A MERry Response After Myocardial Infarction

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Despite a growing body of evidence that impaired clearance of apoptotic cells contributes to chronic autoimmune disease, how apoptotic cell engulfment influences cell death after acute myocardial infarction is not understood. In this issue of *Circulation Research*, Wan et al identify the MER tyrosine kinase receptor as an engulfment receptor important for the clearance of cellular debris generated during acute cardiac injury and a determining factor in infarct size and, in turn, cardiac function.

**Phagocytes in Cardiac Repair**

Because of the limited regenerative capacity within the adult mammalian heart, prompt clearance of cellular debris generated during injury is necessary for activation of reparative remodeling and protection of the remaining cardiomyocytes. Infarct wound repair starts by infiltration of neutrophils and monocytes into the injured heart. These leukocytes act to clear the necrotic and apoptotic cells and degrade released intracellular contents. Using a mouse model of experimental coronary occlusion–induced myocardial infarction, Wan et al show an increased expression of the phagocytic receptor MER, derived from the infiltration of phagocytic cells into the infarcted heart.

Two distinct phases of monocyte recruitment to the injured myocardium have been noticed. The CCR2/Ly6C\(^{hi}\)-expressing monocytes infiltrate early and have been shown to be the predominant phagocytic cell type in the infarct. These cells respond to inflammation initially generated by injured cardiomyocytes, fibroblasts, or endothelial cells, as well as by the mast cells, which are poised to release potent proinflammatory mediators, histamine, and tumor necrosis factor-\(\alpha\) quickly. Recruitment of inflammatory monocytes is required for the clearance of necrotic debris, because their depletion contributes to an increase in postinfarct necrotic lesions and neutrophil-mediated proteolytic injury. However, anti-inflammatory pathways are also needed, because excessive inflammation can be detrimental to the integrity of the myocardium. In the second phase of monocyte recruitment into the cardiac wound, CX3CR1/Ly6C\(^{lo}\) monocytes stimulate angiogenesis, collagen deposition, and myofibroblast accumulation. Both CCR2/Ly6C\(^{hi}\) and CX3CR1/Ly6C\(^{lo}\) monocyte subsets give rise to phagocytic macrophages. Interestingly, Wan et al show that MER expression is predominantly associated with the Ly6C\(^{lo}\) monocyte subset, suggesting that MER-mediated engulfment is most likely required during the resolution phase of the inflammatory response. The authors use MER-deficient mice (Mertk\(^{-/-}\)) in the coronary occlusion model to demonstrate the importance of cell clearance by the infiltrating mononuclear cells. Notably, they find no obvious differences in initial monocyte numbers or the recruitment of inflammatory cells to the injured site compared with wild-type mice, suggesting the importance of MER function during later stages of the inflammatory response (Figure).
TAMing Heart Failure

MER is a member of the TAM receptor family, which includes TYRO3, AXL, and MER tyrosine kinases. Ablation of all 3 TAM receptors in mice leads to degenerative changes of the male reproductive system, the retina, and the hematopoietic system, without any apparent defect in embryonic development. The TAM receptor triple-knockout mice also develop severe systemic autoimmunity, linked to an accumulation of dying cells. Although MER is expressed in all of the affected tissues of the triple-knockout mice, ablation of MER alone in the Mertk−/− mice does not have consequences as severe as those observed in the absence of the entire TAM receptor family. Wan et al find that MER deficiency in the Mertk−/− mice does not affect cardiac development; yet in the myocardial infarction model, MER deficiency leads to a progressive accumulation of dying cardiomyocytes compared with control mice.

Recovery from myocardial infarction requires tissue repair and suppression of inflammation. Recognition of apoptotic cells by phagocyte receptors, including MER, triggers anti-inflammatory signaling pathways, with potent induction of IL-10 production. In fact, administration of apoptotic cell-mimicking phosphatidylserine containing liposomes to healthy rats improves infarct repair. The impaired clearance of dying cardiomyocytes observed in Mertk−/− mice by Wan et al is consistent with the increased levels of inflammatory cytokines in Mertk−/− hearts 7 days postinfarction, along with the parallel decrease in IL-10 levels. At the same time, failure to clear necrotic tissue translates to an increase in the size of infarcted tissue and decrease in ventricle thickness of Mertk−/− mice, leading to impaired cardiac remodeling. Because prolonged inflammation is detrimental to subsequent heart function, the authors tested cardiac function 28 days after infarction. Heart performance, as measured by systolic function, was impaired in Mertk−/− mice when compared with Mertk+/- littermates. Importantly, using bone marrow transfer experiments in irradiated mice, the authors further demonstrate the requirement of MER function in hematopoietic cells. Collectively, these findings by Wan et al suggest that MER is an important receptor that regulates cell clearance in the heart and contributes to tissue healing after cardiac injury.

Future Considerations

Heart failure is a major cause of morbidity and mortality, with significant efforts made toward improving the survival rates in patients with acute myocardial infarction. Wan et al identify MER as the engulfment receptor participating in both the clearance of dying cardiomyocytes and the generation of anti-inflammatory cues needed for cardiac remodeling of the infarcted tissue. Their findings open up a new avenue in the pursuit of therapeutic intervention aimed at improving the cardiac function after ischemic injury. One caution is that their model of permanent coronary artery occlusion does not incorporate the reperfusion phase of the recovery, which comes with its own set of risks and benefits.

**Figure.** MER tyrosine kinase deficiency leads to prolonged inflammation after myocardial infarction and increases the size of infarct. Following myocardial infarction, monocytes and macrophages (MΦ) infiltrate the injury site and clear apoptotic and necrotic cardiomyocytes. Engulfment of apoptotic cells leads to production of anti-inflammatory cytokines by the phagocytes and, in turn, dampening further inflammation in the cardiac tissue. In MER-deficient mice, clearance of dying cardiomyocytes is delayed, resulting in prolonged inflammation and increased infarct size. After cardiac injury, ADAM17-mediated proteolytic cleavage of MER is thought to result in the appearance of the soluble MER ectodomain (sMER), which might further influence clearance or resolution of inflammation in the cardiac tissue.
Finally, Wan et al.\textsuperscript{16} offer an intriguing hypothesis on the possible mechanism of MER inactivation in a natural setting. The authors demonstrate the appearance of a soluble form of MER (solMER) 5 days after the myocardial injury.\textsuperscript{16} SolMER has been shown to inhibit macrophage clearance of apoptotic cells by acting as a decoy receptor for dying cells and, thus, preventing their engulfment by the phagocyte.\textsuperscript{33} Because solMER is generated by ectodomain proteolysis mediated by the Adam-17 metallopeptidase,\textsuperscript{34} whose expression was reported to increase generated by ectodomain proteolysis mediated by the Adam-17 metallopeptidase,\textsuperscript{34} whose expression was reported to increase in patients with acute myocardial infarction,\textsuperscript{35} the possibility of therapeutic targeting of this pathway is speculated. Although potentially interesting, the exact time of the appearance of solMER before or during myocardial infarction needs to be established before the possibility of prophylactic (or therapeutic) protection from MER cleavage might be considered.

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\textbf{Disclosures}

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\textbf{References}

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