Mechanisms of Repair Following Myocardial Injury

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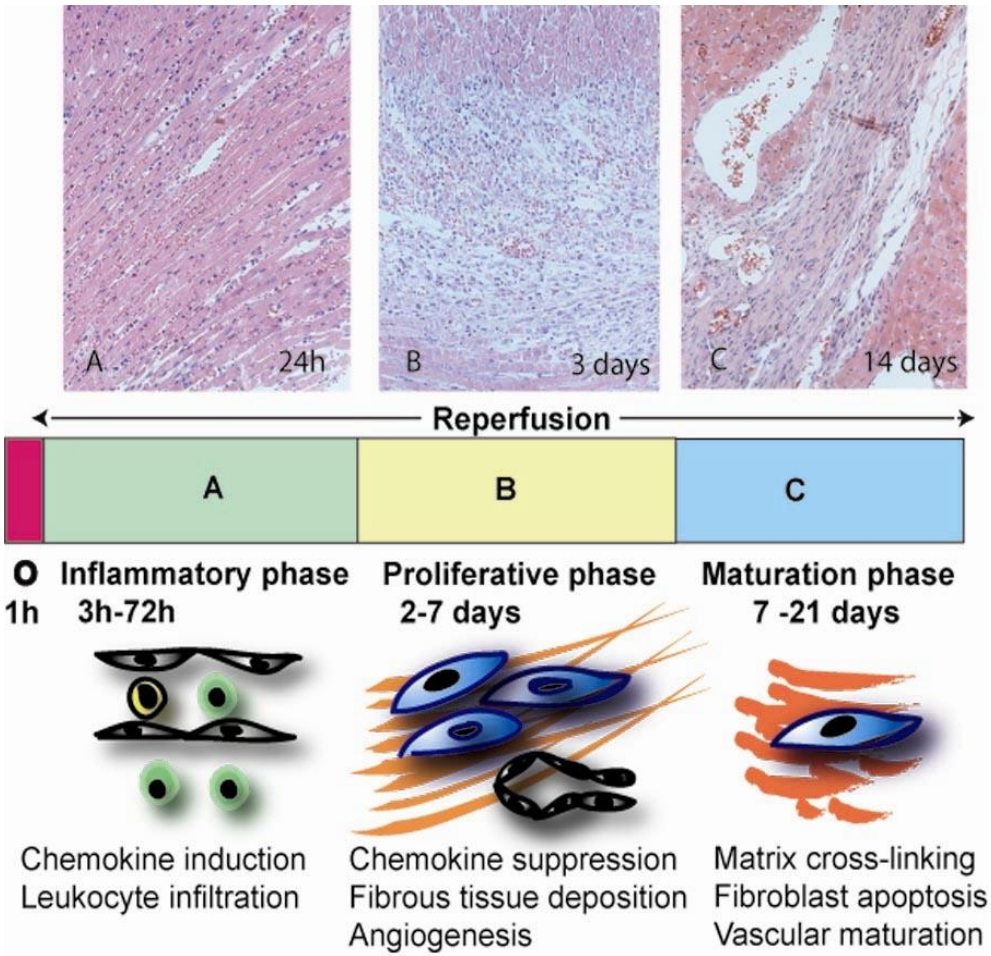
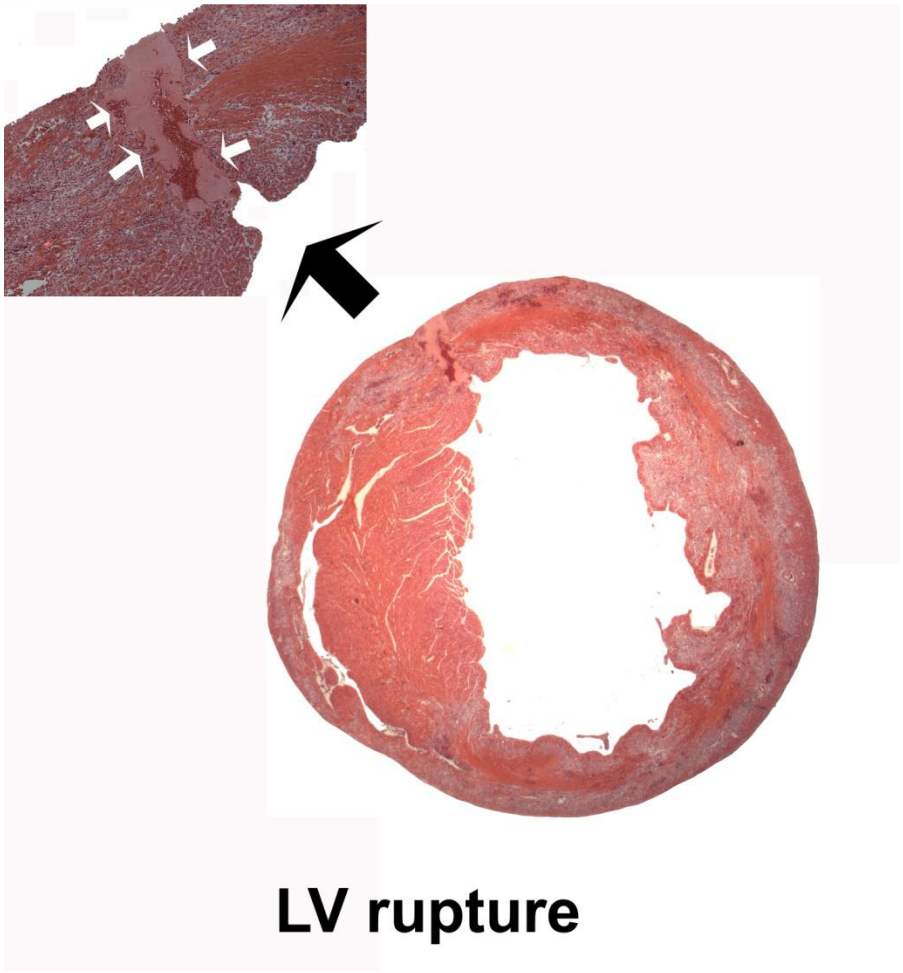
The Phases of Infarct Healing: Infarct Healing Depends on an Inflammatory Response

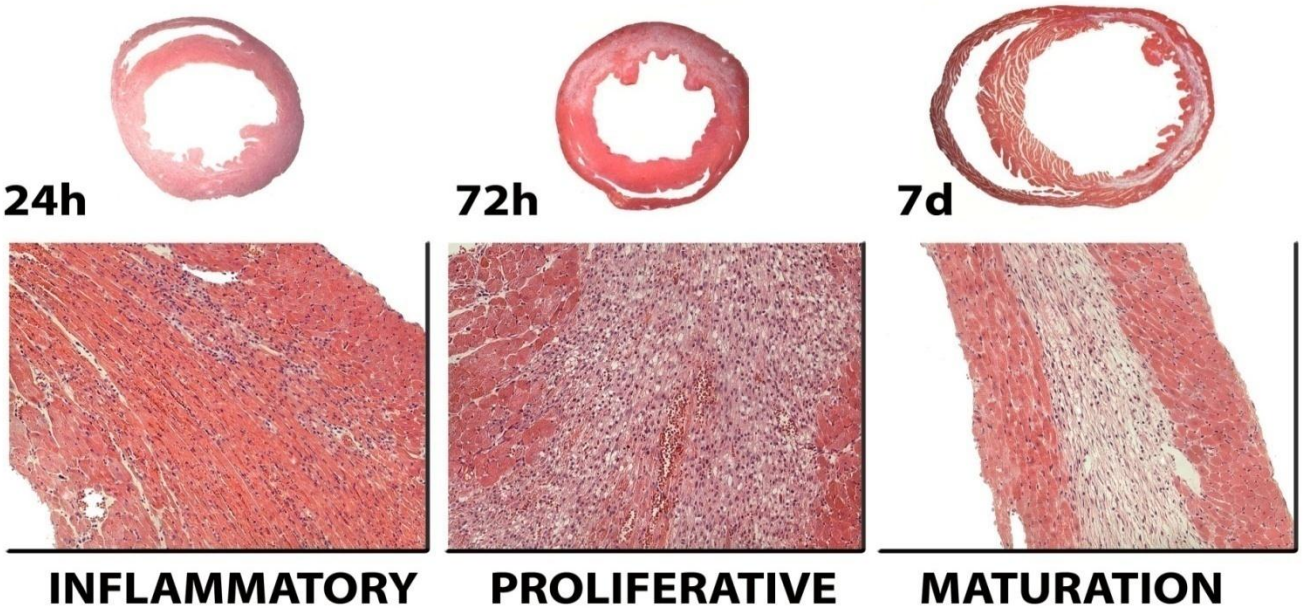


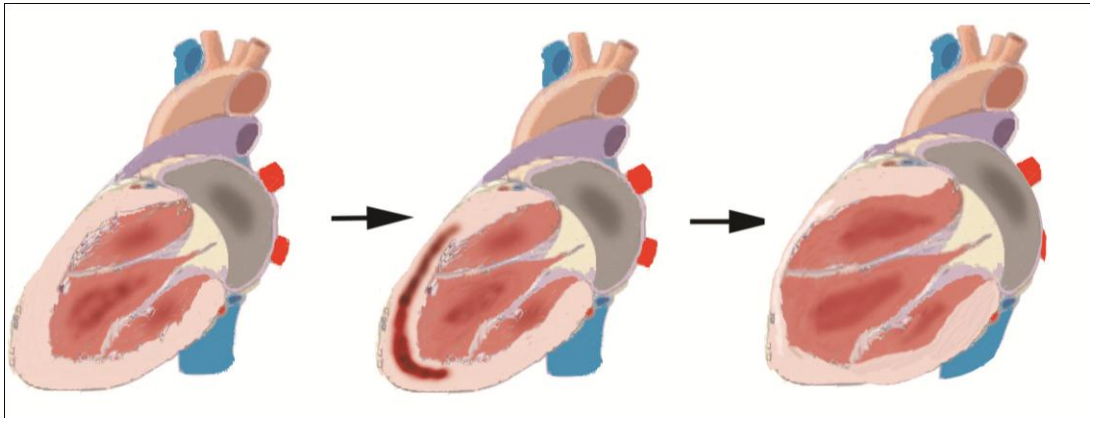
Defective cardiac repair may result in catastrophic acute complications



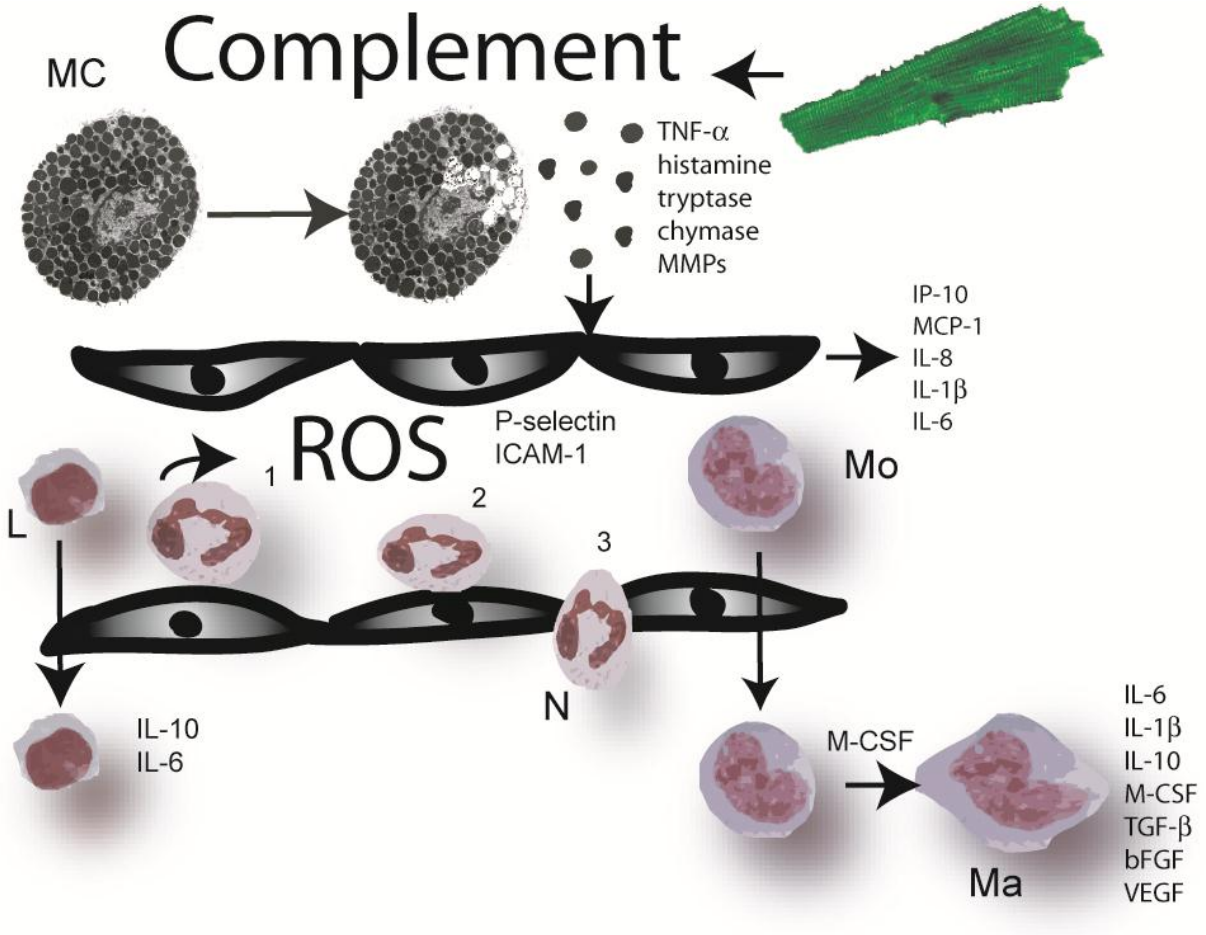
LV rupture

Infarct Healing and the inflammatory reaction are Intertwined with Ventricular Remodeling



