P7 P2Y12 -dependent modulation of emergency hematopoiesis after myocardial infarction

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INTRODUCTION:

Inflammation is essential for cardiac wound healing after infarction (MI). Innate immune cells orchestrate removal of debris and promote tissue remodeling. Next to local recruitment from the blood, leukocyte supply via increased production in the bone marrow or by extramedullary hematopoiesis contributes to local post-ischemic myocardial inflammation. The pathways that carry the signals for increased demand of leukocytes from the site of injury along to hematopoietic stem cells in the bone marrow are incompletely understood. In this study, we investigate the role of P2Y12-receptor mediated regulation of emergency hematopoiesis after MI.

METHODS/RESULTSS:

Myocardial infarction was induced in C57BL/6N and P2Y12-receptor KO mice via permanent coronary ligation to reduce the influence of local reperfusion injury. We found that hematopoietic emergency response on day 2 after MI was significantly reduced in P2Y12-receptor KO mice as compared to age-matched controls with reduced cell cycle activity of upstream hematopoietic stem and progenitor cells (LSK cells). The same effect was observed after treatment with the P2Y12-receptor blocker prasugrel (5mg/kg bw po once daily) as measured by flow cytometry using KI67/DAPI cell cycle staining as well as BrdU incorporation assay. Reduced cell cycle activity of upstream hematopoietic stem cells resulted in reduced numbers of downstream hematopoietic progenitors (GMP/ MDP) on day 3 after MI. Furthermore, inhibition of the P2Y12-receptor led to impaired mobilization of hematopoietic progenitors from the bone marrow into the blood, thus less seeding of hematopoietic progenitors in the spleen. As a consequence, decreased medullary and extramedullary hematopoiesis led to reduced numbers of leukocytes in the blood (neutrophils, inflammatory Ly6Chi monocytes) and reduced infiltration in the infarct zone as measured on day 7 after MI by flow cytometry.

CONCLUSIONS:

In this study, we demonstrate that P2Y12-mediated signaling is involved in emergency hematopoiesis after MI and reduces post-infarct myocardial inflammation. Better understanding of the upstream regulation of the inflammatory cascade after MI may provide new strategies to improve post-infarct myocardial healing.