Developmental origin of cardiac macrophages in steady state and myocardial infarction

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Background: Macrophages are the most abundant immune cells in the myocardial tissue in steady state. The sterile inflammation caused by myocardial infarction triggers a massive immune reaction, which leads to a profound influx of neutrophils and monocytes. In the postacute phase of infarction macrophages play an essential role in reparative processes. Recently, it has become clear that macrophages in the heart have a dual developmental origin from embryonic and bone marrow (BM) hematopoiesis. In this study, we sought to investigate the contribution of embryonic derived macrophages to the cardiac macrophage pool in steady state as well as the acute and chronic phase after ischemia/reperfusion injury.

Methods/Results: To address the origin of macrophages in steady state we used different models of lineage tracing to determine the developmental origin of cardiac macrophages. Using FLT3-Cre mice and radiation-independent CD45.1/2 bone marrow chimera, we found that the resident macrophage population in the heart is mainly independent of definitive hematopoiesis (approximately 70-80% of cardiac macrophages). The BM-dependent population on the other hand is replenished by blood-derived monocytes.

Further we used the radiation-independent CD45.1/2 bone marrow chimera to characterize the origin of macrophages at different time points after I/R-injury. In the acute phase after myocardial infarction we observed a profound influx of BM-derived macrophages in the infarct region and also in the remote area. 30 days after I/R-injury the composition of the resident macrophage pool was mainly comprised of BM-independent macrophages, similar to steady state conditions. To address the role of BM-derived macrophages we used CCR2-ko mice, which have low numbers of inflammatory monocytes in peripheral blood. CCR2-ko mice showed reduced macrophage numbers in the acute phase after myocardial infarction. Using positron emission tomography we investigated the influence of CCR2-deficiency on cardiac function after I/R-injury. In comparison to WT mice, CCR2-ko mice showed a significantly increased infarct size. Cardiac remodeling, determined by end-diastolic volume, on the other hand was improved in CCR2-ko mice. The ejection fraction was similar in both groups.

Conclusion: The cardiac macrophage pool is mainly comprised of BM-independent macrophages. In response to I/R-injury monocyte-derived macrophages transiently enter the myocardium but do not persist in significant numbers over time. The influx of BM-derived macrophages after I/R-injury was reduced using CCR2-ko mice, which led to improved cardiac remodeling. Our findings are of potential importance for understanding the cardiac immune response and for the therapeutic targeting of macrophages in inflammatory conditions.