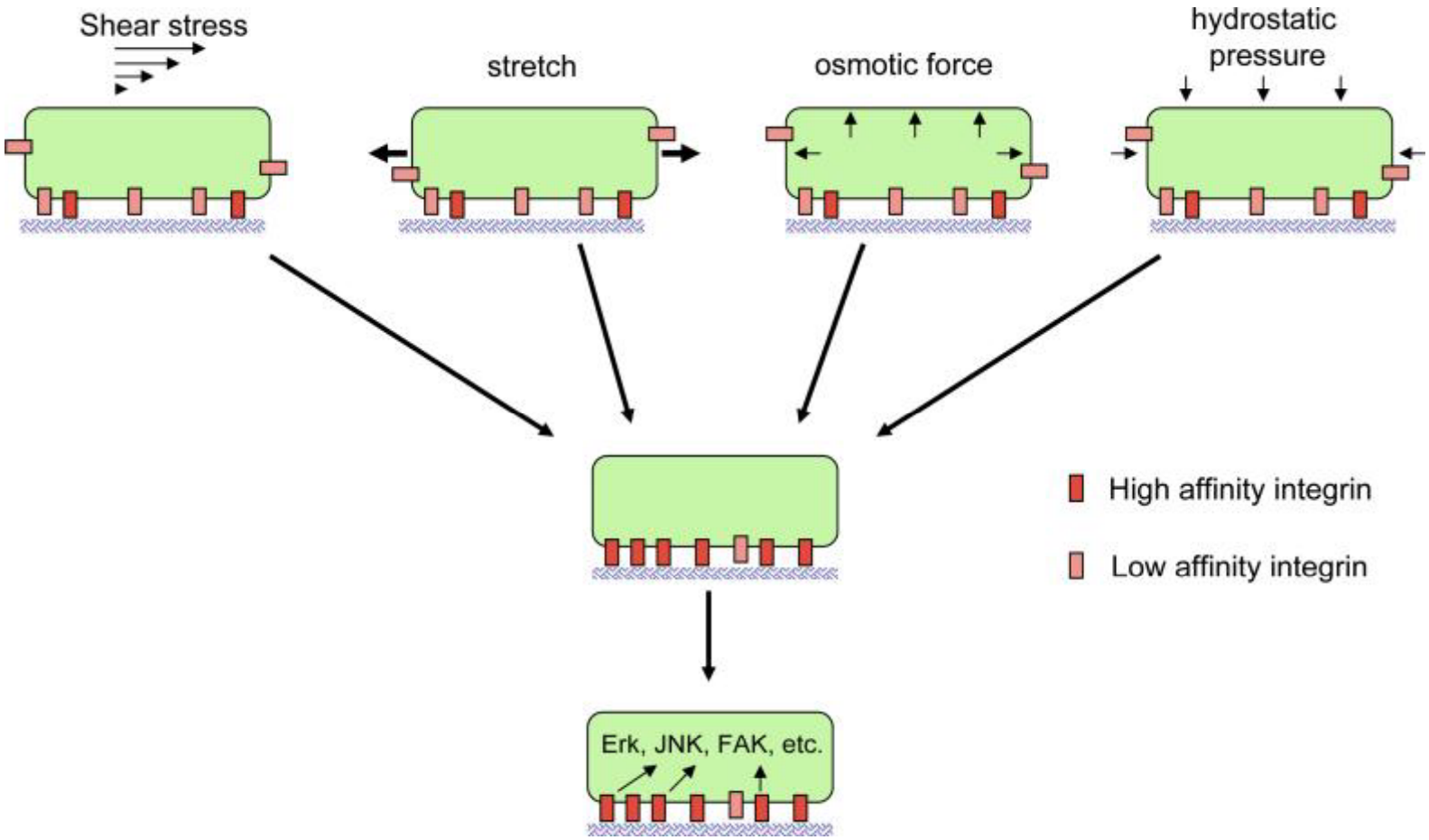
Diez J. J Clin Hypertens 2007;9:546-50.

