STAT1 in myeloid cells promotes extramedullary haematopoiesis during MCMV infection and sterile inflammation

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In the adult organism blood formation takes place in the bone marrow, while under pathological conditions hematopoiesis can also occur outside of the bone marrow, a phenomenon known as extramedullary hematopoiesis (EMH). Most frequently EMH occurs in the spleen, which is able to create a specialized microenvironment to support attraction, proliferation and differentiation of hematopoietic stem and progenitor cells. Cytomegalovirus (CMV) infection is often fatal for immunocompromised patients and induces bone marrow suppression and EMH in humans and mice. Signal transducer and activator of transcription 1 (STAT1) is a crucial mediator of innate antiviral immunity. We have used cell-type restricted deletion of Stat1 to determine the contribution of STAT1 signaling in myeloid cells to EMH during murine CMV (MCMV) infection and CpG-oligonucleotide- (CpG-ODN-) induced inflammation. Using flow cytometry and hematopoietic functional assays we found that myeloid STAT1 drives compensatory erythropoiesis in the spleen in both experimental models and accelerates blood cell recovery upon MCMV infection. Macrophages are central constituents of the erythropoietic niche in the bone marrow and the spleen. During MCMV infection, STAT1 in myeloid cells protects splenic macrophages, neutrophils and NK cells from infection-associated apoptosis and limits early MCMV replication. In contrast, STAT1 did not impact on splenocyte apoptosis upon CpG-ODN challenge, suggesting that the EMH-promoting function of STAT1 is not solely due to its antiviral and pro-survival activities. Taken together, our data demonstrate that myeloid cells control early MCMV replication in the spleen and promote compensatory hematopoiesis during CMV infection and systemic inflammation through STAT1-dependent mechanisms.
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