

Online Supplement

The Macrophage and Cardiac Disease

Part 4 of a 4-part review series: The Macrophage in Cardiovascular Disease

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Online Table 1. Perturbation of monocytes/macrophages in experimental models of cardiac injury and key results/findings.

| Reference | Experimental model/study details | Key results/findings |
|--------------------------|---|--|
| Nahrendorf et al. (1) | <ul style="list-style-type: none"> • clodronate liposome (phase 1 or phase 2 after injury) • MI | <ul style="list-style-type: none"> • reduced macrophages (either phase 1 or 2 depleted) • reduced fibrosis (either phase 1 or 2 depleted) • reduced inflammation • reduced vascularization |
| Kaikita et al. (2) | <ul style="list-style-type: none"> • Ccr2^{-/-} • MI | <ul style="list-style-type: none"> • reduced macrophages • improved cardiac function • reduced proteolytic activity • reduced inflammation |
| Hayashidani et al. (3) | <ul style="list-style-type: none"> • anti-Ccl2 gene therapy • MI | <ul style="list-style-type: none"> • increased survival • reduced macrophages • improved cardiac function • reduced fibrosis • reduced inflammation |
| Dewald et al. (4) | <ul style="list-style-type: none"> • Ccl2^{-/-} • MI | <ul style="list-style-type: none"> • reduced macrophages • reduced fibrosis • reduced vascularization • altered inflammation • improved cardiac function |
| Hilgendorf et al. (5) | <ul style="list-style-type: none"> • Nr4a1^{-/-} • MI | <ul style="list-style-type: none"> • reduced fibrosis • larger scar • reduced cardiac function • increased inflammation |
| Leuschner et al. (6) | <ul style="list-style-type: none"> • Splenectomy • MI | <ul style="list-style-type: none"> • reduced cardiac function • smaller scar • reduced fibrosis • reduced macrophages |
| Gao et al. (7) | <ul style="list-style-type: none"> • MIF^{-/-} • I/R MI | <ul style="list-style-type: none"> • reduced inflammation • reduced macrophages • reduced myocyte apoptosis • reduced infarct size |
| van Amerongen et al. (8) | <ul style="list-style-type: none"> • clodronate liposome • cryoinjury | <ul style="list-style-type: none"> • reduced survival • reduced vascularization • larger scar • reduced fibrosis |
| Frantz et al. (9) | <ul style="list-style-type: none"> • clodronate liposome | <ul style="list-style-type: none"> • reduced survival • increase LV thromboembolic events • reduced fibrosis • increased inflammation |
| Zhao et al. (10) | <ul style="list-style-type: none"> • Cxcr6^{-/-} • I/R MI | <ul style="list-style-type: none"> • improved cardiac function • reduced infarct size |

| | | |
|-----------------------|---|--|
| DeBerge et al. (11) | <ul style="list-style-type: none"> • MerTK^{-/-} • I/R MI | <ul style="list-style-type: none"> • increased infarct size • increased inflammation • reduced cardiac function |
| Meyer et al. (12) | <ul style="list-style-type: none"> • Wif1^{-/-} • MI | <ul style="list-style-type: none"> • larger scar • reduced cardiac function • reduced macrophages |
| Howangyin et al. (13) | <ul style="list-style-type: none"> • Mertk^{-/-}Mfge8^{-/-} • MI | <ul style="list-style-type: none"> • reduced cardiac function • reduced fibrosis |
| Leblond et al. (14) | <ul style="list-style-type: none"> • GW2580 treatment • MI | <ul style="list-style-type: none"> • increased inflammation • reduced cardiac function |
| Lorchner et al. (15) | <ul style="list-style-type: none"> • Oxmr^{-/-} and Reg3b^{-/-} • MI | <ul style="list-style-type: none"> • reduced macrophages • reduced survival • reduced fibrosis |
| Hayasaki et al. (16) | <ul style="list-style-type: none"> • Ccr2^{-/-} • I/R MI | <ul style="list-style-type: none"> • reduced infarct size • reduced macrophages • reduced fibrosis |
| Leuschner et al. (17) | <ul style="list-style-type: none"> • Ccr2-siRNA nano-particles • I/R MI | <ul style="list-style-type: none"> • reduced infarct size • reduced macrophages |
| Majmudar et al. (18) | <ul style="list-style-type: none"> • Ccr2-siRNA nano-particles • ApoE^{-/-} • MI | <ul style="list-style-type: none"> • reduced macrophages • reduced inflammation • improved cardiac function |
| Liehn et al. (19) | <ul style="list-style-type: none"> • Ccl2 competitor treatment • I/R MI | <ul style="list-style-type: none"> • improved cardiac function • reduced fibrosis • reduced macrophages |
| He et al. (20) | <ul style="list-style-type: none"> • Lp-PLA2 BM chimeras • MI | <ul style="list-style-type: none"> • improved cardiac function • reduced inflammation • reduced fibrosis • increased vascularization |
| Panizzi et al. (21) | <ul style="list-style-type: none"> • ApoE^{-/-} • MI | <ul style="list-style-type: none"> • increased macrophages • increased inflammation • increased vascularization • reduced cardiac function |

