Seeing is repairing: how imaging-based timely interference with CXCR4 could improve repair after myocardial infarction

Yvonne Döring1,2,3, Heidi Noels4, Emiel van der Vorst1,2,3,4,5,6, and Christian Weber2,3,7,8*

1Department of Angiology, Swiss Cardiovascular Center, Inselspital, Bern University Hospital, University of Bern, Switzerland; 2Institute for Cardiovascular Prevention (IPEK), Ludwig-Maximilians-Universität München, Munich, Germany; 3DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany; 4Institute for Molecular Cardiovascular Research (IMCAR), RWTH Aachen University, Aachen, Germany; 5Department of Pathology, Cardiovascular Research Institute Maastricht (CARM), Maastricht University Medical Centre, Maastricht, The Netherlands; 6Interdisciplinary Center for Clinical Research (IZKF), RWTH Aachen University, Aachen, Germany; 7Department of Biochemistry, Cardiovascular Research Institute Maastricht (CARM), Maastricht University Medical Centre, Maastricht, The Netherlands; and 8Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

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This editorial refers to ‘Molecular imaging-guided repair after acute myocardial infarction by targeting the chemokine receptor CXCR4’, by A. Hess et al., on page 3564.

Applying CXCR4-guided imaging to mediate myocardial repair after MI

Myocardial infarction (MI) occurs when coronary arteries become obstructed by ruptured atherosclerotic lesions, resulting in ischaemic injury to the heart tissue that is normally oxygenized by this vessel. Shortly after the ischaemic insult, the cardiac repair process starts, which entails a complex and fine-tuned series of events, including inflammatory and reparative responses.1 In this issue of the European Heart Journal, Hess et al.2 explore the value of the chemokine receptor CXCR4 in molecular imaging-guided therapy after acute MI.

The authors examined the effect of administering the CXCR4 antagonist AMD3100 on cardiac function after MI, guided by positron emission tomography (PET) imaging of CXCR4 expression as read-out of inflammatory cell accumulation in the heart in order to determine the best timing of therapeutic CXCR4 targeting. Building on their previous observations of molecular imaging of CXCR4 in the infarcted heart using the radiotracer [68Ga]pentixafor,3 cardiac CXCR4 expression was confirmed to increase directly after MI and to remain significantly up-regulated up to 3 days after infarction. The CXCR4 signal localized in the infarcted region and coincided both locally and temporally with the accumulation of neutrophils and monocytes. Of note, early infarct CXCR4 signal could predict subsequent cardiac outcome as measured as acute left ventricular rupture as well as left ventricular ejection fraction 6 weeks after MI, independent of infarct size. Based on these findings, the therapeutic value of timely CXCR4 targeting was examined (Figure 1). This revealed that single-dose on-peak CXCR4 blockade, but not off-peak blockade, with AMD3100 improved cardiac function after MI, which was associated with a reduced cardiac infiltration of mainly neutrophils and proinflammatory monocytes.2

Cardiac repair after MI: a delicate balance between inflammatory and reparatory processes

The first cells that respond to myocardial injury, already within minutes, are resident mast cells by releasing pre-formed granules, as well as resident macrophages and cardiomyocytes that start producing inflammatory cytokines and chemokines.4 This initial inflammatory trigger produced by resident cells results in the recruitment of neutrophils and Ly6Chi monocytes from the circulation into the cardiac tissue within 1 day.4 Recruited cells mainly participate in the phagocytosis of dead and dying cardiomyocytes and produce more inflammatory cytokines to further stimulate the inflammatory response. Neutrophils disappear rather quickly again from the cardiac tissue, with their numbers decreasing already after 3 days and a complete

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1 doi:10.1093/eurheartj/ehaa625
2 Corresponding author. Institute for Cardiovascular Prevention, LMU Munich, Pettenkoferstr. 9, D-80336 München, Germany, Tel: +49 89 4400 54350, Fax: +49 89 4400 54352, Email: cweber@med.lmu.de
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absence after 7 days. Apoptotic neutrophils release transforming growth factor-β (TGF-β), lactoferrin, and annexin A1, and thereby trigger the rise of anti-inflammatory, reparative macrophages (M2-like).4,5 In contrast to neutrophils, monocytes persist and continue to accumulate. However, during the transition from the inflammation phase to the reparative phase around day 7, predominantly Ly6C^low monocytes accumulate and differentiate into M2-like macrophages.6

Besides the role of these innate immune cells, lymphocytes have also been demonstrated to be involved in cardiac repair after MI. During the early inflammatory phase, CD4^+ helper T cells and CD8^+ cytotoxic T cells accumulate in the cardiac tissue, fuelling the inflammatory response. During the reparative phase, regulatory T cells prevail and secrete interleukin-10 (IL-10) and TGF-β, thereby contributing to inflammatory resolution and stimulating the differentiation of macrophages towards an M2-like phenotype.7 M2-like macrophages predominantly produce TGF-β and vascular endothelial growth factor (VEGF), thereby promoting fibrosis and angiogenesis.8 Fibrosis, comprised of fibroblast proliferation and matrix production, is needed to form a collagen-rich scar at the site of injury. This scar formation tends to increase the physical load on the neighbouring viable myocardium.9 Therefore, angiogenesis, in part contributed by mobilized progenitor cells, is important to provide sufficient perfusion of the surrounding tissues to overcome the effects of scar formation. Viewed in conjunction, the process of cardiac repair involves a complex interaction of different immune cells and tissue resident cells that cooperate in a timely manner to optimally repair the damaged cardiac tissue.