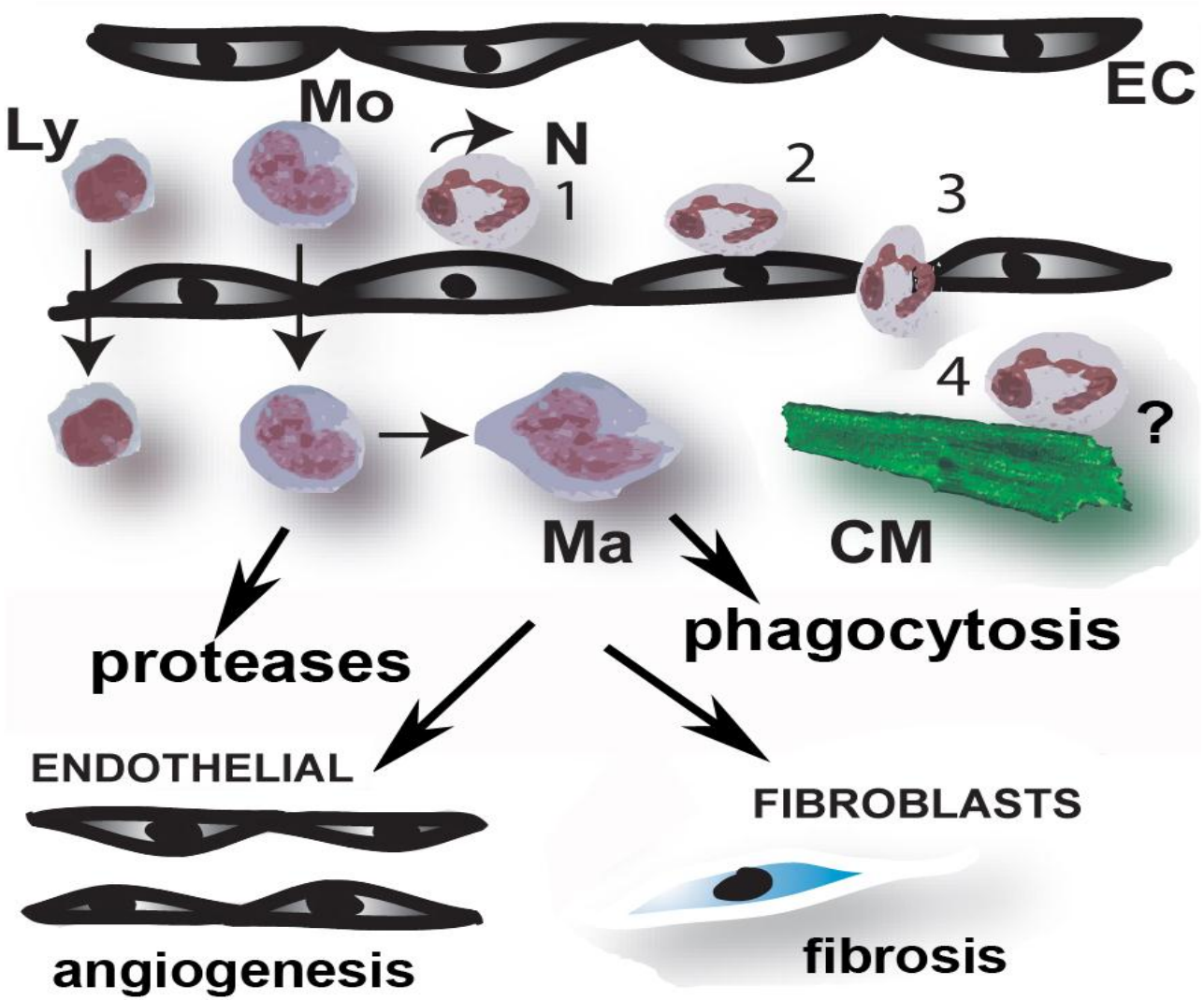


Initiation of the Inflammatory Cascade

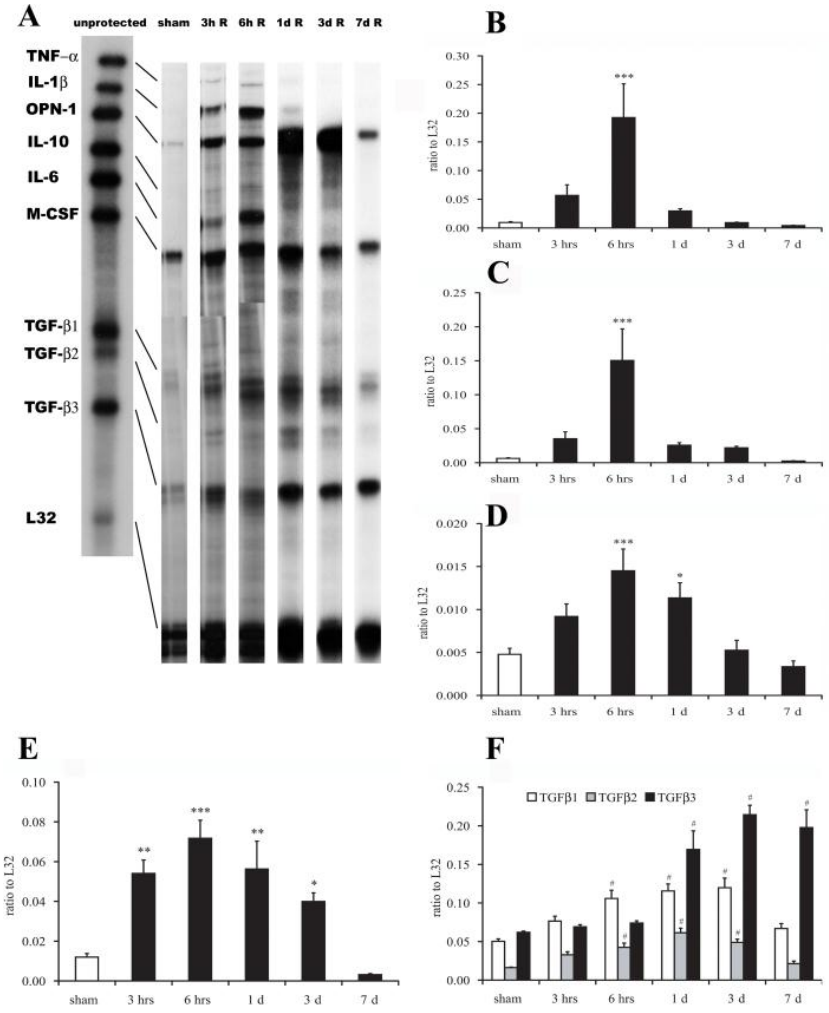


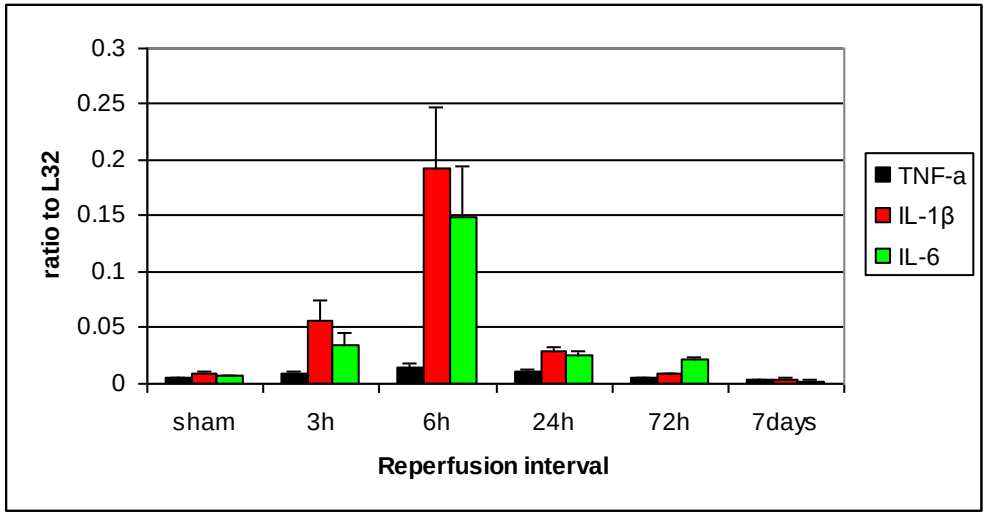
- The complement cascade
- Reactive Oxygen Species (ROS)
- TLR-mediated pathways
- NF–κB activation

Inflammatory leukocytes in infarct healing

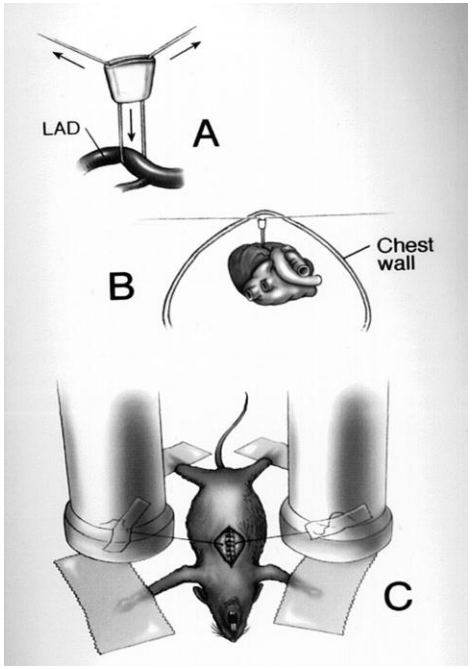


Cytokine induction in murine infarcts

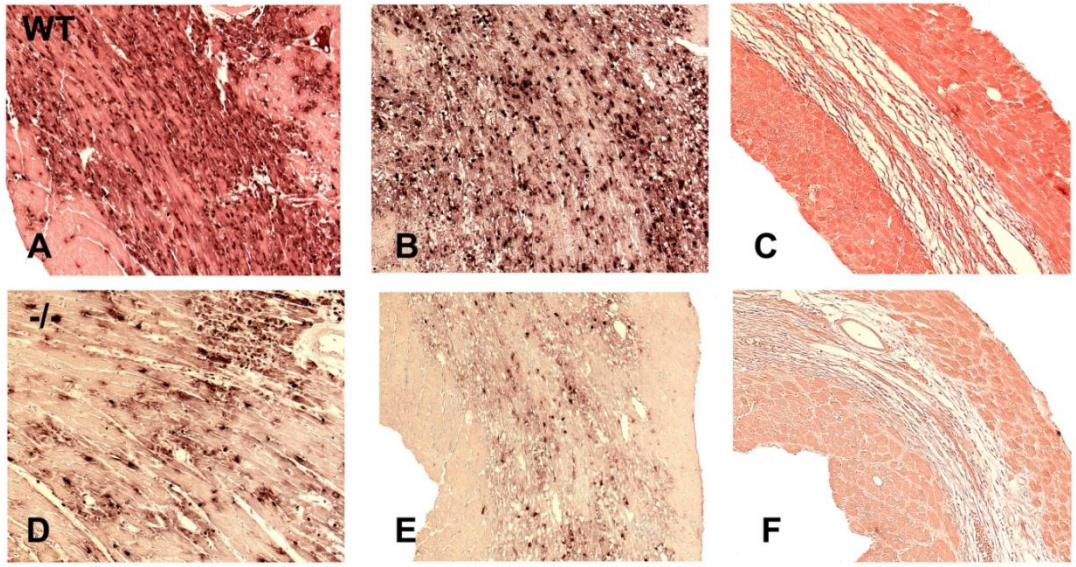


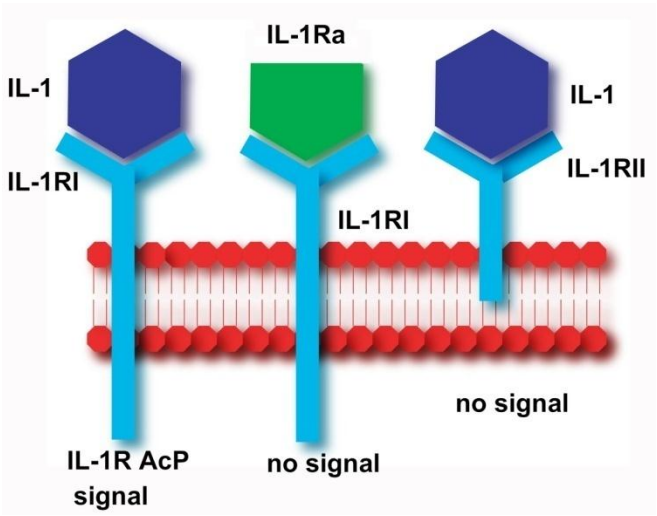


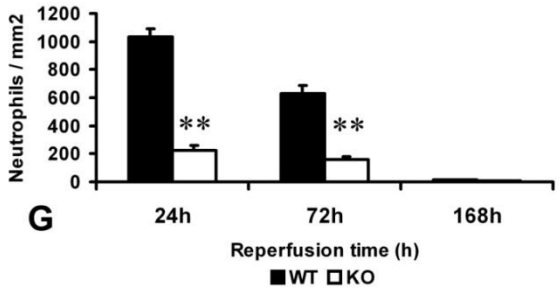
•Dewald et al. Am J Pathol 2004



Defective IL-1 signaling results in markedly attenuated post-infarction inflammation

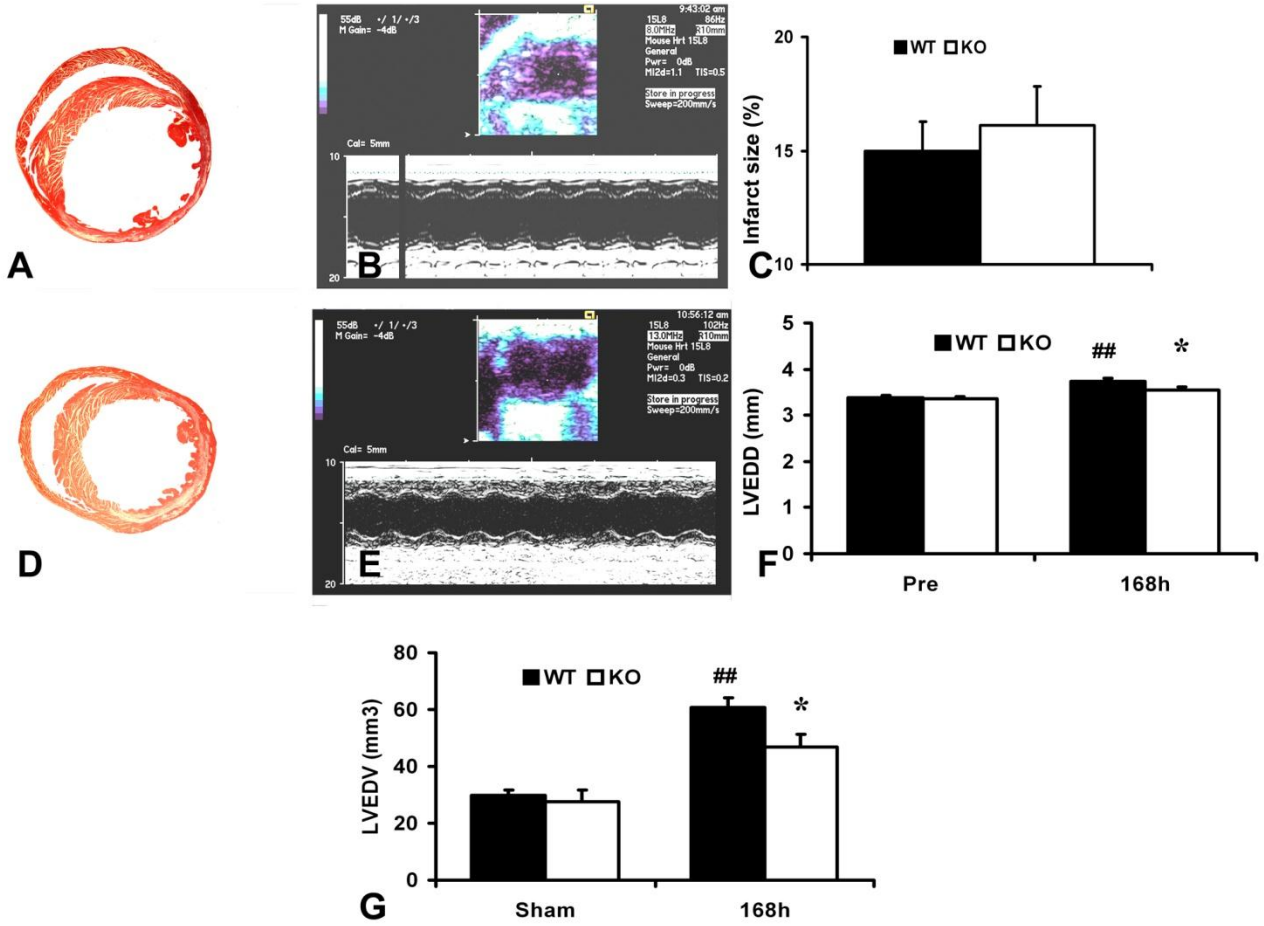






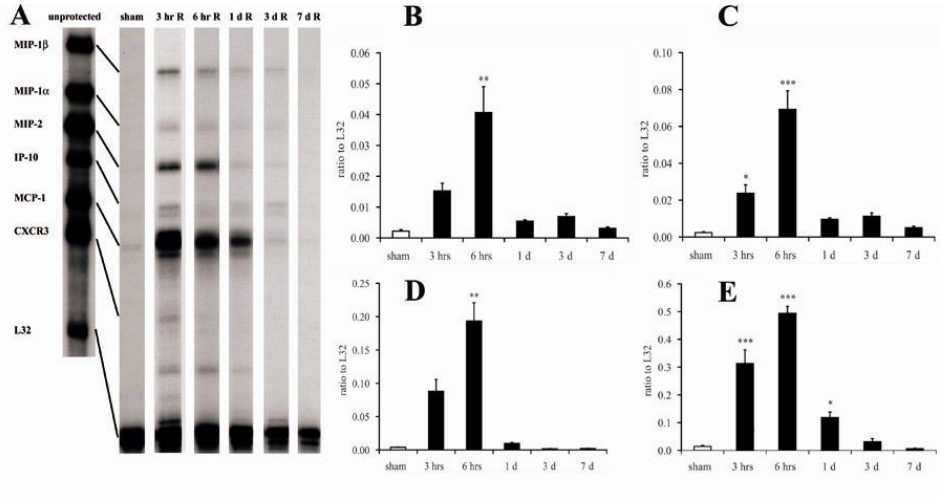
- Bujak et al. Am J Pathol 2008

Disruption of IL-1 signaling results in attenuated remodeling without affecting the size of the infarct

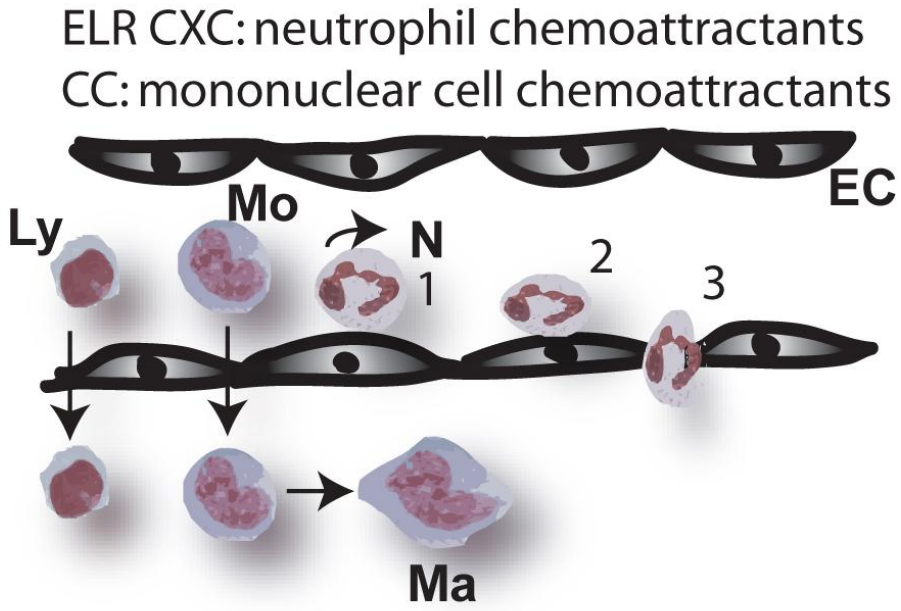


IL-1 signaling does not accentuate ischemic cardiomyocyte injury, but enhances adverse remodeling by increasing MMP expression

