Myelopoiesis Following Myocardial Ischemia (MI) Involves Activation of the Nlrp3 Inflammasome by Neutrophil-Derived S100a8/a9

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Ischemic myocardial damage triggers leukocytosis, particularly the production of monocytes and neutrophils from the bone marrow and spleen (myelopoiesis). These cells infiltrate the evolving myocardial wound, degrade extracellular matrix, and aid in the clearance of dead cardiac myocytes and their debris. Although this inflammatory process is a prerequisite for tissue healing, it is non-specific and often blunt. If unchecked, excessive production of monocytes and neutrophils may result in abnormal ventricular remodeling and heart failure. The myocardial cellular and molecular events that orchestrate with the BM/spleen to regulate myelopoiesis remain unclear. We report here that the number of circulating monocytes and neutrophils peak within 24 hours following coronary artery ligation (LAD) in mice. This is due to expansion and proliferation of hematopoietic stem and multi-potential progenitor cells (HSPC) in the BM as well as extramedullary hematopoiesis in the spleen. MI induced-myelopoiesis was associated with a dramatic increase in the expression of S100a8/a9 (a damage associated molecular pattern), its receptor (Tlr4), the Nlrp3 inflammasome, and pro-IL1ß in the heart. Cell separation studies revealed that the infiltrating neutrophils and cardiac fibroblasts are the predominant source of S100a8/a9 and the Nlrp3 inflammasome respectively in the heart. Furthermore, deletion of S100a8/a9 not only reduced MI-induced myelopoiesis but also significantly improved the mortality and cardiac function in mice following LAD. These data support our hypothesis that neutrophil-derived S100a8/a9 interact with Tlr4 on cardiac fibroblasts to induce the Nlrp3 inflammasome and produce IL1ß, which in turn stimulates IL-1R on HSPCs to promote myelopoiesis. Pharmacological strategies aimed at inhibition of S100a8a/9 or the Nlrp3 inflammasome-mediated production of IL1ß may be a promising approach to limit inflammation following acute coronary syndrome.

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