**POSTER 27: MafB in HSCs: A Journey from Myeloid Commitment to Innate Memory**

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Hematopoietic stem cells (HSCs), residing within the bone marrow, are long-life cells with self-renewal capacity, required to replenish the blood and immune compartment over the course of a lifetime. Due to these features, HSCs face the challenge of striking a delicate equilibrium between self-renewal and extensive proliferation to replenish depleted blood cells. This delicate equilibrium is crucial for maintaining homeostasis and responding to the ever-changing demands of the hematopoietic system.

During normal myelopoiesis to maintain homeostasis, the transcription factor MafB and the myeloid cytokine M-CSF play critical roles in the early commitment of HSCs towards the myeloid lineage. Conversely, in response to infection, pathogen-associated molecular patterns (PAMP) and inflammatory cytokines become crucial factors, alongside MafB and M-CSF, in driving emergency myelopoiesis.

Additionally, our recent findings have demonstrated that HSCs possess the ability to retain a memory of previous infectious signals, which subsequently enables them to mount an enhanced response upon encountering a second identical stimulus. This memory, characterized by epigenetic reprogramming, has been referred to as "trained immunity". Initially observed in monocytes and macrophages, this phenomenon has significant implications. Given its known role in regulating the macrophage-specific enhancer repertoire and governing the self-renewal gene network in macrophages, we postulate that the transcription factor MafB, which is also expressed in HSCs, may serve as another factor involved in imprinting the innate memory of HSCs.

In order to bind to DNA and activate transcription, it is essential for MafB, a bZip transcription factor, to form dimers. MafB can form two types of dimers: a homodimer with itself and heterodimers with other members of the AP1 family including Fos. Interestingly, both MafB and Fos are expressed in HSC but the role of alternate dimers on HSC biology has not been evaluated yet neither in early myeloid commitment of HSC nor during imprinting of innate memory.

The aim of this work will be to investigate the molecular mechanisms underlying MafB-controlled early myeloid commitment of HSC as well as potential role in innate memory imprinting. For this objective, two mouse models have been created. The first one involves the targeted depletion of MafB in M-CSFR expressing cells in the bone marrow including HSC (MafB flox:csf1R iCre, herein called MafB KO), while the second model enforces heterodimerization with Fos by introducing an amino acid modification at position 269 (MafB flox/E269R csf1R iCre, herein referred as MafB-E269R). Both mouse strains are viable and fertile. So far, we characterized HSPCs compartment in MafB KO at steady state and observe a drastic reduction of cell number as well as repopulating capacity in 1:1 competitive transplantation experiments. Challenges with different stimuli inducing either early myeloid commitment and/or innate memory are in progress in both MafB KO and MafB-E269R mice. We plan to investigate both transcriptomic pathways involved through RNAseq and sc-RNAseq and epigenetic memory acquisition thanks to ATACseq.

This study should unveil novel insights into the role of MafB in governing early myeloid commitment of HSCs and its potential involvement in their innate memory, opening the door to the discovery of previously unknown mechanisms that shape immune responses.