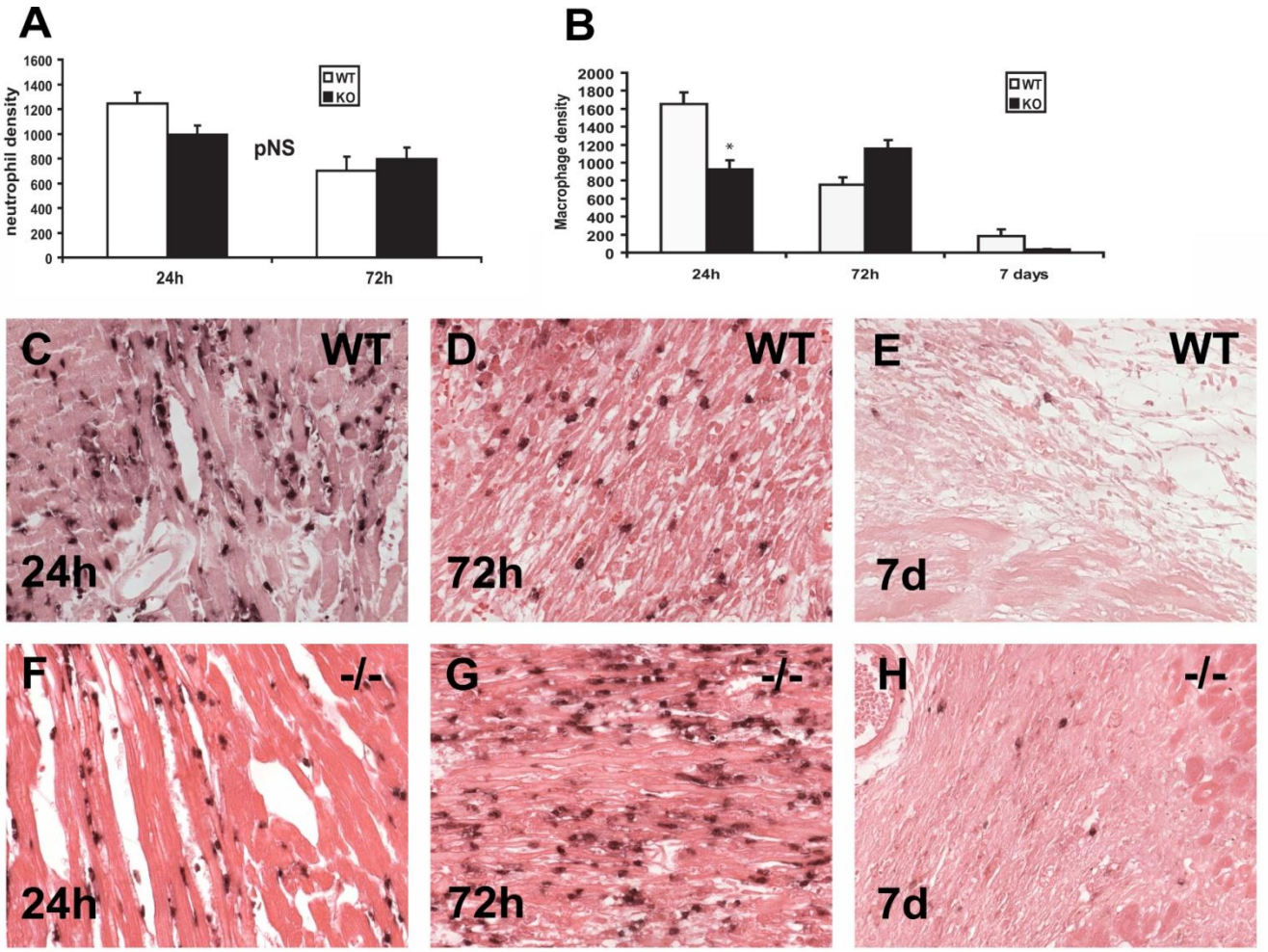
Chemokine induction in mouse infarcts



Dewald et al., Am J Pathol 2004

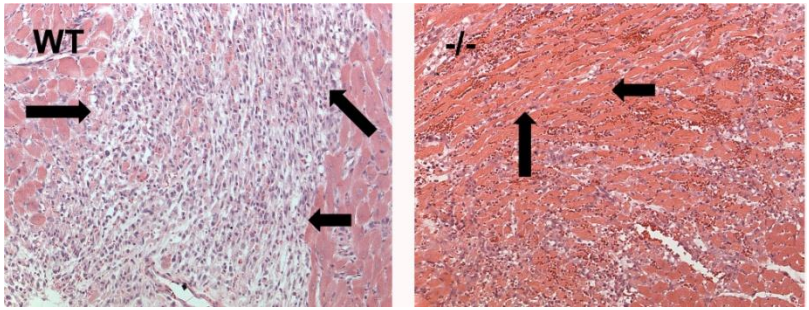


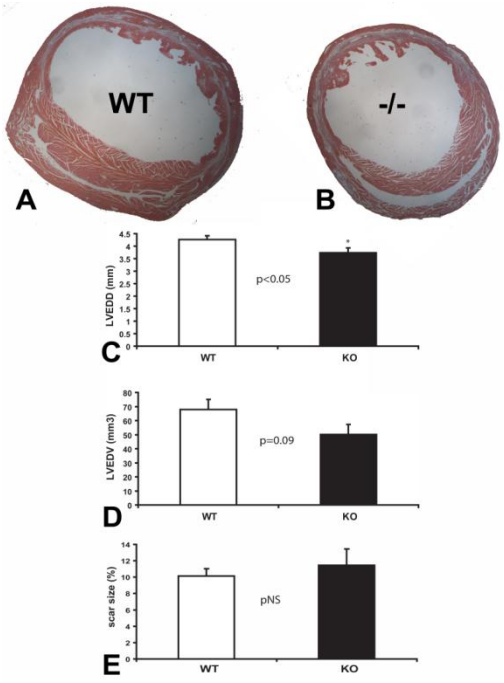
MCP-1 -/- mice exhibit decreased and delayed macrophage recruitment in the infarct

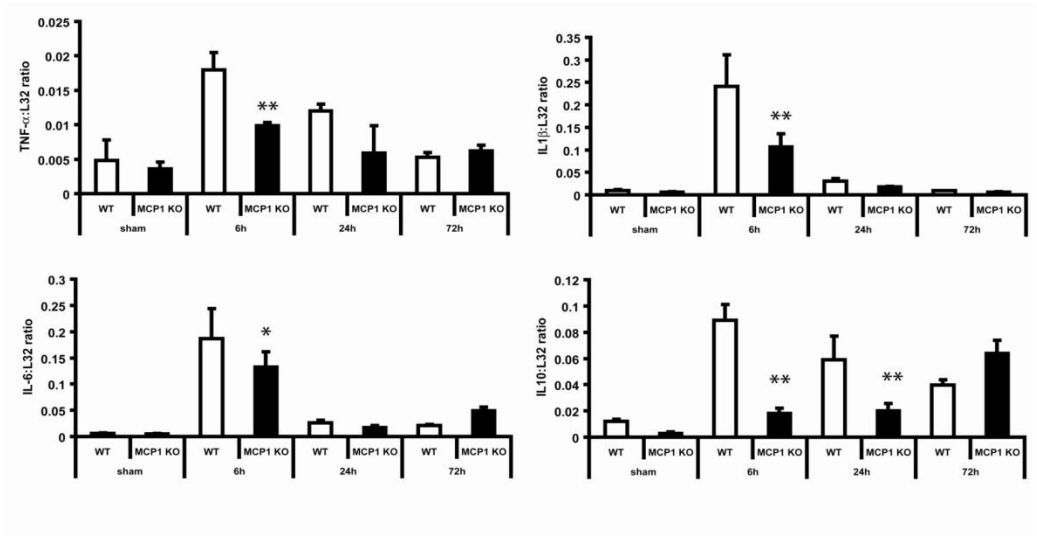


(Dewald et al., Circ Res 2005)

MCP-1 -/- mice show delayed granulation tissue formation





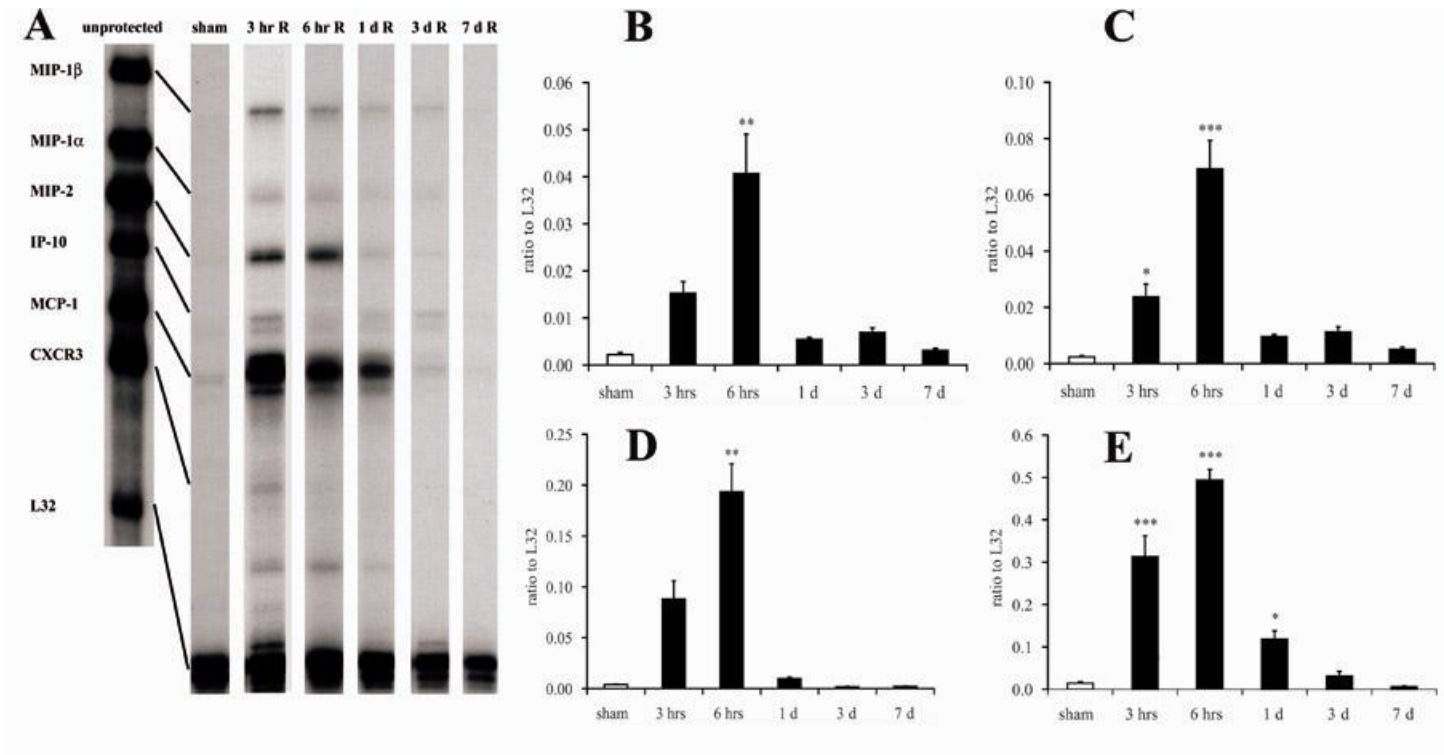


Dewald et al. Circ Res 2005

Conclusion

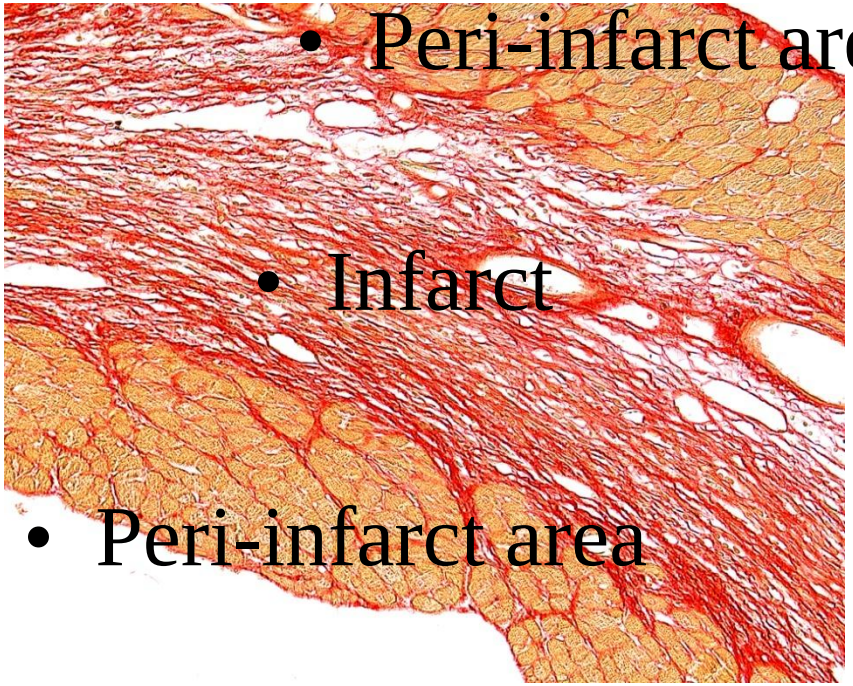
- Abrogation of key pro-inflammatory pathways does not save cardiomyocytes, but prevents adverse remodeling, possibly due to attenuation of MMP activity and reduced matrix degradation.

Optimal Healing Requires Timely Resolution of Inflammation



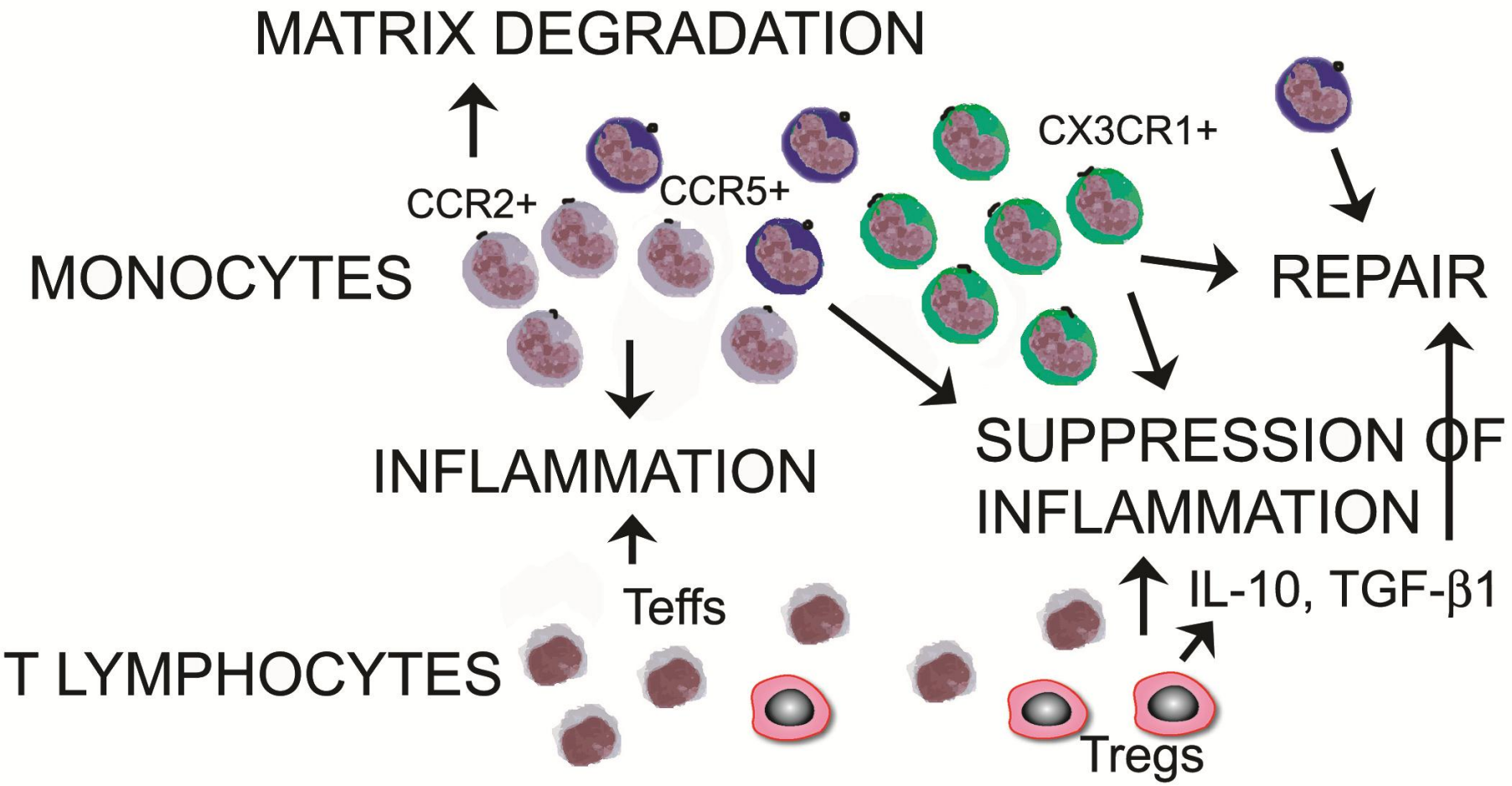
The Catastrophic Consequences of Uncontrolled Inflammation in the Infarcted Heart

- Extension of the inflammatory reaction beyond the infarct.
- Extensive matrix degradation resulting in a less supportive scar.
- Persistent upregulation of mediators with adverse functional effects.
- Activation of pro-apoptotic pathways by inflammatory mediators.