Supplemental References

1. Nahrendorf M, Swirski FK, Aikawa E et al. The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions. *J Exp Med* 2007;204:3037-47.
2. Kaikita K, Hayasaki T, Okuma T, Kuziel WA, Ogawa H, Takeya M. Targeted deletion of CC chemokine receptor 2 attenuates left ventricular remodeling after experimental myocardial infarction. *Am J Pathol* 2004;165:439-47.
3. Hayashidani S, Tsutsui H, Shiomi T et al. Anti-monocyte chemoattractant protein-1 gene therapy attenuates left ventricular remodeling and failure after experimental myocardial infarction. *Circulation* 2003;108:2134-40.
4. Dewald O, Zymek P, Winkelmann K et al. CCL2/Monocyte Chemoattractant Protein-1 regulates inflammatory responses critical to healing myocardial infarcts. *Circ Res* 2005;96:881-9.
5. Hilgendorf I, Gerhardt LM, Tan TC et al. Ly-6Chigh monocytes depend on Nr4a1 to balance both inflammatory and reparative phases in the infarcted myocardium. *Circ Res* 2014;114:1611-22.
6. Leuschner F, Rauch PJ, Ueno T et al. Rapid monocyte kinetics in acute myocardial infarction are sustained by extramedullary monocytopoiesis. *J Exp Med* 2012;209:123-37.
7. Gao XM, Liu Y, White D et al. Deletion of macrophage migration inhibitory factor protects the heart from severe ischemia-reperfusion injury: a predominant role of anti-inflammation. *J Mol Cell Cardiol* 2011;50:991-9.

8. van Amerongen MJ, Harmsen MC, van Rooijen N, Petersen AH, van Luyn MJ. Macrophage depletion impairs wound healing and increases left ventricular remodeling after myocardial injury in mice. *Am J Pathol* 2007;170:818-29.
9. Frantz S, Hofmann U, Fraccarollo D et al. Monocytes/macrophages prevent healing defects and left ventricular thrombus formation after myocardial infarction. *FASEB J* 2013;27:871-81.
10. Zhao G, Wang S, Wang Z et al. CXCR6 deficiency ameliorated myocardial ischemia/reperfusion injury by inhibiting infiltration of monocytes and IFN-gamma-dependent autophagy. *Int J Cardiol* 2013;168:853-62.
11. DeBerge M, Yeap XY, Dehn S et al. MerTK Cleavage on Resident Cardiac Macrophages Compromises Repair After Myocardial Ischemia Reperfusion Injury. *Circ Res* 2017;121:930-940.
12. Meyer IS, Jungmann A, Dieterich C et al. The cardiac microenvironment uses non-canonical WNT signaling to activate monocytes after myocardial infarction. *EMBO Mol Med* 2017;9:1279-1293.
13. Howangyin KY, Zlatanova I, Pinto C et al. Myeloid-Epithelial-Reproductive Receptor Tyrosine Kinase and Milk Fat Globule Epidermal Growth Factor 8 Coordinately Improve Remodeling After Myocardial Infarction via Local Delivery of Vascular Endothelial Growth Factor. *Circulation* 2016;133:826-39.
14. Leblond AL, Klinkert K, Martin K et al. Systemic and Cardiac Depletion of M2 Macrophage through CSF-1R Signaling Inhibition Alters Cardiac Function Post Myocardial Infarction. *PLoS One* 2015;10:e0137515.

15. Lorchner H, Poling J, Gajawada P et al. Myocardial healing requires Reg3beta-dependent accumulation of macrophages in the ischemic heart. *Nat Med* 2015;21:353-62.
16. Hayasaki T, Kaikita K, Okuma T et al. CC chemokine receptor-2 deficiency attenuates oxidative stress and infarct size caused by myocardial ischemia-reperfusion in mice. *Circ J* 2006;70:342-51.
17. Leuschner F, Dutta P, Gorbатов R et al. Therapeutic siRNA silencing in inflammatory monocytes in mice. *Nat Biotechnol* 2011;29:1005-10.
18. Majmudar MD, Keliher EJ, Heidt T et al. Monocyte-directed RNAi targeting CCR2 improves infarct healing in atherosclerosis-prone mice. *Circulation* 2013;127:2038-46.
19. Liehn EA, Piccinini AM, Koenen RR et al. A new monocyte chemotactic protein-1/chemokine CC motif ligand-2 competitor limiting neointima formation and myocardial ischemia/reperfusion injury in mice. *J Am Coll Cardiol* 2010;56:1847-57.
20. He S, Chousterman BG, Fenn A et al. Lp-PLA2 Antagonizes Left Ventricular Healing After Myocardial Infarction by Impairing the Appearance of Reparative Macrophages. *Circ Heart Fail* 2015;8:980-7.
21. Panizzi P, Swirski FK, Figueiredo JL et al. Impaired infarct healing in atherosclerotic mice with Ly-6C(hi) monocytosis. *J Am Coll Cardiol* 2010;55:1629-38.