Epigenetic innate immune memory in hematopoietic stem cells

Hematopoietic stem cells (HSCs) are rare cells that can give rise to the entire blood system. In case of infection, they can respond to pathogens by increased differentiation especially towards the myeloid lineage. One of the most important characteristics of immune cells is a memory of previous infection to respond better to a second stimulation. It has been shown in macrophages that such a memory implicates epigenetic modifications. Here, we hypothesized that HSCs might keep a memory of previous infection by a similar mechanism.
We observe that mice transplanted with HSCs of mice pre-stimulated with LPS 4 weeks before, have a better survival after infection with Pseudomonas aeruginosa compared to mice transplanted with un-stimulated HSC. This better survival is link to an increase of myeloid progenitors cells (GMP) in their spleen. This effect is despite only transient and quick changes in HSCs progeny and gene-expression as check by FACS and RNA-Seq. To investigate whether this functional effect was linked to epigenetic changes in chromatin conformation, we performed ATAC seq analysis on HSCs 4 and 12 weeks after acute LPS stimulation. Compared to controls we observed differential chromatin accessibility in trained HSCs. Gene ontology analysis of genes link to enriched peaks in trained HSCs showed that they are related to immune response. Using H3K4me1 Chip-seq of all hematopoietic lineage of the BM, we observed increased chromatin accessibility in enhancers of myeloid lineage. RNA-seq analysis of LT-HSC from naïve of trained mice 1 day after a re-stimulation with LPS show an increased responsiveness and especially an increase of neutrophil specific genes expression. These enhancers were enriched for targets of the myeloid transcription factor C/EBPb, a central mediator of emergency hematopoiesis. ATAC-seq analysis show that C/EBPβ deletion erased the long-term inscription of LPS induced epigenetic marks thus abolishing the innate memory.
In conclusion, a single LPS injection induces stable and cryptic chromatin changes in HSCs without affecting their gene expression. Our results suggest that acute stimulation of HSC, that are at the top of the hematopoietic hierarchy, can be beneficial by establishing an epigenetic memory that protects the host from future pathogen challenges.

Keywords : HSC, epigenetic memory, trained immunity, innate immune response, C/EBPb, emergency hematopoiesis
Authors :
References : , , ,

Authors

De Laval Bérengère 1, Maurizio Julien 1, Kandalla Prashanth 2, Brisou Gabriel 1, Matcovitch-Natan Orit 3, David Eyal 3, Mildner Alexander 4, Leutz Achim 4, Nadel Bertrand 1, Bordi Christophe 5, Amit Ido 3, Sarrazin Sandrine 1, Sieweke Michael 6,

1. CIML, Marseille, FRANCE
2. CRTD, Dresden, GERMANY
3. Weizmann Institute of Science, Rehovot, ISRAEL
4. MDC, Berlin, GERMANY
5. Institut de Microbiologie de la Méditerranée, Marseille, FRANCE
6. CRTD/CIML, Dresden, GERMANY