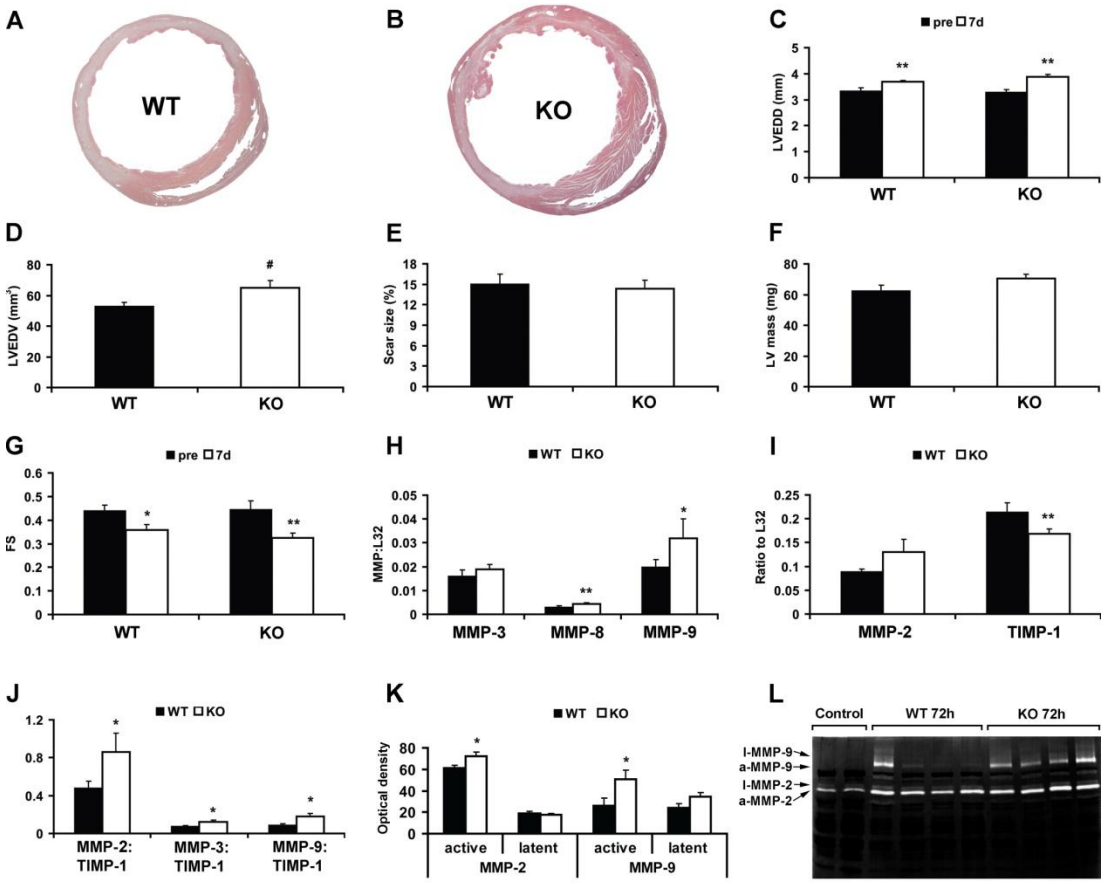


- Activation of endogenous “stop signals” that suppress inflammation may protect from adverse remodeling.

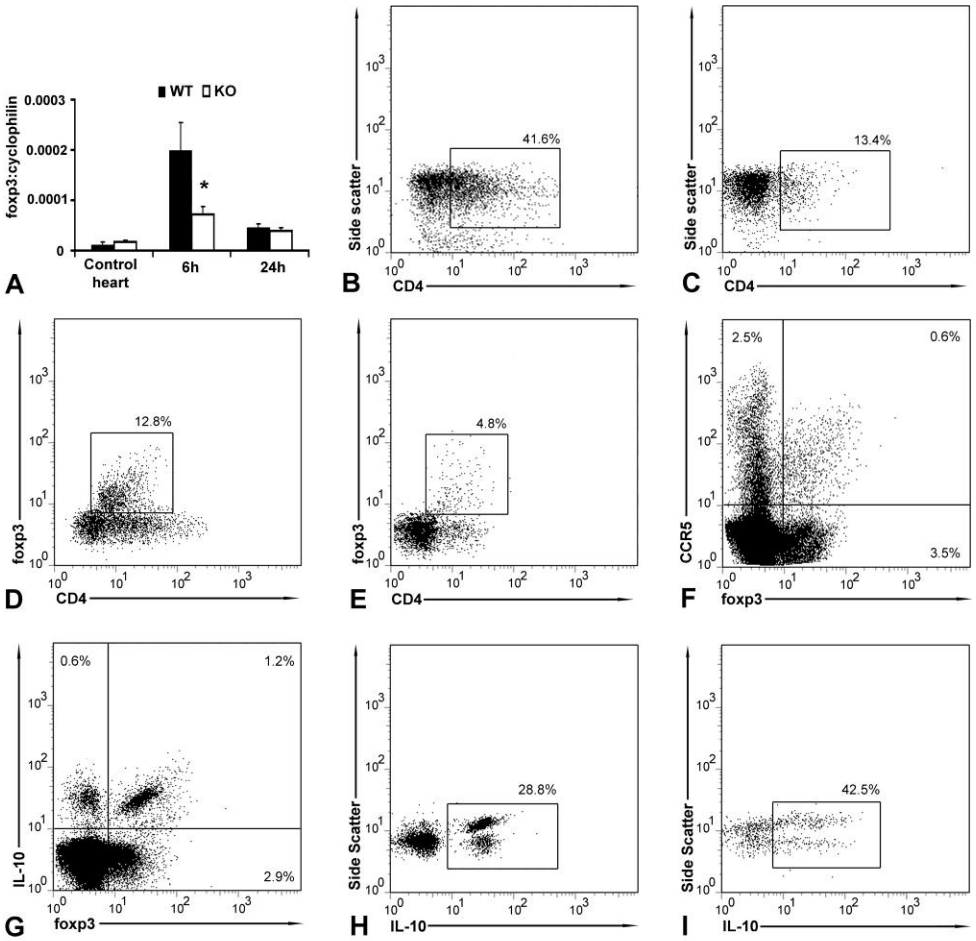
The cellular effectors of suppression of inflammation: mononuclear cell subsets with inhibitory properties



Enhanced inflammation in CCR5 -/- infarcts is associated with increased MMP expression and accentuated remodeling

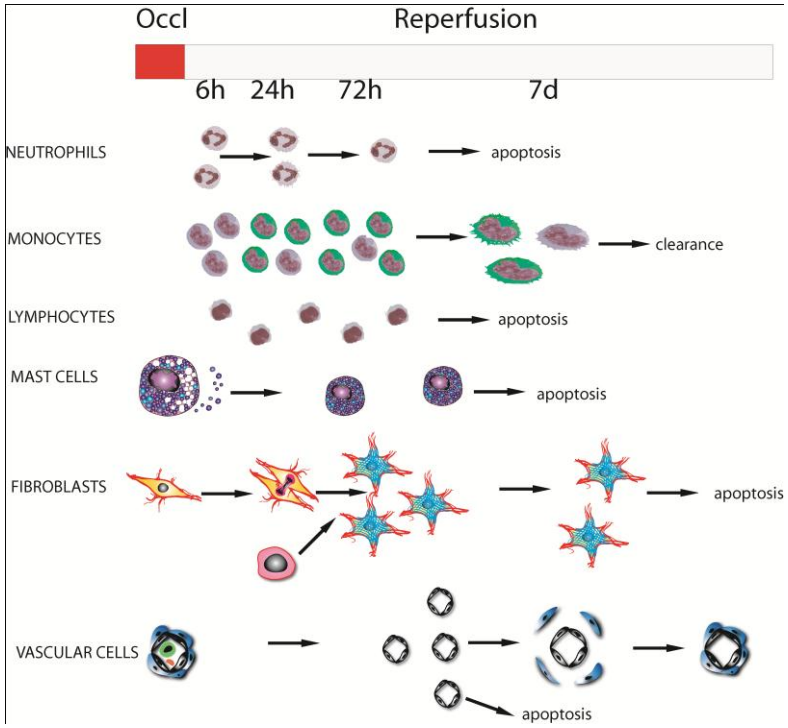


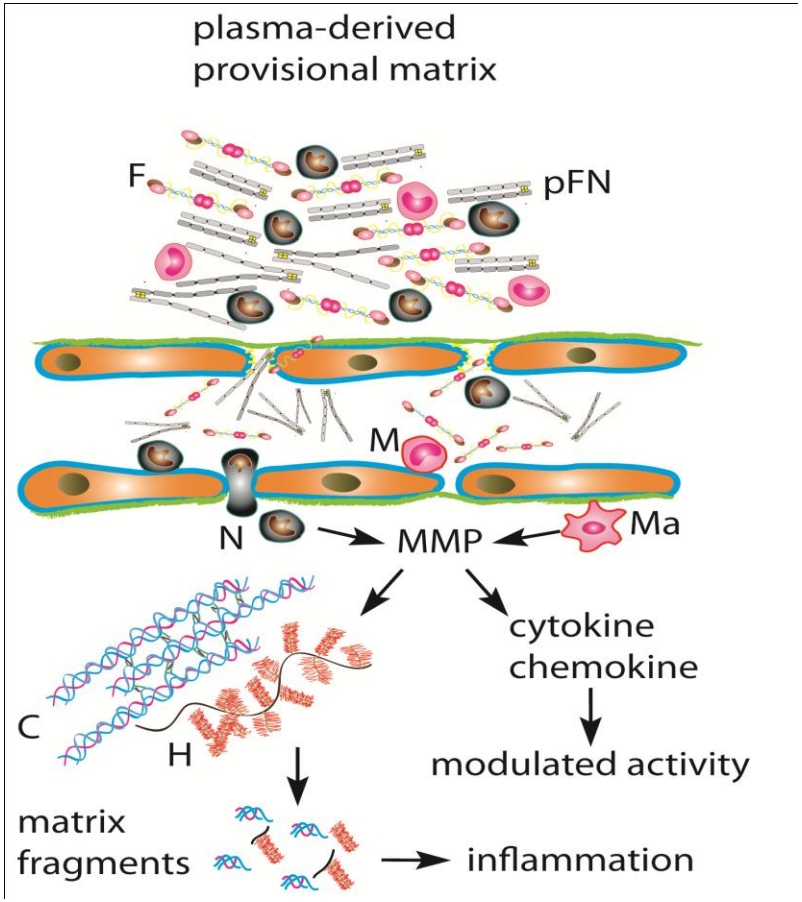
Accentuated inflammation in CCR5 null infarcts is associated with impaired recruitment of Tregs



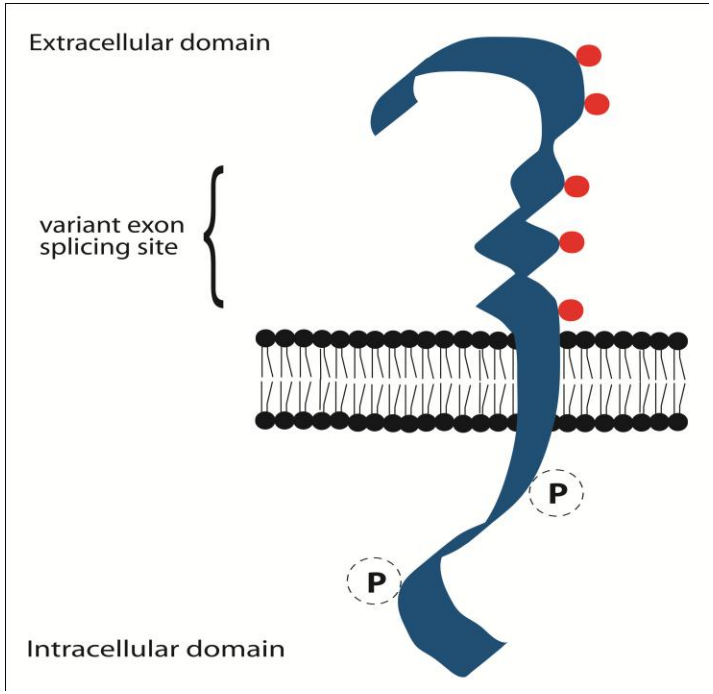
Dobaczewski et al. Am J Pathol 2010

Additional molecular pathways for resolution of inflammation may be mediated through clearance of dead cells



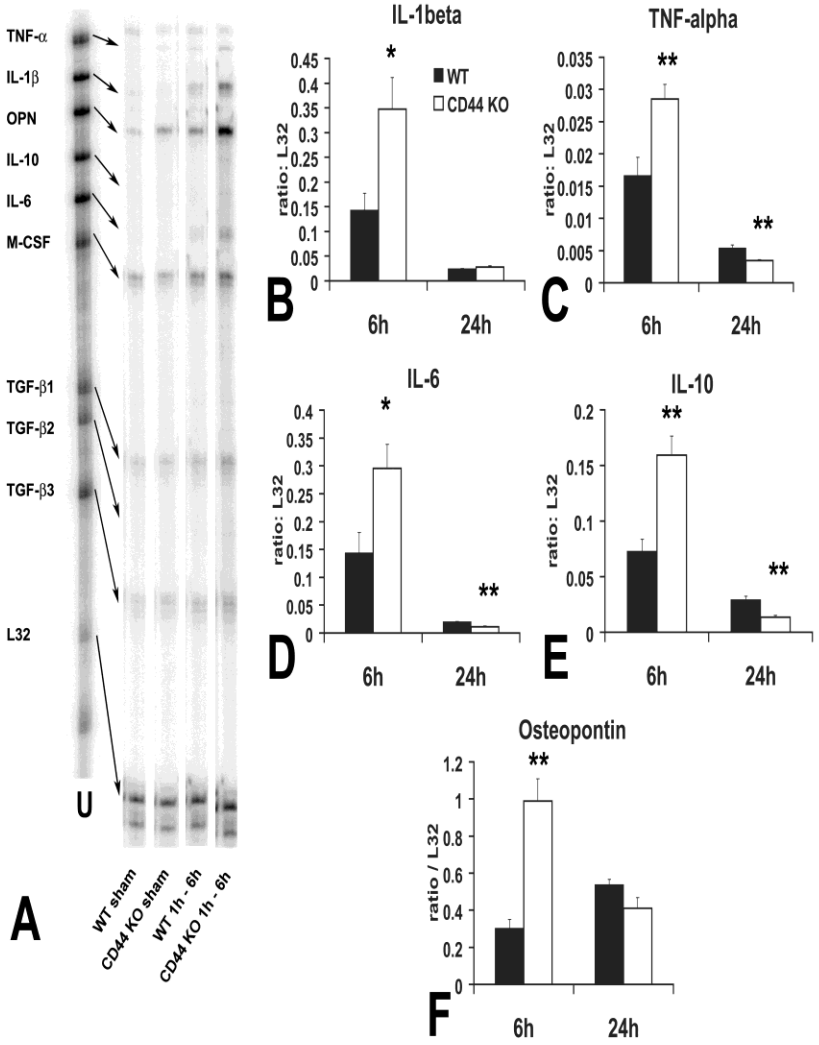


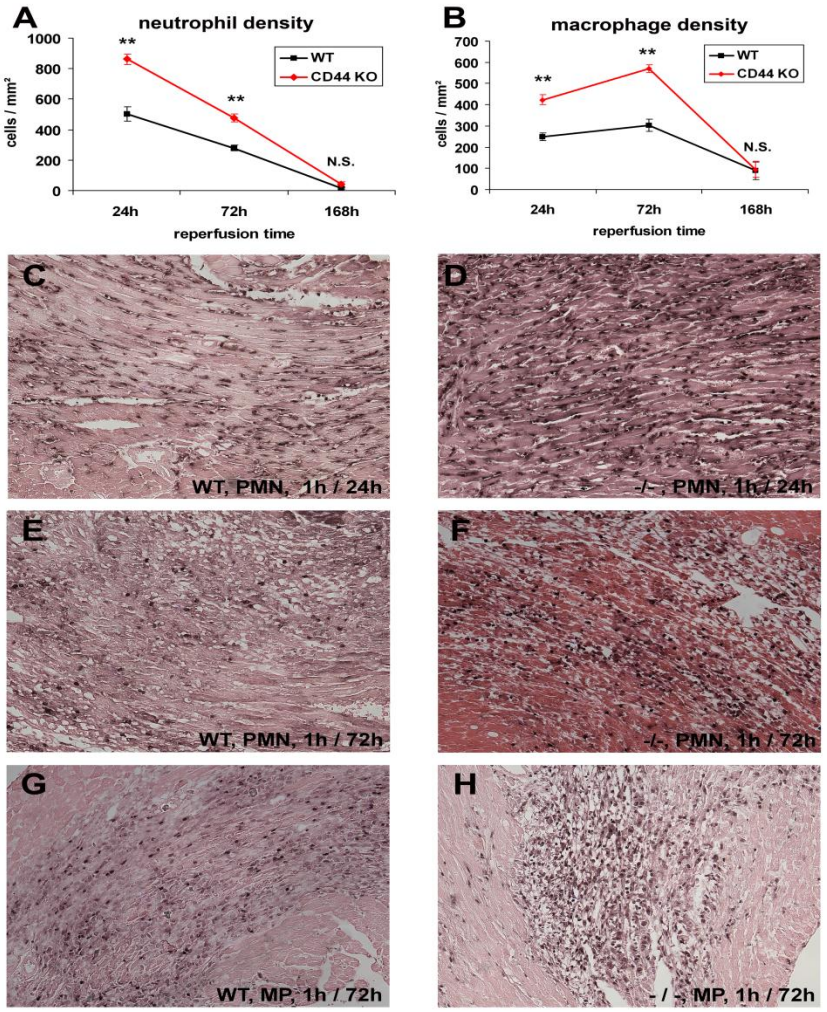
Clearance of matrix fragments may be essential for regulation of the post-infarction inflammatory response: the role of CD44 in clearance of hyaluronan fragments



- In the absence of CD44 impaired clearance of low molecular weight hyaluronan fragments may result in prolonged inflammatory chemokine synthesis and adverse remodeling.

