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POSTER ABSTRACTS

501.HEMATOPOIETIC STEM AND PROGENITOR CELLS AND HEMATOPOIESIS: BASIC AND TRANSLATIONAL

Acute Inflammation Redirect Bone Marrow Hematopoietic Stem Cell Cycling and Differentiation Program By Reshaping Their Chromatin Architecture at Long-Term

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Background: Acute and persistent inflammation induced by microbial infections/sepsis or by therapeutic interventions, such as whole-body irradiation and CAR-T therapy, triggers a rapid overwhelming immune response in the host. While these responses are well defined in the short-term, the long-term impact of the inflammatory injury on the hematopoietic system still needs to be unveiled.

Using a murine model of severe inflammation induced by bacteria *P. aeruginosa* (*P. aer.*) or LPS, our group has previously reported that bone marrow (BM) hematopoietic stem cells (HSC) respond to infections with an aberrant expansion associated with their transitory inability to generate the downstream myeloid progenitors. Such dysfunctions correlated with the suppression of transcription factors governing stem-cell self-renewal and myeloid differentiation. Furthermore, when transplanted into healthy mice, the "inflamed" HSC showed reduced ability to contribute to the myeloid lineage and to engraft at long-term, suggesting that they retain memory of the LPS-mediated insult and maintain long-lasting changes. Thus, we hypothesized that severe inflammation alters the HSC epigenome, reshaping their transcriptional programs and affecting cell fate decisions and differentiation.

Methods: We performed time-course experiments in WT mice challenged with a single dose of LPS or PBS, as control, and investigated 1) the kinetics of hematopoietic recovery by flow-cytometric immunophenotypic characterization, including cell-cycle 2) changes in the chromatin landscape of Lin- sorted BM subpopulations identified by the expression of the CD150 and CD48 markers as Long-Term (LT-HSC), Short-Term (ST-HSC), and Multipotent Progenitors (MPP1/2 and MPP3/4) using ATAC-seq.

Results: Our studies revealed that the LPS challenge resulted in a significant increase in the cell-cycle of LT-HSC, ST-HSC, MPPs, common myeloid progenitors (CMP), and granulocyte-monocyte progenitors (GMP), which persisted up to 3 days from the inflammatory injury. Immunophenotypic analysis showed that while HSC frequencies returned to baseline at 5 days from LPS, the abundance and cell-cycle of myeloid progenitors and mature cells remained altered. Surprisingly, at 15 days post LPS, the cell-cycle of HSC markedly decreased, and such dysregulation was maintained until our last observation at 30 days from LPS. The pool of BM HSC was severely depleted and associated with exhaustion of T-cells but increased B-cells. GMP and Gr1+Mac1+ cells were also significantly decreased in the BM whereas mature lineages were increased in the peripheral blood, exhibiting high WBC, lymphocytes, and platelet count, neutrophilia, monocytosis, basophilia, and eosinophilia.

ATAC-seq analysis revealed prominent differences in the chromatin architecture of the four HSC subpopulations at steady state (PBS). In all of them, LPS induced both i) a transient reorganization of the chromatin in some loci, and ii) the formation of persistently reshaped regions. Deeper investigations into the long-term changed sites revealed that chromatic accessibility was altered in proximity of CTCF-enriched regions fundamental to mediate chromatin reorganization and drive gene expression. Moreover, LPS modified the accessibility of genomic loci involved in the maintenance of HSC stemness and quiescence as well as regulation of their cell-cycle, self-renewal, and cell fate decision.

Conclusions: Taken together these results suggest that LPS-mediated acute inflammation has long-lasting effects on HSC epigenetic regulation, influencing their cell-cycle and multilineage decisions.

Relevance: The association between the resulting phenotype and the persistency of epigenetically remodeled HSC loci identified here may provide potential insights for future therapeutic approaches to re-direct "inflamed" HSC to a normal differentiation program, thereby enabling an efficient innate host response.
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