Changes in the immune cell landscape in the infarcted mouse heart

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Background: Myocardial Infarction (MI) and Ischemic Heart Failure represent the leading causes of death globally. Myocardial remodeling after MI is accompanied and driven by a strong immune response with an accumulation of several, partially opposing immune cell types. The temporal and spatial dynamics of this cardiac specific immune cell infiltration, however, have not been systematically evaluated.

Purpose: We characterized the dynamics of the immune cell repertoire in murine hearts following myocardial infarction by multi-color flow cytometry using a novel 12-marker panel allowing us to characterize major principal leukocyte lineages with a total of 10 distinct leukocyte populations. In parallel, we studied the immune response after MI in secondary lymph organs such as heart’s draining lymph nodes and the spleen. In addition, we performed transcriptional analysis of the healthy and infarcted hearts by bulk RNA at selected time points.

Methods: Permanent ligation of the left descending coronary artery (LAD), ischemic/reperfusion injury (I/R) and sham surgery was performed on C57BL6/J, 10 weeks old male mice. Leukocytes dynamics and T cell responses were screened in infarcted and remote areas of the heart, as well as in blood, spleen, and heart’s draining lymph nodes after 1, 3, 7, 14 and 28 days by multi-color flow cytometry. Also, immune activation and exhaustion transcription analysis by bulk RNA of healthy and infarcted hearts was performed at day 3, 7 and 28 days after MI.

Results: We describe a sequential shift in the resident heart leukocyte population, a change in T cell activation states and identified potential new targets such as NK and γδ T cells. While macrophages area the most frequent leukocytes under steady state, making up to 75% of the total relative leukocyte population, at day 28 Lymphocytes represent 50%, among which B cells represent the most of them, followed by T helper cells. At early stages, CD4+ T cells secret pro inflammatory cytokines in the heart and in the heart’s draining lymph nodes, however, as stable scar in the heart is formed at day 7 immunomodulatory cytokines secretion such as IL-10 was observed. This is consistent with the build-up of a relevant adaptive immune response involving antigen presenting DCs and effector T and B cells in the healing heart.

Conclusions: Our findings contribute to identify novel cellular and transcriptional targets in the fight against ischemic heart failure.