CD44 null mice exhibit enhanced peak inflammation following infarction



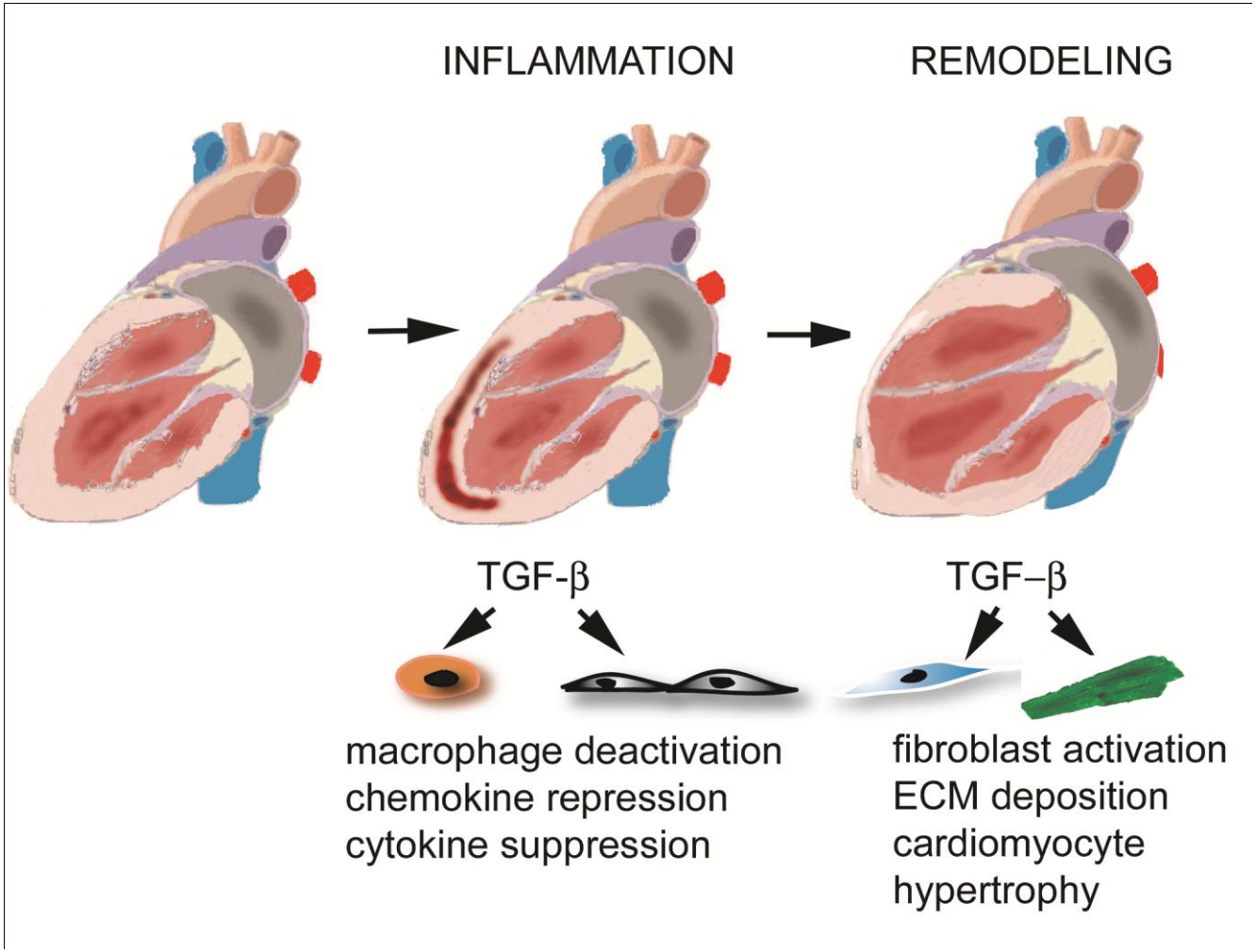


Huebener et al. J Immunol 2008

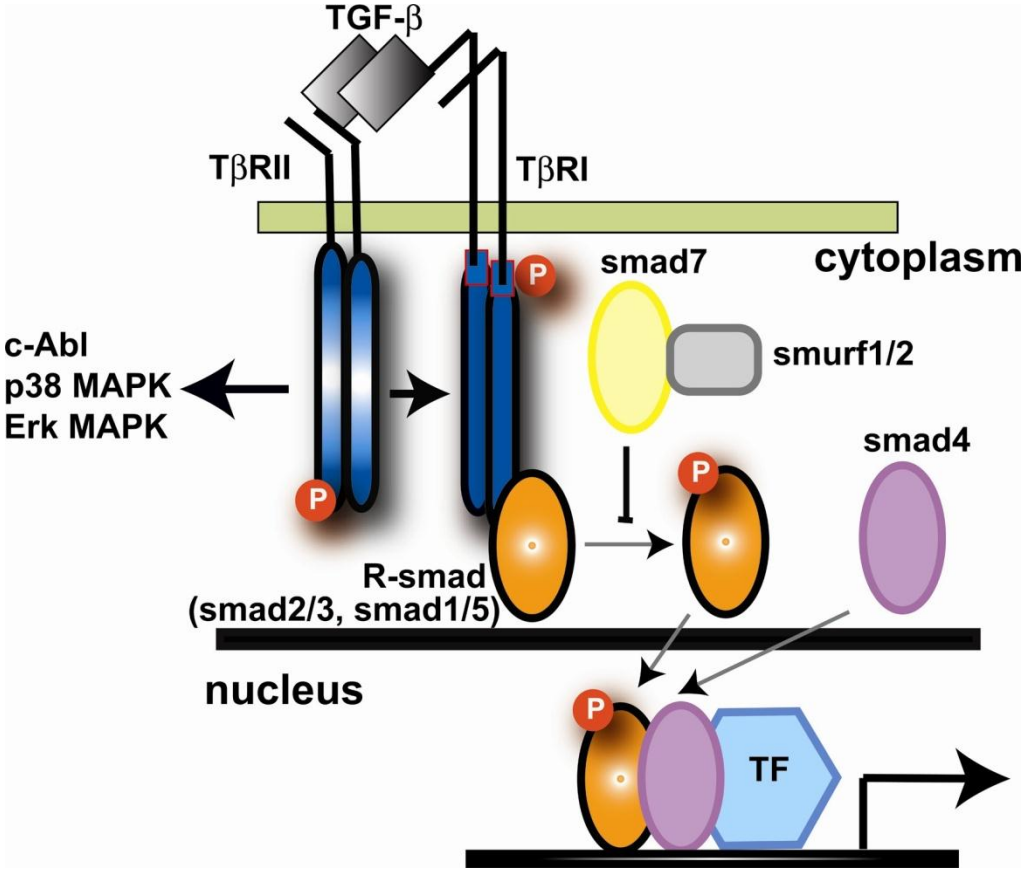
Conclusion

- The cellular response to cardiac injury activates multiple endogenous pathways leading to resolution of inflammation.

Is TGF-beta the “master switch” responsible for transition from inflammation to fibrosis?

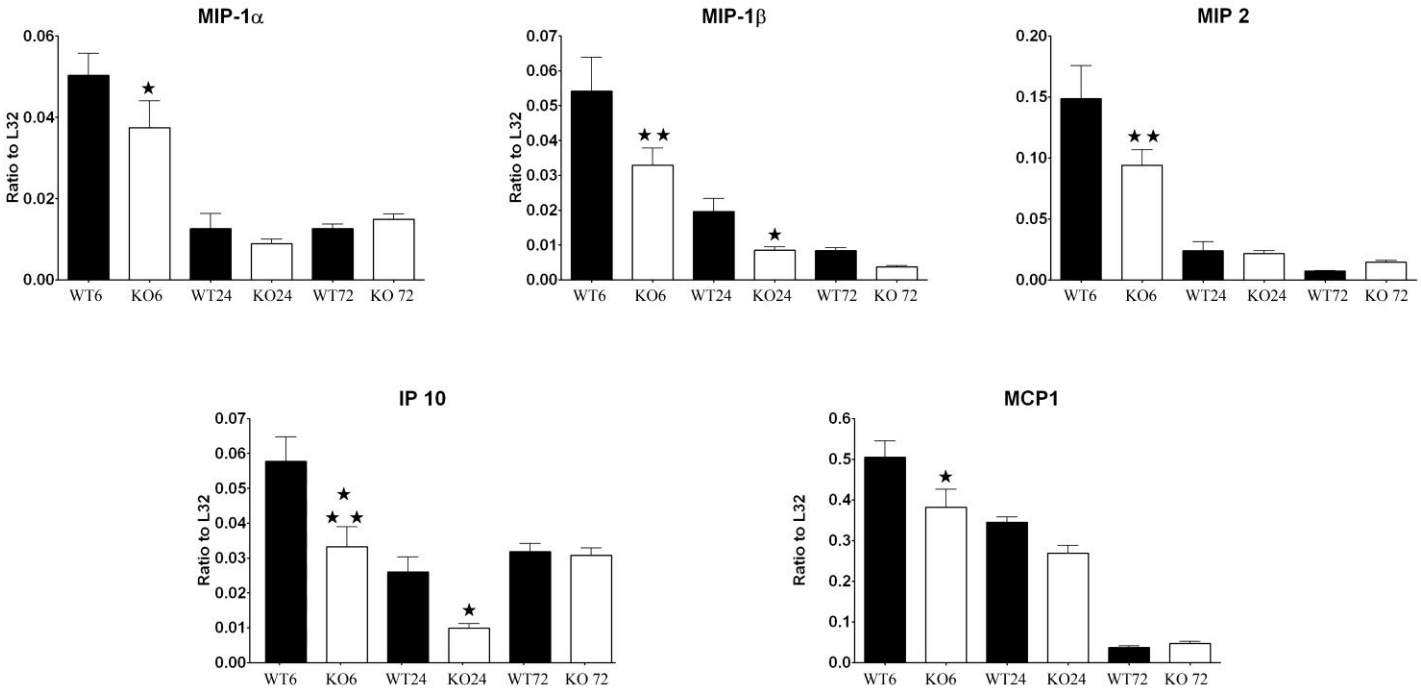


TGF-β signaling



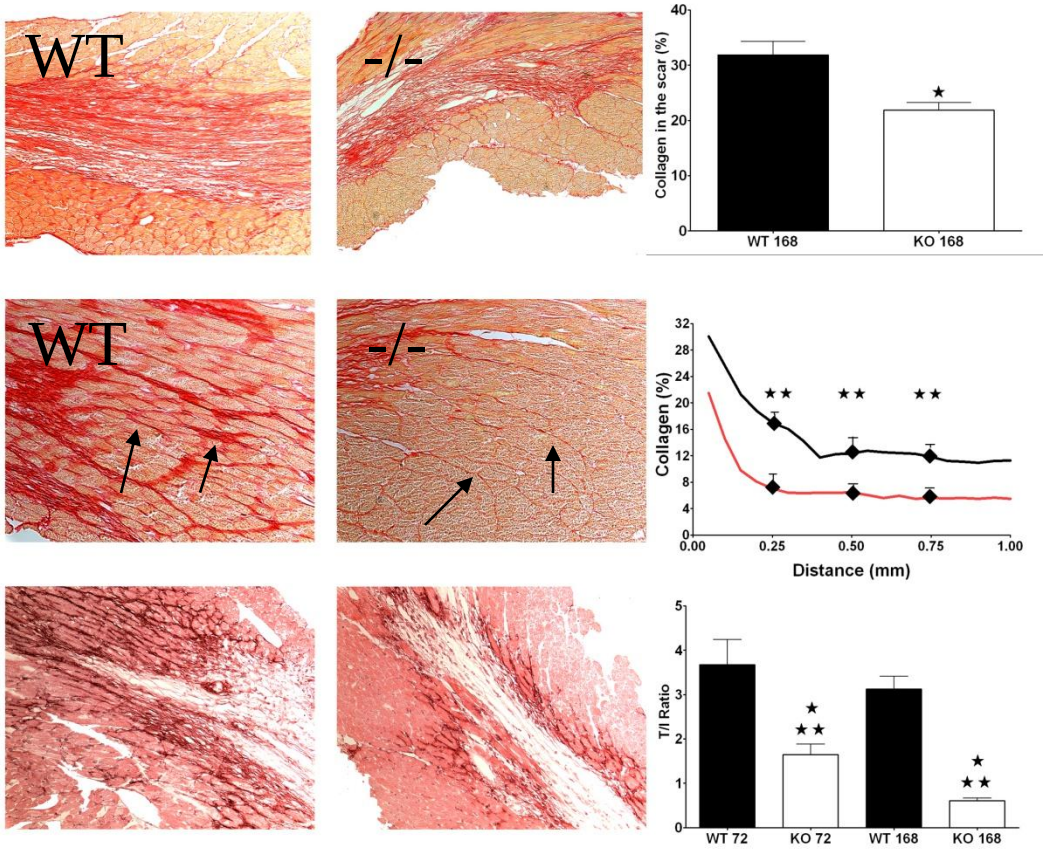
- TGF-beta activates several pathways.