Since inflammation is a crucial player in cardiac remodelling after ischaemia, a careful balance between proinflammatory and reparatory aspects of inflammation is extremely important to prevent myocardial damage by unconstrained inflammation, and therapeutic strategies to improve this delicate balance are highly challenging. This holds especially true for patients subjected to fast reperfusion therapy following MI, which itself evokes considerable myocardial reperfusion injury and thereby significantly contributes to heart failure complications in patients initially surviving MI.8

### A complex role for the chemokine receptor CXCR4 in cardiac remodelling after myocardial ischaemia

A role for CXCR4 in inflammation and cardiac remodelling after myocardial ischaemia as well as ischaemia/reperfusion (I/R) injury has been intensely investigated over the last decades, revealing a dual role for CXCR4 and its bona fide ligand CXCL12. For example, intramyocardial injection of CXCL12 in animal models reduced infarction size and increased cardiac function after MI. The latter was attributed to improved survival of hypoxic myocardium, and increased neoangiogenesis.10 Moreover, CXCL12-overexpressing adenovirus, CXCL12-transgenic skeletal myoblasts, or CXCL12-releasing hydrogels revealed enhanced recruitment and incorporation of CXCR4^+ stem and progenitor cells in the infarcted area.11 Hence, progenitor cell recruitment through local engagement of the CXCL12–CXCR4 axis may contribute over increased neovascularization to cardiac repair after MI. Within this concept, animal models of MI investigating pharmacological blockade of CXCR4 in mice and pigs with small-molecule antagonists plerixafor (AMD3100) or burixafor (TG-0054) revealed improved heart function after MI.8–10 Here, beneficial effects of CXCR4 blocking after MI were again associated with enhanced mobilization and cardiac recruitment of endothelial progenitor cells and increased infarct vascularization,8,9 in line with the role of CXCR4 in regulating progenitor cell homing in the bone marrow and its unleashing upon systemic CXCR4 antagonism.9

Furthermore, POL551 (another CXCR4 antagonist) promotes tissue repair and functional adaptation after MI, mobilizing splenic T_reg cells into the peripheral blood, followed by enhanced T_reg cell accumulation in the infarcted region.11 In this regard, the CXCL12–CXCR4 axis provides protective effects by recruiting T_reg and progenitor cells into the heart after ischaemic insult.

On the other hand, reduced CXCR4 expression by Cxcr4 heterozygosity in mice reduced infarct size after MI along with reduced proinflammatory cell recruitment in the heart, delaying and shifting monocyte subset infiltration.12 In turn, adenovirus-mediated overexpression of CXCR4 in the heart increased infarct size and reduced cardiac function, associated with an enhanced recruitment of proinflammatory cells, presence of inflammatory mediators, and increased apoptosis of cardiomyocytes.13 Thus, with CXCR4 widely expressed in the haematopoietic system, local CXCL12/CXCR4 stimulation mediates the recruitment of reparatory cells vs. proinflammatory leukocytes in ischaemic tissue, whereas systemic CXCR4 antagonism mobilizes not only haematopoietic stem and progenitor cells but also CXCR4^+ leukocytes, affecting all haematopoietic lineages in patients and mice.14
Molecular imaging to guide timely therapeutic targeting of CXCR4 after MI

Over the last years, the value of molecular PET imaging of cardiac CXCR4 expression after MI using $^{68}$Ga-pentixafor has been studied in pre-clinical as well as clinical settings. $^{3,13}$ Similar efforts of PET-based molecular imaging were previously also performed to track proinflammatory CCR2 + leucocyte accumulation in the heart over time after myocardial I/R injury in mice $^{14}$ as well as to trace VCAM-1 expression as a biomarker of local inflammation in the heart after MI. $^{15}$ Also, PET tracing of superoxide production as read-out of oxidative stress in the injured heart recently revealed a correlation of signal intensity with reduced chronic cardiac function. $^{16}$ Such local imaging provides advantages over analysis of systemic inflammation biomarkers by directly providing insights into the ongoing molecular mechanisms in the injured tissue itself. In the current study, Hess et al. further build on these insights and elegantly illustrate the advantages of molecular imaging in guiding therapeutic intervention by identifying the most promising time point for drug application in a pre-clinical model. $^{2}$ Although the findings are mainly related to myocardial ischemia, patients early after ST-elevation MI and reperfusion revealed increased, albeit highly variable, CXCR4 expression in the infarcted region. As this signal inversely correlated with cardiac functional recovery after ischemia/reperfusion injury via endothelial nitric oxide synthase-dependent mechanism. $^{12}$

In conclusion, building on the virtues of molecular PET imaging for non-invasive analysis of biomarker expression within injured tissue in a pre-clinical as well as in a clinical setting, the study of Hess et al. demonstrates the value of CXCR4 PET imaging in identifying the best time point of anti-inflammatory treatment by CXCR4 antagonism with respect to chronic cardiac function. $^{2}$

Conflict of interest: none declared.

References