Exploring Experimental Hematology: January 2020 (Volume 81)

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Deconstructing Blood Cell Research
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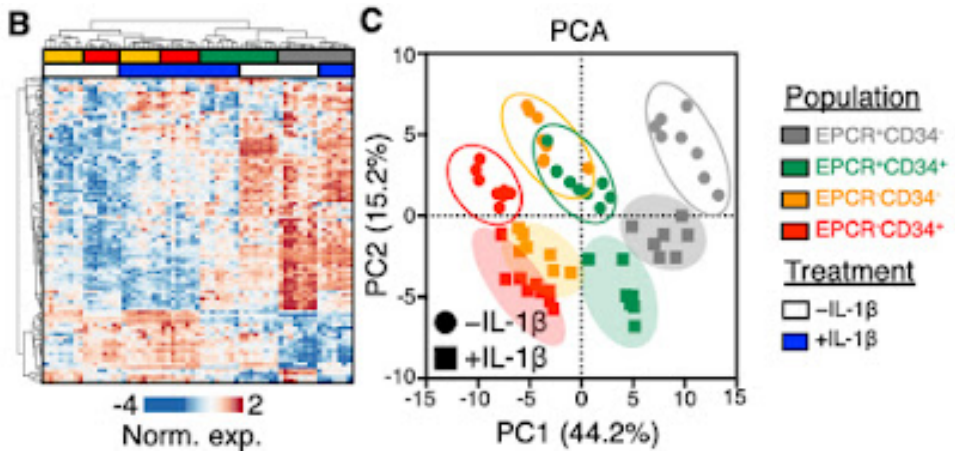
Exploring Experimental Hematology: CD34 and EPCR coordinately enrich functional murine hematopoietic stem cells under normal and inflammatory conditions

In this issue of Simply Blood, Grant Challen is exploring *Experimental Hematology* by highlighting and deconstructing one of his favorite manuscripts from the ISEH society journal: "CD34 and EPCR coordinately enrich functional murine hematopoietic stem cells under normal and inflammatory conditions."



Gene expression profile and principal component analysis of SLAM HSC subpopulations after chronic IL-1 treatment. Adapted from Rabe et al Figure 2.

Exp Hematol. 2019 Dec 18.

Rabe JL, Hernandez G, Chavez JS, Mills TS, Nerlov C, Pietras EM.

In a recent study in the laboratory of Dr. Eric Pietras (University of Colorado), Rabe et al use the cell surface markers EPCR and CD34 to coordinately distinguish HSCs with distinct functional and molecular properties within the SLAM (Lineage- c-Kit+ Sca-1+ CD48- CD150+) gate under conditions of chronic inflammation. By giving wild-type mice a 20-day treatment course of the pro-inflammatory cytokine IL-1, the authors show that the EPCR+ CD34- cells within the SLAM gate are largely unaffected. The numbers of EPCR+ CD34- HSCs does not dramatically change under chronic inflammation mediated by IL-1, and importantly their functional potential is not compromised in transplantation assays (unlike other EPCR / CD34 populations within the SLAM gate). In a complementary study, the authors also use an Fgd5-ZSGreen reporter mouse to show that the HSCs marked by this transgene also retain functional potential under chronic inflammatory stress. Cumulatively, the authors define a CD34- EPCR+ (or Fgd5-ZSGreen+) population of SLAM HSCs that retains dormancy and functional potential even in the face of strong external pressure from chronic IL-1 exposure.

My reason for reading the paper:
Inflammation is being increasingly implicated as a cell extrinsic factor that influences both the short-term and long-term function of HSCs in the bone marrow. And importantly, inflammation may be a selective pressure that supports certain mutations in clonal hematopoiesis.

Strategy used in this paper:
The authors used stringent flow cytometric gates to observe dynamic changes in HSC populations under chronic inflammatory stress. This was coupled with functional assays by bone marrow transplantation, and microfluidics-based transcriptional analyses.

Reasons you should read this paper:
This paper further dissects important molecular changes that occur in the most primitive, long-term HSCs in response to inflammation, which has implications for basic research as well as clinical conditions. One particularly important finding is the observation that the most primitive long-term HSCs (defined by EPCR+ CD34- SLAM) do not dramatically alter their cell cycle in response to chronic inflammation. This is opposed to the traditional view that inflammatory stress induces HSCs to exit quiescence, but the claim is well justified by the authors data. The discrepancy between this finding and previous studies likely results from less “pure” populations of long-term HSCs analyzed by other groups.

Quote from the author:
Chronic inflammatory disease – whether obesity, autoimmunity or aging - is a major public health concern that will impact many, if not most, of our lives. Understanding the impact of inflammation on hematopoiesis can unlock new approaches to treating and/or preventing co-morbidities ranging from anemia to bone marrow failure to leukemia. But first, we have to know what we’re looking at. This is particularly true as many of the common marker systems

we’ve relied upon to prospectively isolate HSC and their progeny in mice and humans were identified under homeostatic conditions. Many of them don’t identify the same populations in stress contexts. We see exactly that here – the composition of the SLAM gate changes significantly following IL-1 treatment, such that transplant of unfractionated SLAM cells versus the marker combinations we tested give distinct results. In the meantime, we’ve been studying some of the molecular programs HSC engage to maintain their function under chronic inflammatory stress. Altogether this story is part of a growing conversation about how best to study hematopoiesis in diverse conditions, to ensure our findings can contribute to improved health outcomes for individuals with inflammatory diseases.

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