The Smad3 pathway is not crucial for repression of the cytokine and chemokine response

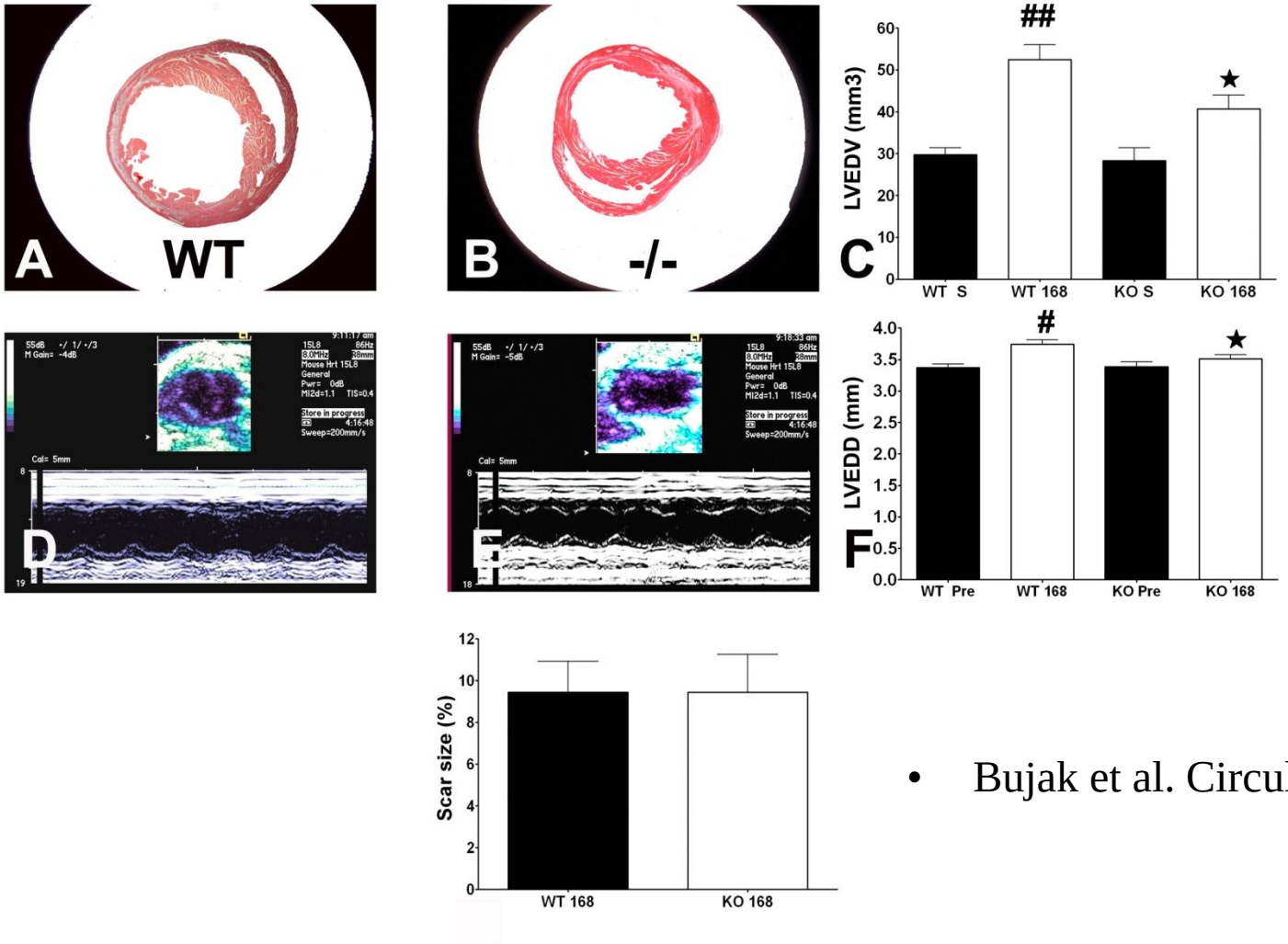


- Bujak et al. Circulation 2007

Smad3 null mice exhibit attenuated fibrotic remodeling following infarction

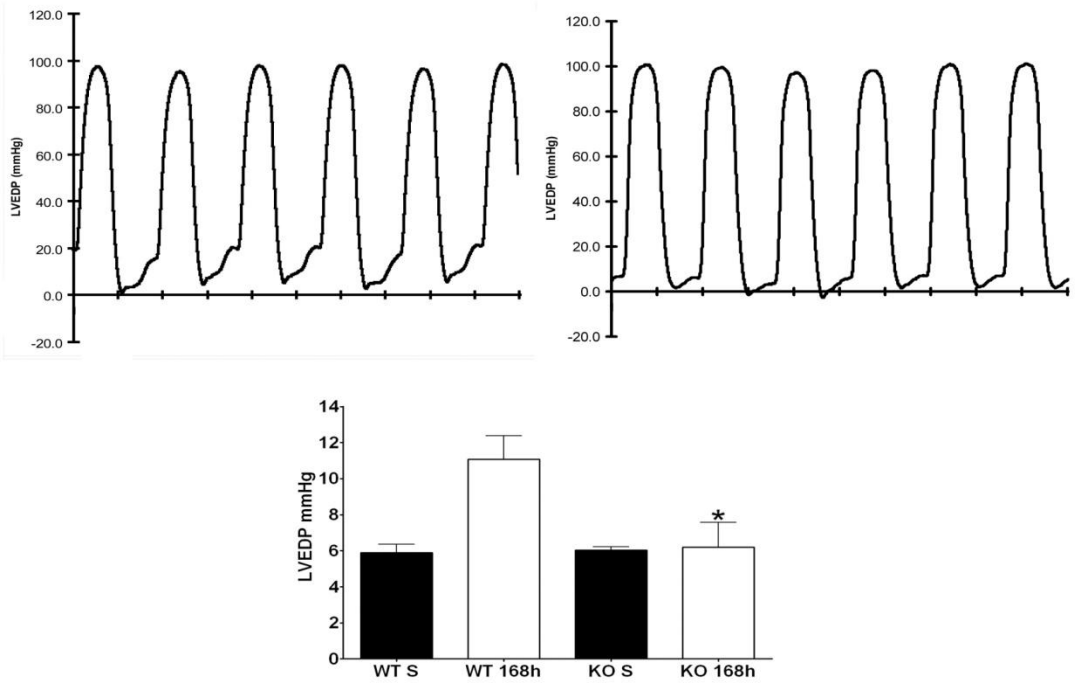


Smad3 null mice show reduced dilative remodeling following myocardial infarction

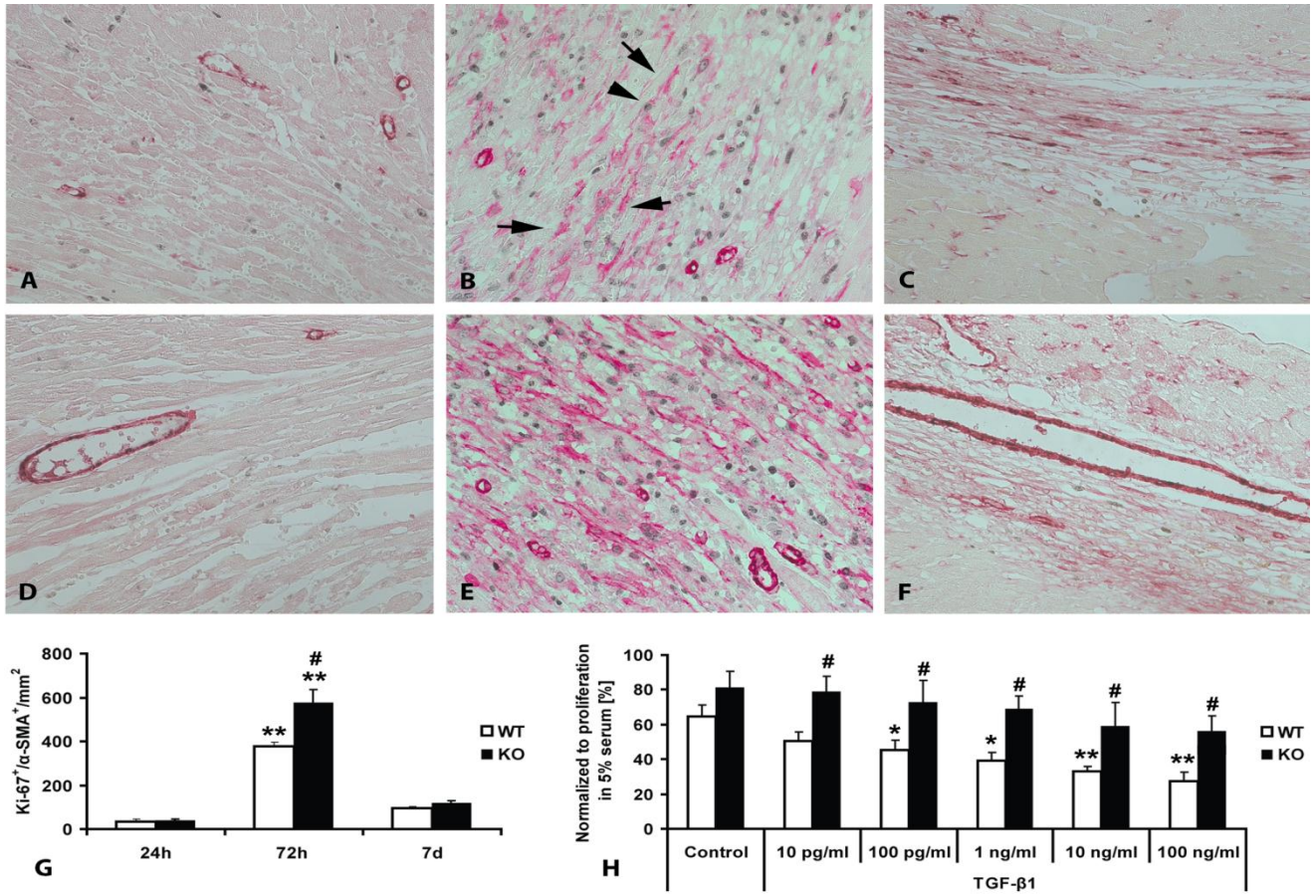


- Bujak et al. Circulation 2007

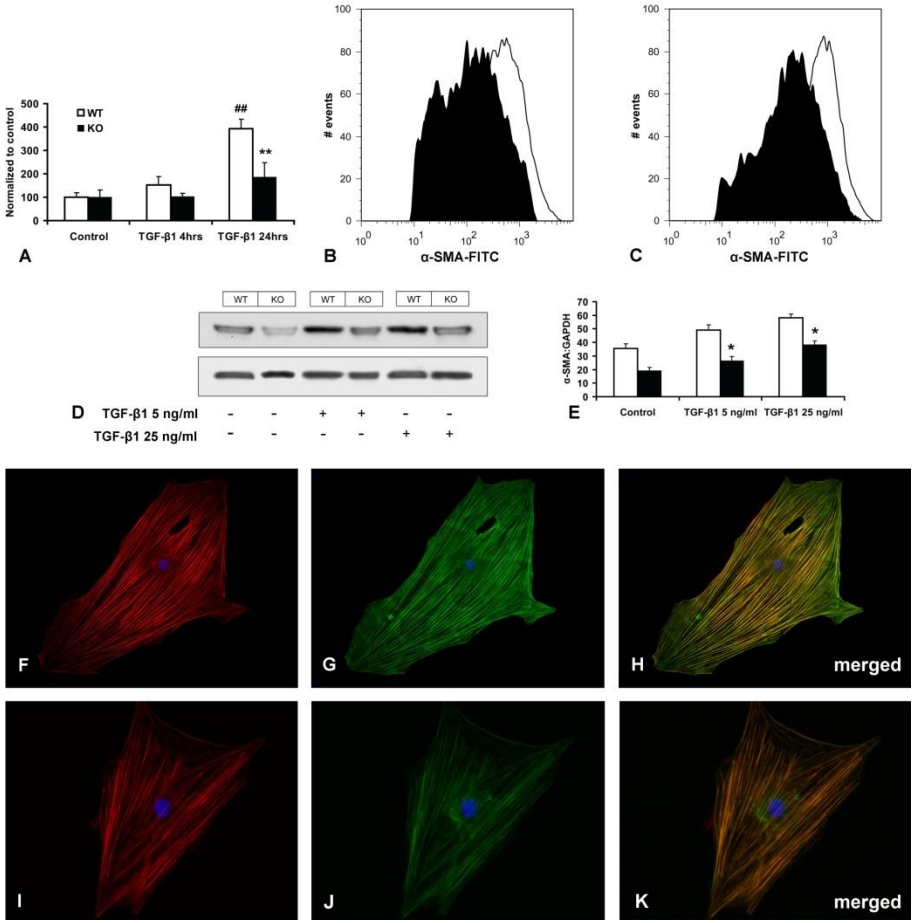
Smad3 -/- mice exhibit attenuated diastolic dysfunction following myocardial infarction



What are the mechanisms responsible for the profibrotic effects of Smad3 signaling?



Smad3 null cardiac fibroblasts exhibit impaired myofibroblast transdifferentiation

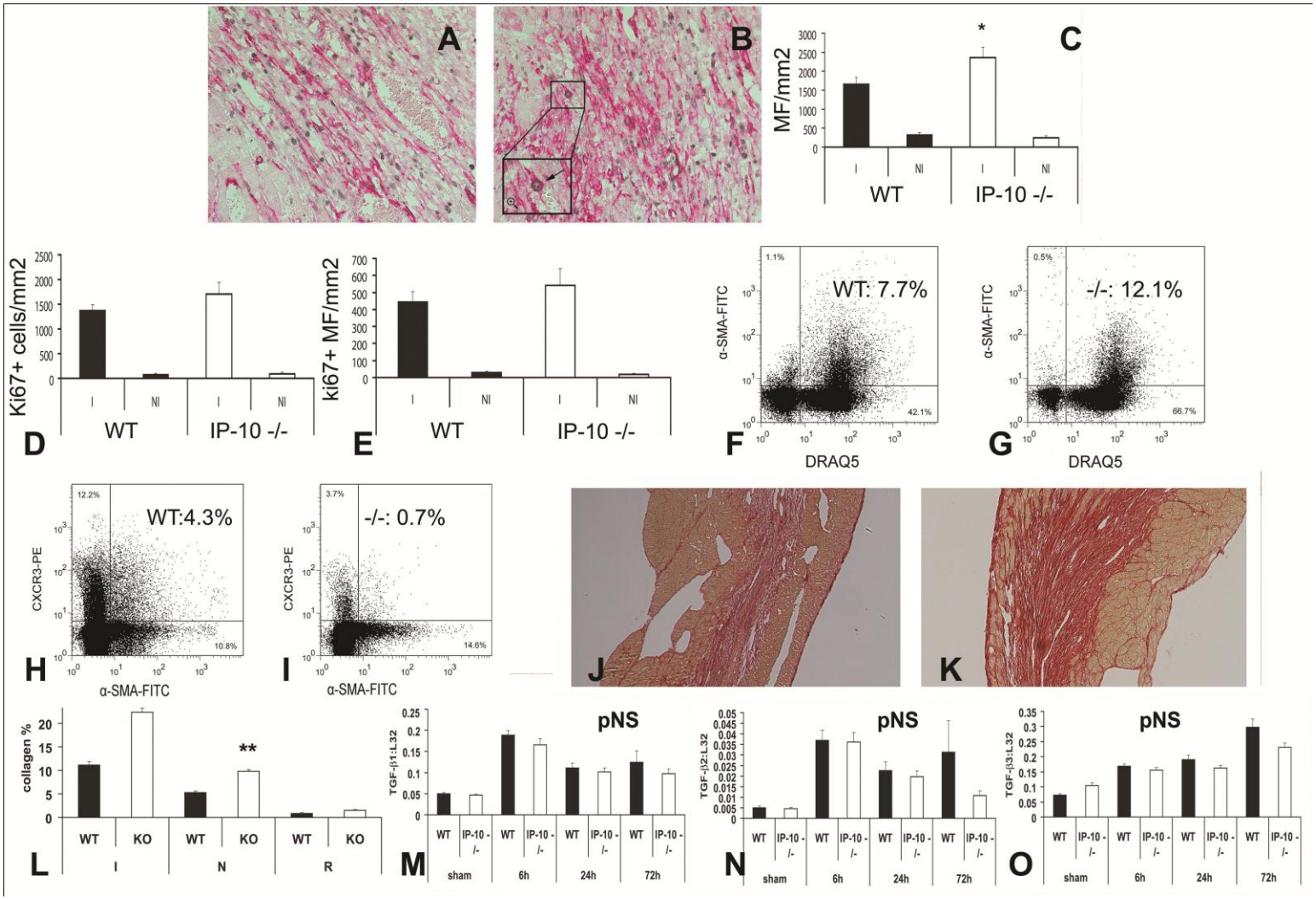


- Dobaczewski et al. Circ Res 2010

Regulation of fibroblast function and activity

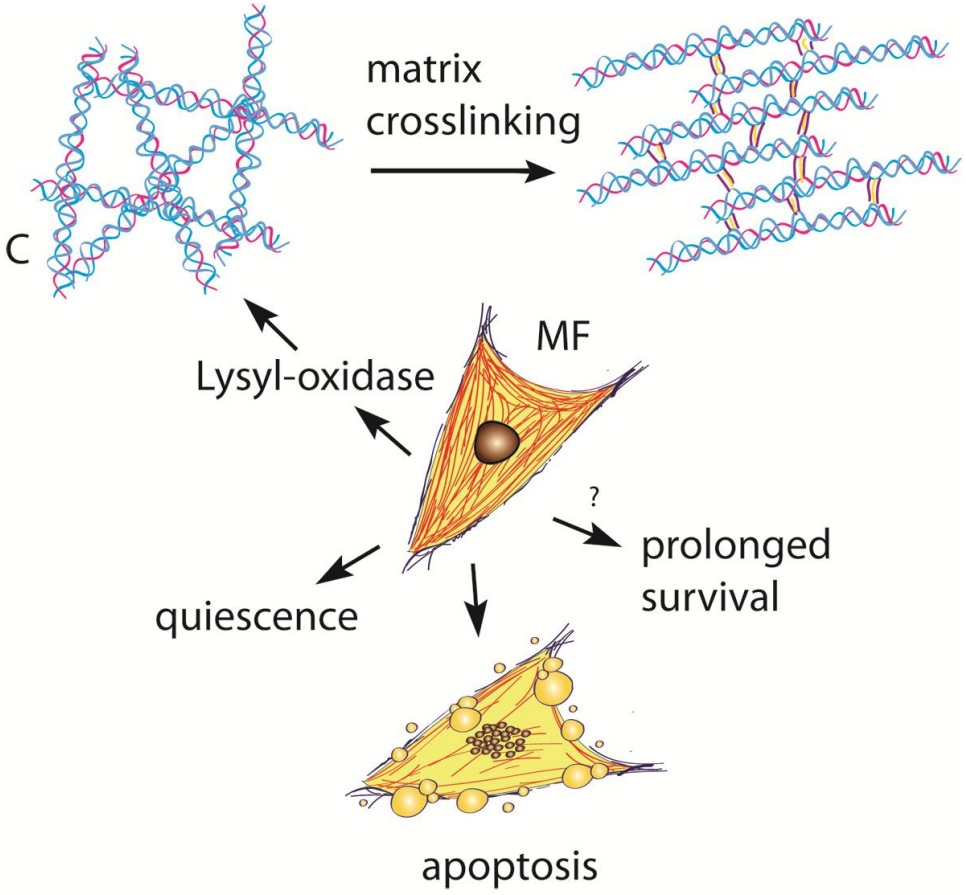
- Myofibroblasts are important for the formation of a scar that provides mechanical support to the infarcted myocardium.
- However, excessive and uncontrolled fibrosis is associated with defective repair, and increased dysfunction.