Cardiac Fibroblasts



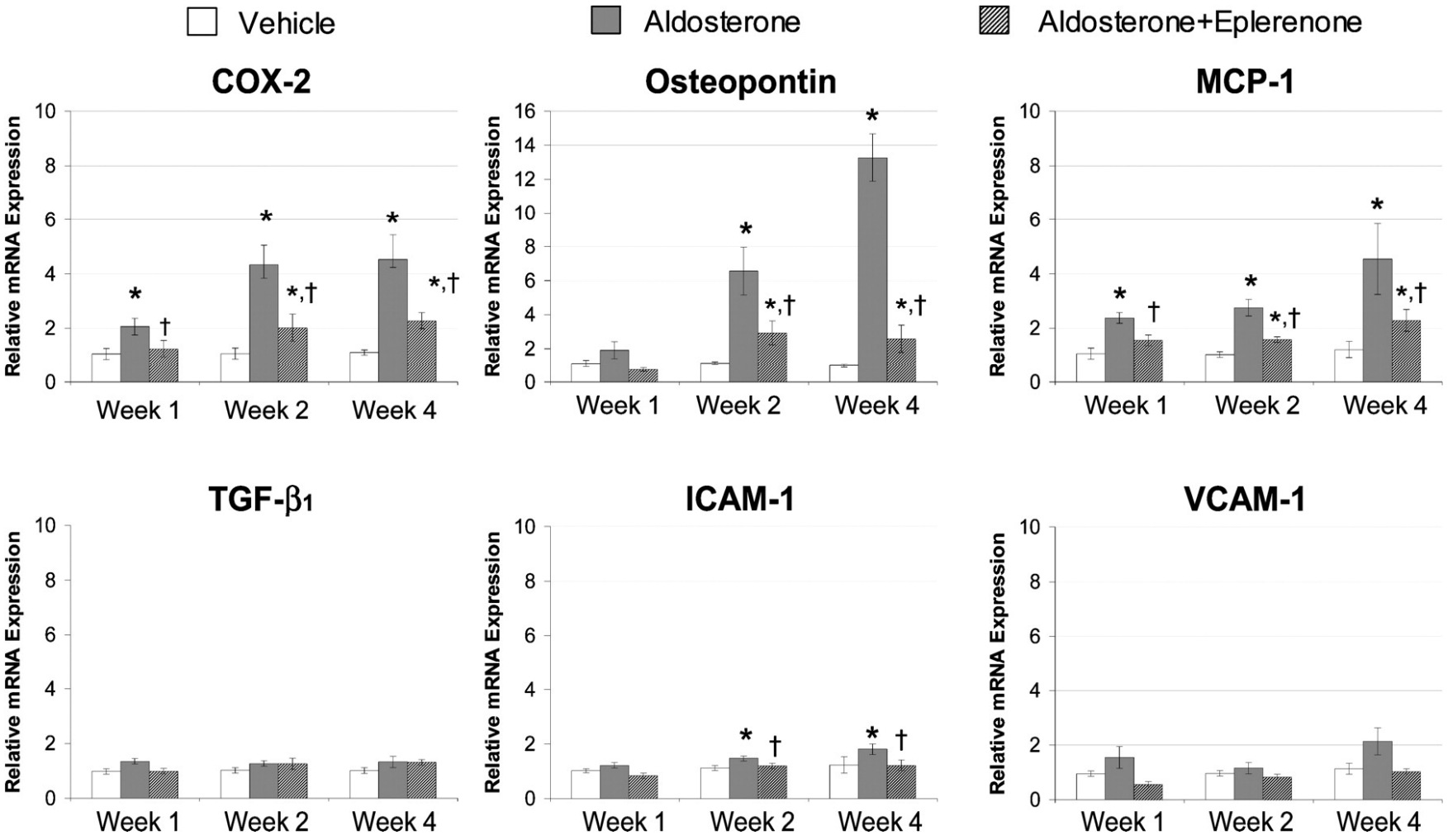
Camelliti P. Cardiovac Res 2005;65:40-51.

