

‘Turning the right screw’: targeting the interleukin-6 receptor to reduce unfavourable tissue remodelling after myocardial infarction

Helge Möllmann^{1,2*}, Holger M. Nef^{1,2}, and Christian Troidl²

¹Kerckhoff Heart and Thorax Center, Department of Cardiology, Benekestr. 2–8, 61231 Bad Nauheim, Germany; and ²Franz-Groedel-Institute of the Kerckhoff Heart and Thorax Center, Benekestr. 2–8, 61231 Bad Nauheim, Germany

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This editorial refers to ‘Antibody against interleukin-6 receptor attenuates left ventricular remodelling after myocardial infarction in mice’, by M. Kobara et al., pp. 424–430, this issue.

#1 To be upfront about it: left ventricular remodelling (LVR) and scar formation, including compensatory effects on the remote tissue, is urgently warranted and life-saving for the patient suffering from myocardial infarction (MI) because they avert life-threatening ventricular ruptures. However, in addition to these beneficial effects, LVR often initiates secondary complications due to unfavourable changes in LV geometry that subsequently lead to heart failure—a process that considerably impacts patients’ morbidity and mortality.¹

Experimental investigations of the molecular and cellular mechanisms underlying LVR after MI raise the hope of developing new therapeutic strategies. In particular, inflammation-targeting strategies have rushed into the spotlight. These strategies influence myocardial remodelling, resulting in the reduction of necrosis and the advancement of discrete but resilient scar formation.

#2 In this context the experimental data presented by Kobara et al.² from a mouse MI model represent a promising therapeutic approach. Targeting inflammation by interfering with interleukin-6 (IL-6) signalling using an antibody directed against the IL-6 receptor (MR16-1) led to an increased survival rate (80.6%) after 28 days compared with untreated MI controls (59.5%). Further investigation revealed that IL-6 receptor inhibition suppressed infiltration of polymorphonuclear leucocytes (neutrophils), thereby reducing myeloperoxidase (MPO) activity not only in the infarct area but also within the border zone. MPO is known to be an important source of oxidants leading to myocyte apoptosis and adverse LV remodelling. MR16-1 treatment also reduced macrophage infiltration and was accompanied by a strong decrease in MCP-1 expression soon after MI. The authors demonstrated a marked reduction in matrix metalloproteinase MMP2 activity even though attenuated interstitial fibrosis was observed, especially in the border zone. Finally, a reduced cross-sectional area of myocytes within the border zone was reported. Interestingly, the beneficial effects of MR16-1 were caused neither by a reduced infarct size nor by diminished apoptosis within the infarct zone.

Acute hypoxaemia induced by coronary artery occlusion subsequently leads to the death of ischaemically damaged cardiomyocytes, which initiates a complex network of cellular and subcellular processes. The distinct inflammatory response, followed by reorganisation of the extracellular matrix, is accompanied by removal of disrupted ventricular tissue that is replaced with a resilient scar. Very soon after MI, local secretion of inflammatory cytokines and signals (TNF α , IL-1 β , and IL-6) initiates recruitment of numerous bone marrow-derived cells through MCP1 and MIP-1 α/β signalling, involving adhesion molecules such as the integrins, ICAM1, and VCAM.³ Leucocytes (neutrophils and monocytes/macrophages) in particular infiltrate the infarcted area, playing a pivotal role during scar tissue formation and remodelling processes by orchestrating degradation of the extracellular matrix, removing necrotic cells and cellular debris, and further recruiting inflammatory cells. Macrophages trigger the differentiation of fibroblasts into myofibroblasts within the infarct area, mainly through TGF β -dependent signalling, and trigger neoangiogenesis by releasing growth factors (VEGF). Myofibroblasts serve as the main source of stabilising extracellular matrix proteins such as collagen1/3 and fibronectin. Finally, a scar fills the gap that was left over from the loss of contractile myocardial tissue.^{4,5}