IP-10 -/- mice exhibit expansion of fibrosis following myocardial infarction



- Bujak et al. Circ Res 2010

Fibroblast apoptosis: a critical step in maturation of the healing infarct



Conclusion

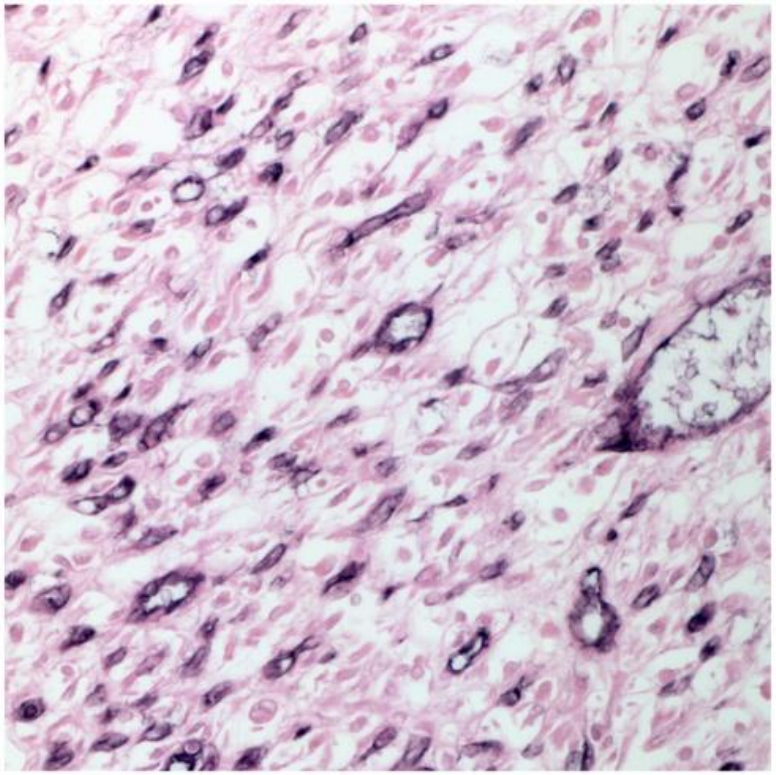
- Endogenous anti-fibrotic pathways mediate containment of the fibrotic response and de-activation of fibroblasts.

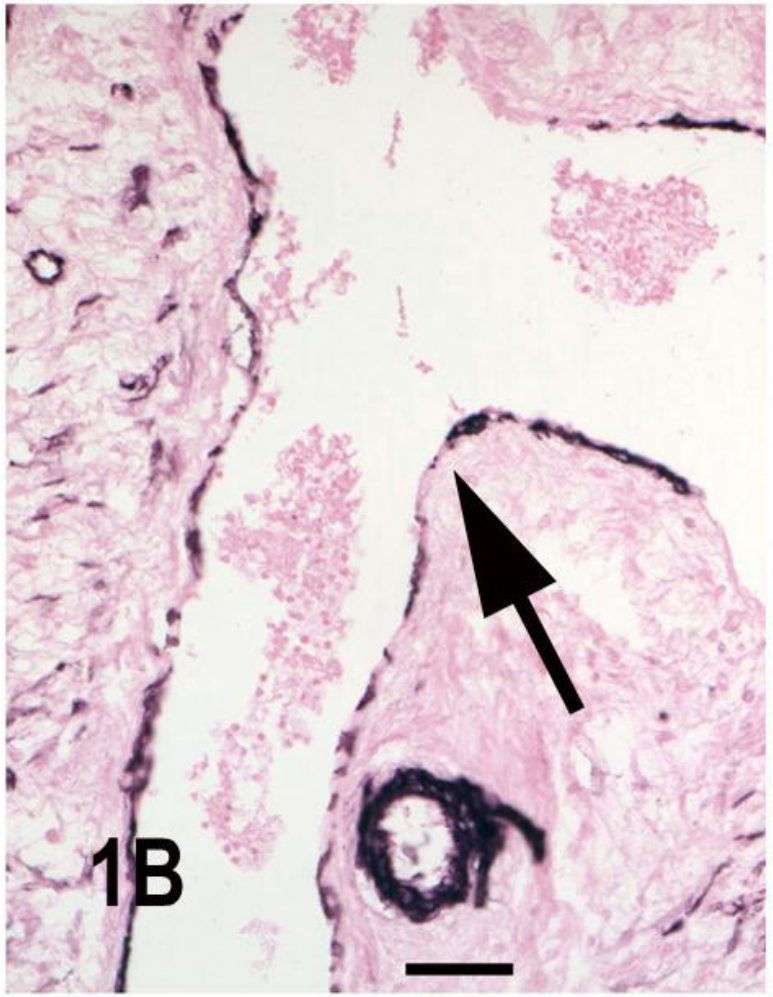
Regulation of angiogenesis is critical for cardiac repair

In permanent coronary occlusion rapid angiogenesis may provide blood supply to remaining cardiomyocytes

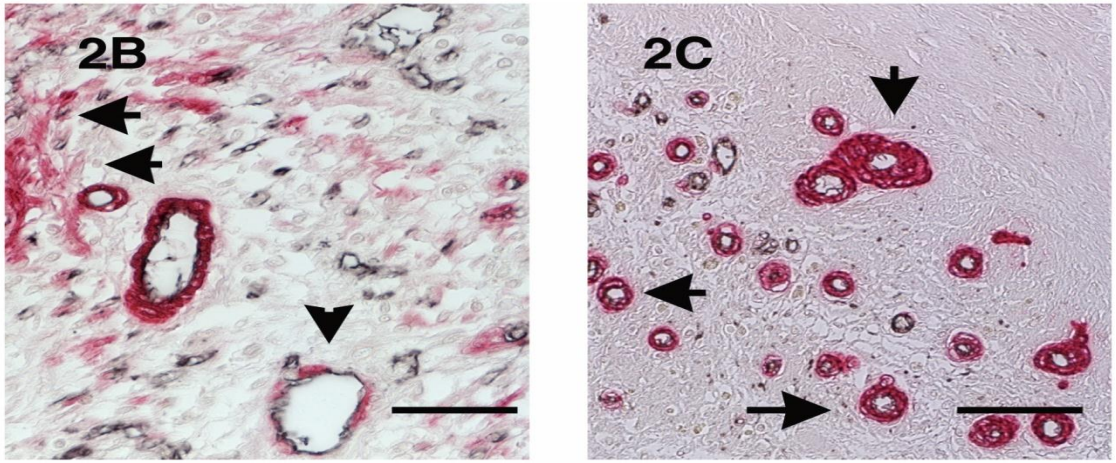
Even in the reperfused infarcted myocardium, wound angiogenesis may be important for infarct healing because reparative cells require blood supply (oxygen and nutrients).

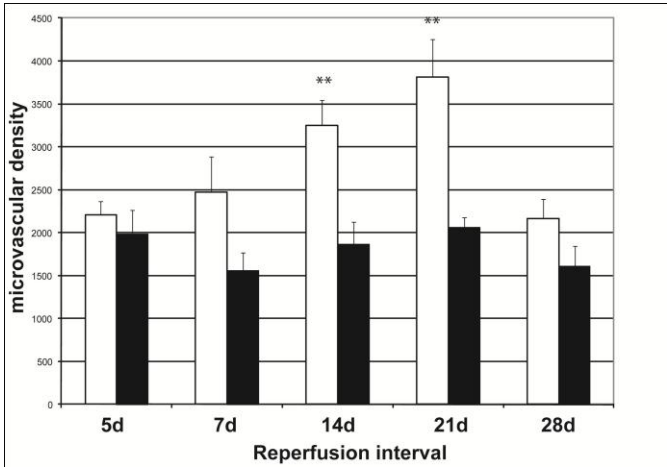
Infarct Angiogenesis

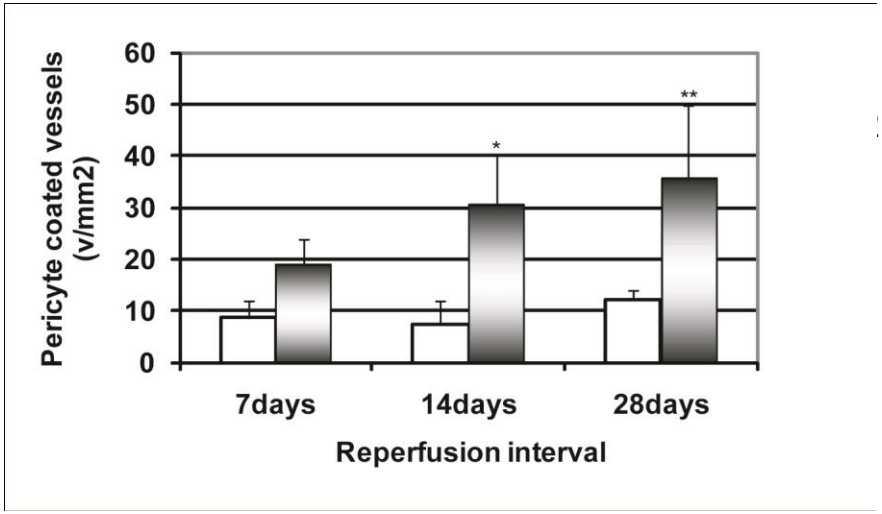




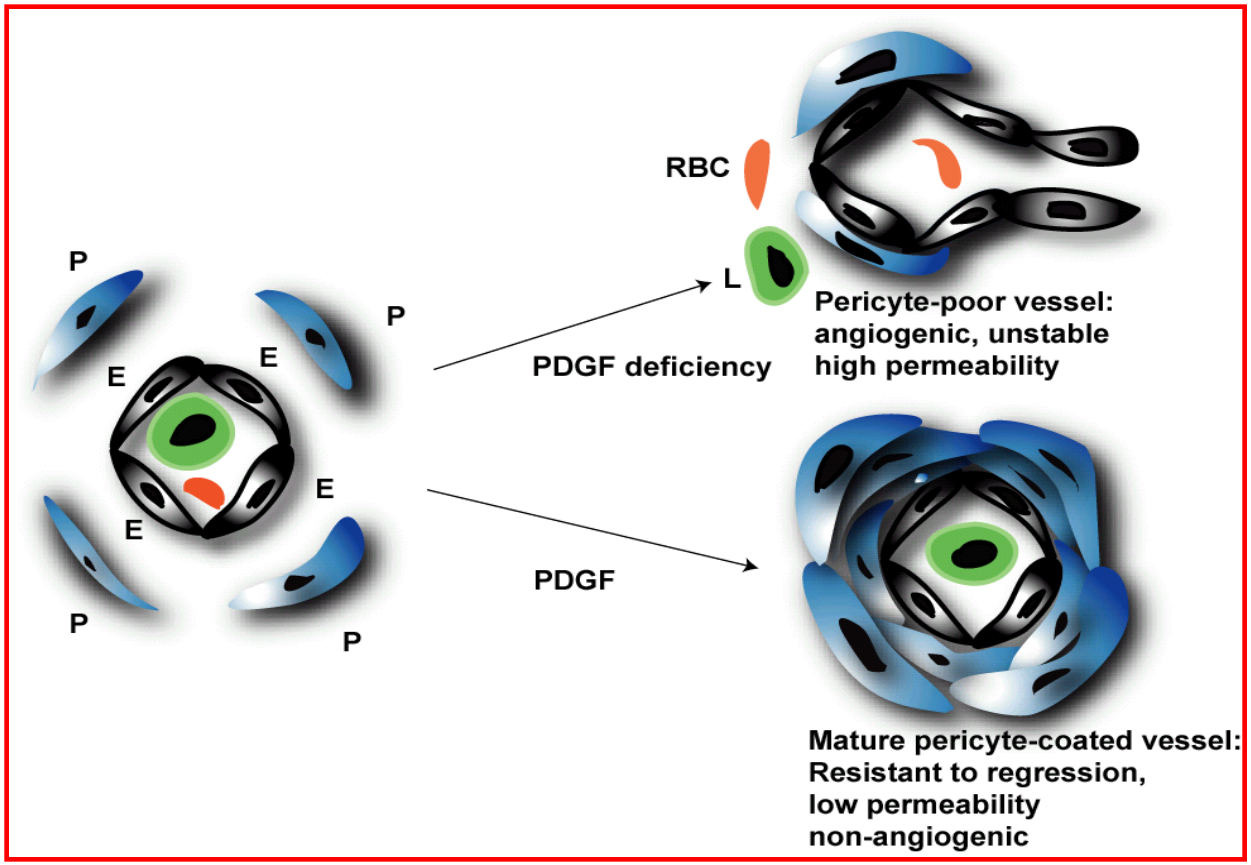
Vascular maturation in the healing wound



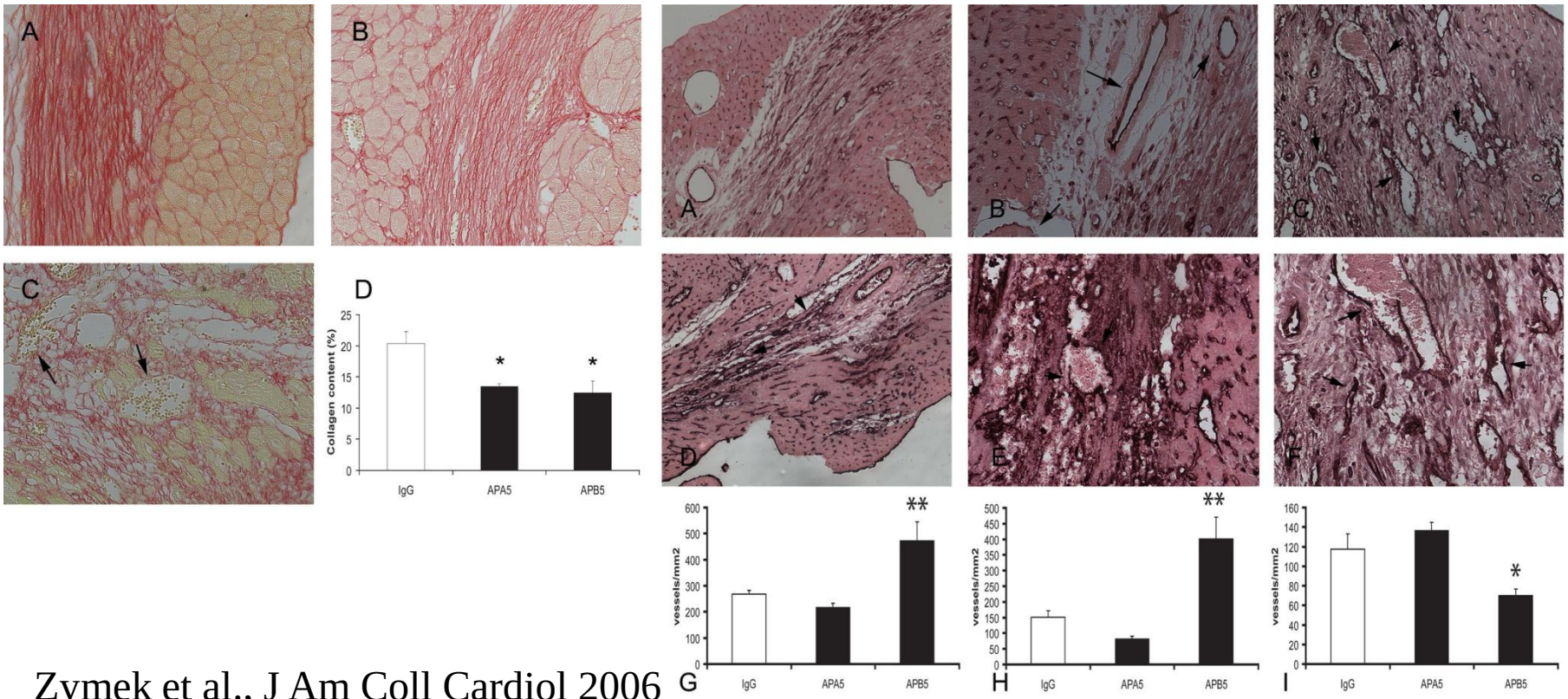




During the maturation phase suppression of angiogenesis and stabilization of the vasculature may prevent uncontrolled inflammation/matrix degradation and excessive formation of granulation tissue



PDGFR-β , but not PDGFR-α neutralization impairs vascular maturation in healing mouse infarcts



