Myeloid type I IFN sensing facilitates splenic stress erythropoiesis

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Type selection
Choose your preferred presentation format: Oral presentation

General data
Track: Innate Immunity
Topic: Monocytes and macrophages

Abstract text
Text: Infections and inflammation can impair steady-state erythropoiesis and induce alternative extramedullary stress erythropoiesis in organs like liver or spleen. To date, there is limited understanding of how the erythroblastic islands' microenvironment facilitate stress erythropoiesis.

Here, we studied erythropoiesis in the murine spleen upon exposure of mice to the synthetic TLR9 agonist CpG ODN. We sorted myeloid and progenitor cells for single cell transcriptome sequencing (scRNA-seq) and modelled erythroid development by combining RNA-velocity and trajectory inference methods. To functionally determine the role of myeloid type I interferon (IFN) signaling, we challenged CD169$^{cre/+}$ and LysM$^{cre/+}$ *Ifnar*$^{fl/fl}$ (interferon alpha/beta receptor) mice and analyzed the impact on stress erythropoiesis at different time points.

Exposure to CpG strongly enhanced the transition of pro-erythroblasts towards the erythroblast stage at single cell level. Interestingly, dysregulation of Gata1/2 and altered IFN signaling in pre-erythroblasts explained enhanced erythropoiesis under stress conditions. CpG activated pre-red pulp macrophages (RPM) expressed the IFN-inducible chemokine ligand 2 (*Ccl2*), an agonist of the atypical chemokine receptor 1 (ACKR1) expressed on erythroblasts, which had been shown to be an essential regulator of hematopoiesis. Using CD169$^{cre/+}$ *Ifnar*$^{fl/fl}$ mice, we confirmed that effective stress erythropoiesis required type I IFN mediated activation of pre-red pulp macrophages (pre-RPM) and the effect was even more pronounced in CpG-challenged LysM$^{cre/+}$ *Ifnar*$^{fl/fl}$ animals. In these mice, the loss of IFNAR signaling in monocytes strongly reduced *Ccl2* expression and hampered the induction of stress erythropoiesis at day 1 and day 3.

Our results indicate that stress erythropoiesis depends on myeloid IFNAR signaling and uses alternative transcriptional programs. We are currently analyzing bulk and scRNA-seq time course experiments. Further, we use *Ackr1*$^{-/-}$ mice to study the role of ACKR1 during stress erythropoiesis. We anticipate that our results provide fundamental insights to improve our understanding of anemia of inflammation in the clinical setting.

Conflict of Interest statement
Do you have any conflict of interest to declare?: No

Affirmation
1. Consent to participate and present onsite: Yes
2. Consent to publication publication: Yes
3. Consent on treatment of contact details saved in this system: Yes