Model for common pathways in mechanotransduction



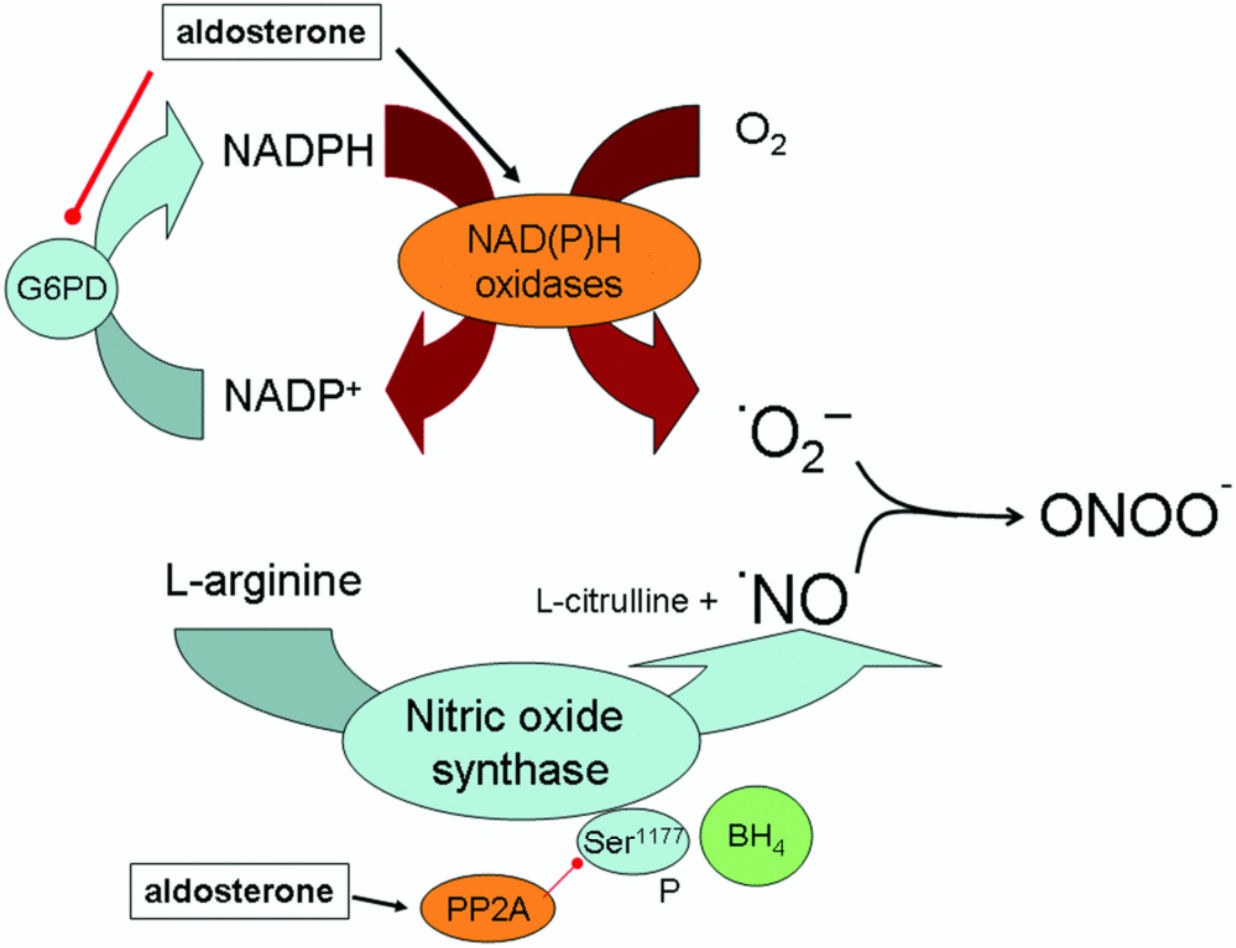
Schwartz MA, et al. Curr Opin Cell Biol 2008;20:551-56.

Aldosterone induces a vascular inflammatory phenotype in the rat heart



Rocha R, et al. Am J Physiol Heart Circ Physiol 202;283:H1802-10.

Aldosterone induces oxidative stress and endothelial dysfunction



Marney AM, et al. Clin Sci 2007;113:267.