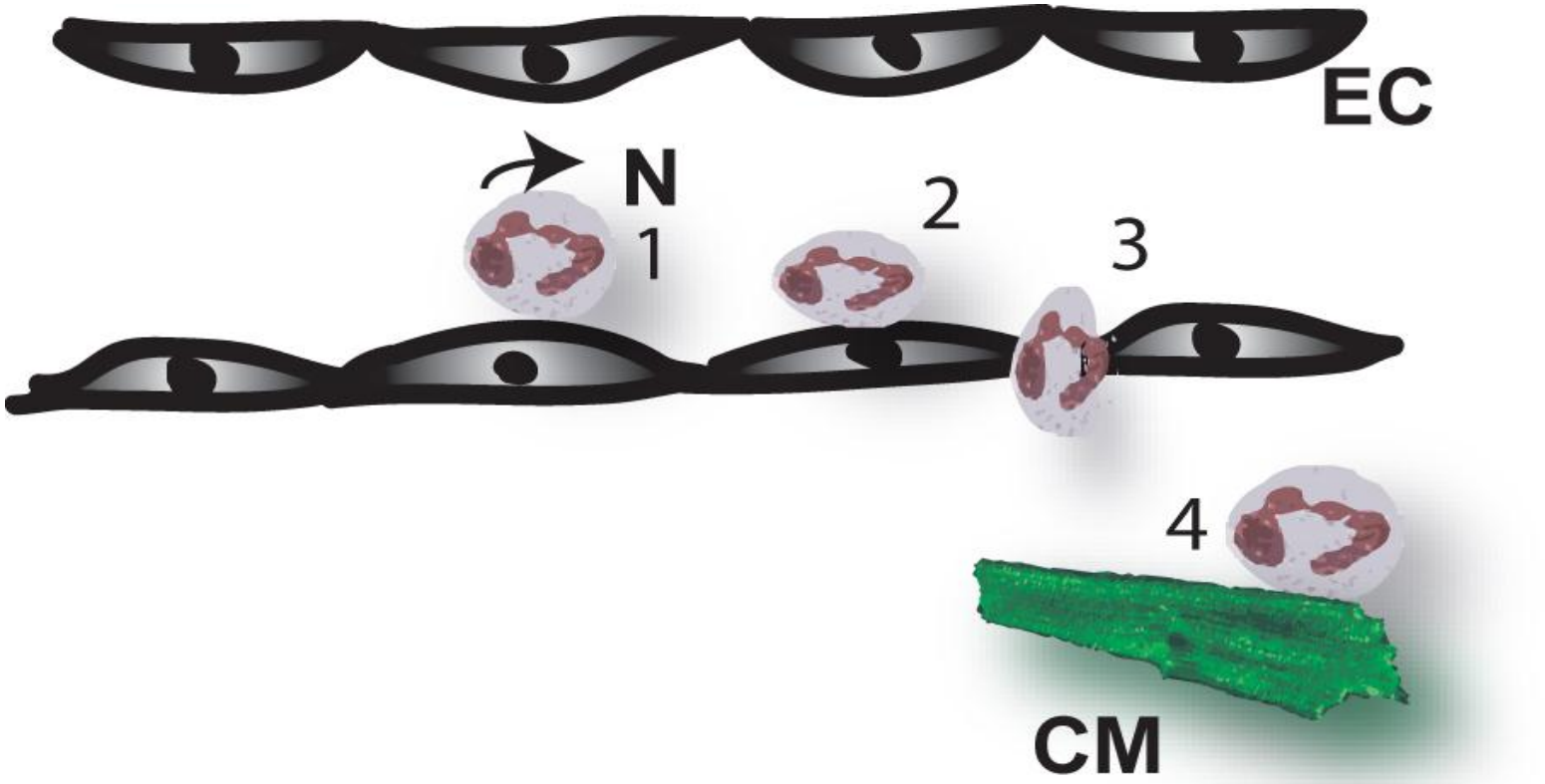
Zymek et al., J Am Coll Cardiol 2006

CONCLUSION

- Timely suppression of the inflammatory, fibrogenic and angiogenic pathways activated in the healing infarct is required for optimal repair.
- Defects in the “stop signals” may be responsible for accentuated adverse remodeling in patients with myocardial infarction.

The clinical implications:
Can we reduce adverse remodeling in patients with myocardial infarction by targeting selected inflammatory/reparative pathways?

Lessons From the Past:
The concept of leukocyte-induced cardiomyocyte injury

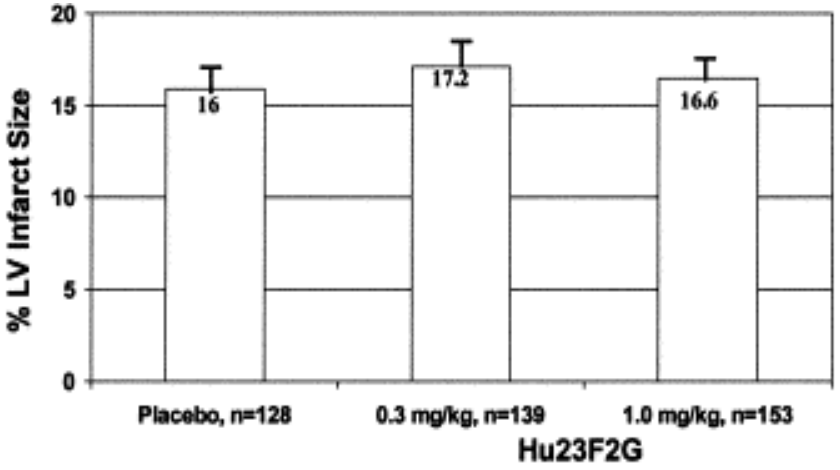


Effect of anti-inflammatory strategies in reducing infarct size in experimental models of myocardial infarction

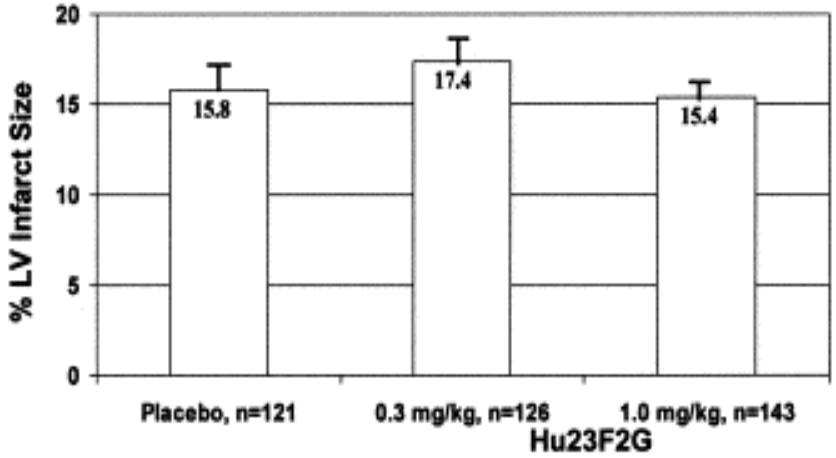
Antibody	% decrease infarct size	Animal model	Reference
PECAM-1	54	Rat	Circulation 1996
IL-8	45	Rabbit	JTCS 1998
MCP-1	48	rat	Lab Invest 1999
CD18	50	dog	JACC 1996
CD11b	46	dog	JCI 1988

Did early inhibition of inflammatory pathways have beneficial effects in patients with acute myocardial infarction?

Anti-CD18 therapy did not affect infarct size in patients with MI



A Imputed Values, Mean ± SE



B Observed Data, Mean ± SE

CD18 trials disappoint again

Genentech (S. San Francisco, CA) has announced disappointing phase II trial results of its anti-CD18 monoclonal antibodies in treating heart attacks. Preliminary analysis of the data in June showed the antibody failed to meet its primary objective of improved coronary blood flow 90 minutes after treatment. Genentech is the fourth biotech company to run aground with CD18 as a target, but researchers and analysts say that rather than being the product of bad decision-making during clinical development, the failures represent the inherent risk of using animal models in research—a problem unlikely to be dispelled by advances in preclinical target screening.

CD18 is a key signaling receptor in lymphocyte adhesion—the process by which white blood cells leave the bloodstream and enter nearby tissues. The hope was that anti-CD18 monoclonal antibodies would block the receptor, thereby reducing lymphocyte infiltration into inflamed tissue and decreasing tissue damage caused by the immune system during reperfusion injury when blood flow to an area is stopped, then re-started. Because this type of damage is common to both heart attacks and ischemic stroke—two of the leading causes of mortality in the industrialized

Faxon et al. JACC 2002 for the HALT-MI study

Why did early anti-inflammatory strategies fail?

The underlying hypothesis may be incorrect. Early inflammatory cardiomyocyte injury may not be significant.

Is there a fundamental problem in translating animal model investigations into clinical practice?

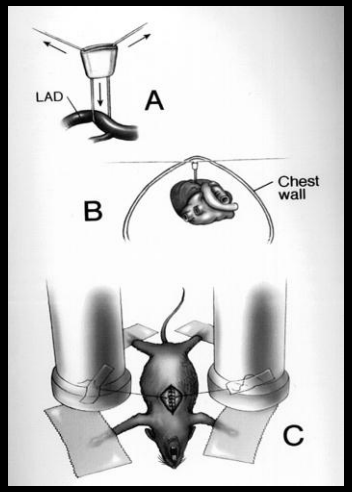
Of mice and men: can we translate conclusions from animal studies into the human pathologic condition?

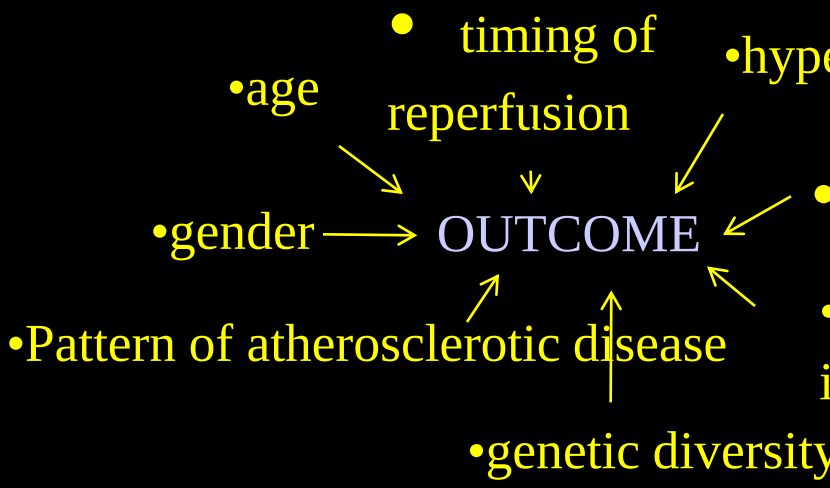
- Animal studies provide us valuable information on the pathobiology of cardiac remodeling, but cannot predict the success of an intervention in patients with myocardial infarction.

Challenges due to the use of mouse models of heart disease

- Assessment of function and structure in the mouse is challenging.
- Species differences in cardiovascular biology.
- **Optimally-designed mouse studies can assess functional, molecular, morphometric and proteomic endpoints, but cannot provide information on outcome and clinical events.**

Challenges due to the complexity of the clinical context



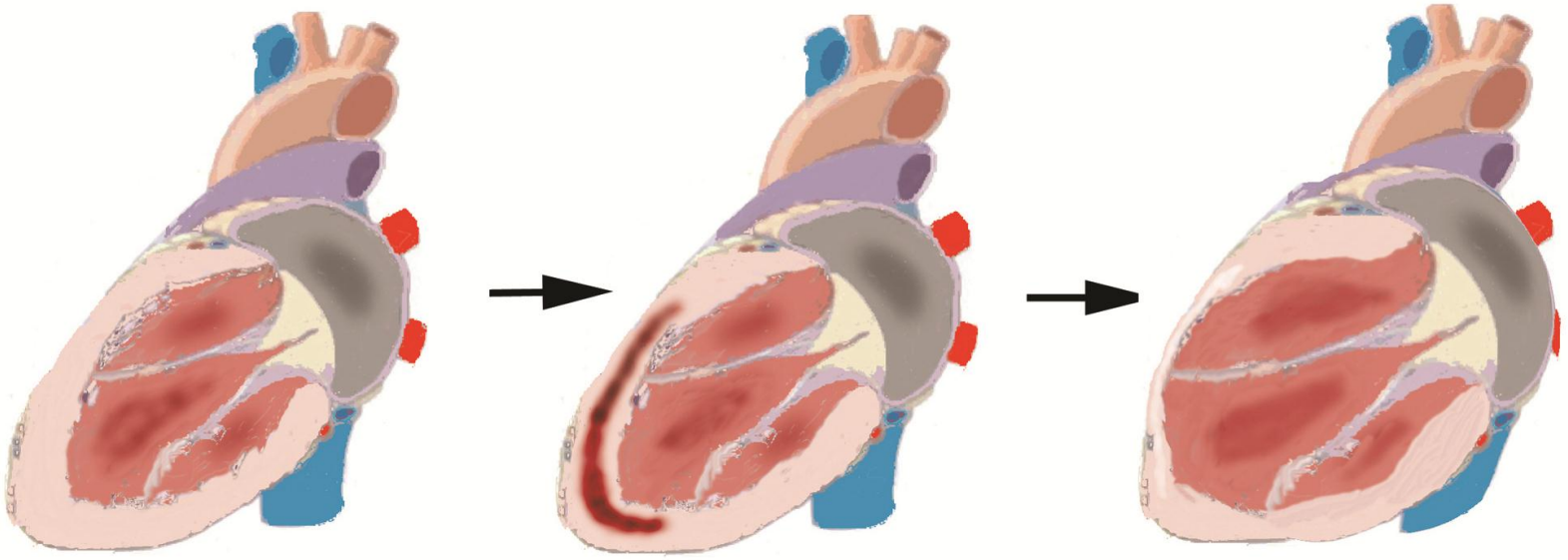


- Animal model experiments aim at simplifying the context in order to test a specific hypothesis.

The complexity of the clinical context cannot be simulated by an animal model.

Should we target inflammatory pathways?

- Our studies suggest that even if no additional cardiomyocytes are saved, modulation of inflammation may attenuate adverse remodeling by altering the qualitative characteristics of the wound.

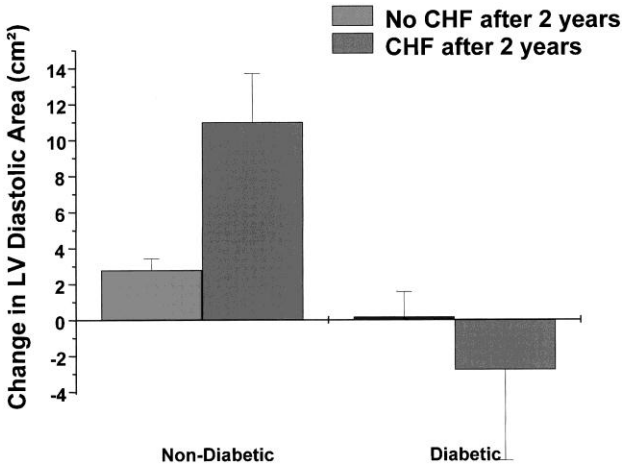


A focus on resolution and containment of inflammation

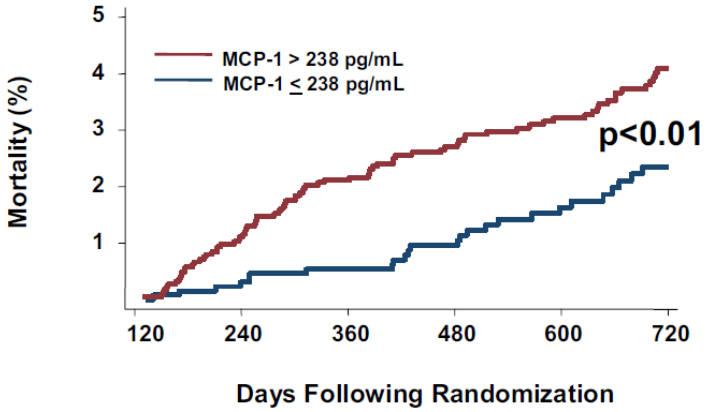
- Patients exhibiting worse remodeling following infarction may have defects in suppression and containment of the inflammatory fibrotic or angiogenic response.
- Specific patient populations (the elderly, the diabetics etc.) may exhibit impaired resolution of inflammation and distinct healing defects resulting in increased adverse remodeling. These subpopulations may be good candidates for interventions targeting the inflammatory response.

Important considerations in order to identify new therapeutic strategies targeting the inflammatory and reparative response following myocardial infarction

1) Identify groups of patients with adverse prognosis



Solomon et al. Circulation 2002



De Lemos et al JACC 2007 from the A to Z trial

2) Understand the mechanisms involved in adverse remodeling and dysfunction using relevant animal models.

3) Exploit the lessons learned from the mouse model at the mechanistic level, and process this information to identify a therapeutic target, while recognizing the complexity of the clinical context.

4) Understand the importance of spatial and temporal parameters in designing a therapeutic strategy

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From Baylor to Albert Einstein…

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