#3 It has recently become apparent that the function of monocytes and macrophages is not restricted to the induction of inflammation and to the clearance of cellular debris in order to provide space for the scar-forming myofibroblasts. Different subpopulations of monocytes harbouring specific activation profiles are sequentially recruited from the blood^{6,7} to control the various phases of myocardial remodelling. The proportion of alternatively activated macrophages significantly increases after the inflammatory phase. Induction of alternative activation is known to trigger tissue repair.^{8,9} The arginase-induced reduction of nitric oxide and the production of polyamines and proline as the central components of collagen point toward an important scar formation function of alternatively activated macrophages.¹⁰

#4 The balance between extracellular matrix reconstruction and degradation—not only in terms of quality and quantity, but also regarding time dependency—critically determines the degree of complications

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*Corresponding author. Tel: +49 6032 996 2819; fax: +49 6032 996 2827, Email: h.moellmann@kerckhoff-fgi.de

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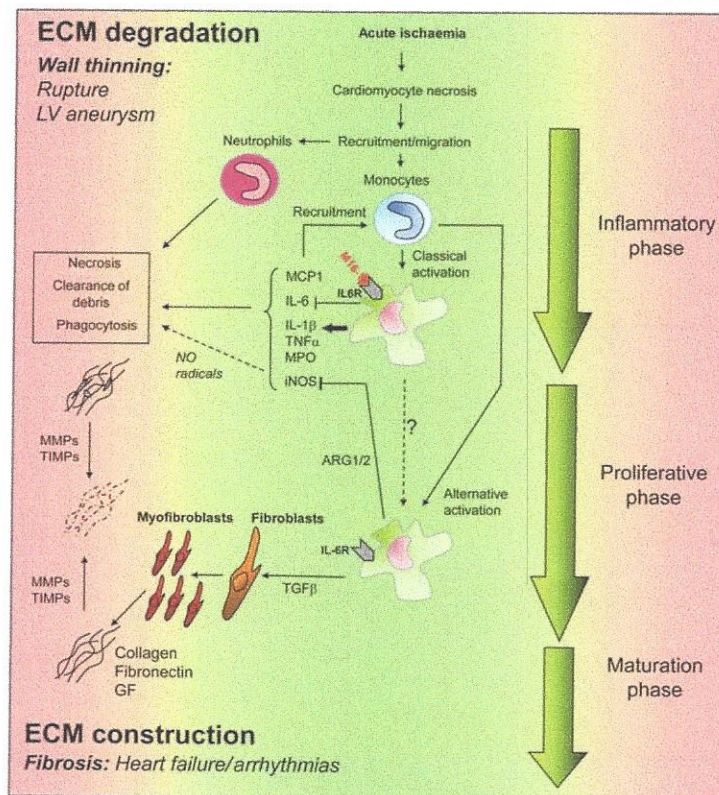


Figure 1 Partial overview of targets and mechanisms involved in LV remodelling after myocardial infarction (MI). Early inhibition of IL-6 signalling using an anti-IL-6 receptor antibody (M16-1) leads to decreased mortality after MI, mainly through reduction of inflammation and extracellular matrix remodelling of the healthy surrounding myocardial tissue. Infarct size and apoptosis were not altered by interference with IL-6 receptor signalling.

and long-term outcome following MI¹¹ (Figure 1). Furthermore, the inflammatory response and the subsequent extracellular matrix remodelling extend into the surrounding unaffected myocardial tissue. Inhibiting this ostensible 'overshooting' inflammation may represent an appealing therapeutic approach, although previous attempts to interfere with these processes had no impact or even caused adverse effects.¹²

This surprising and disappointing result may stem from our still-incomplete understanding of the complex mechanisms of LVR after MI, indicating that a therapeutic approach requires a more detailed understanding of the underlying molecular and cellular mechanisms. Therefore, the most important finding of Kobara *et al.* may be that only an early and time-limited interference with IL-6 signalling leads to a favourable outcome. Using this approach, the adverse remodelling of the border zone can be reduced without negative effects on the infarct size or the incidence of ventricular ruptures. Therefore, Kobara *et al.* demonstrate that 'turning the right screw at the right time' in the highly complex post-MI network of cellular mechanisms leads to a promising outcome of infarct remodelling, and may indeed reduce secondary complications.

Conflict of interest: none declared.

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