Exploring Experimental Hematology: November 2017 (Volume 55)

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Exploring Experimental Hematology: Unboxing "Tet2 restrains inflammatory gene expression in macrophages" By Cull et al.

My reason for reading this paper:
It provides a new perspective on mechanisms of pathology attributed to Clonal Hematopoiesis of Indeterminate Potential (CHIP), which is so hot right now. CHIP has been implicated not only in blood disorders including leukemias, but also more recently in cardiovascular disease. The mechanisms that drive clonal hematopoiesis from hematopoietic stem and progenitor cells is of intense interest in the field, and the study of mutations that drive clonal dominance have identified mutations in TET2 as a driver of CHIP. TET2 encodes an epigenetic regulator of hydroxymethylation, and loss of TET2 function results in hypermethylation, particularly in enhancer regions. The negative impact of TET2 mutations and deficiency on hematopoietic stem cell function and differentiation is intensely investigated, but the effects on mature cells are less often examined. This paper was of great interest to me as it extended investigation of TET2 loss of function one step further by looking into the effects of TET2 deficiency on a mature cell type that regulates that microenvironment.

What to expect in this paper:
The authors shift the focus of the TET2 driving mutation from the hematopoietic stem and progenitor compartment to mature myeloid lineage cells - macrophages. TET2 is abundantly expressed in macrophages and monocyte precursors, and is upregulated upon activation with LPS. Importantly, the authors demonstrated that murine Tet2-deficient macrophages exhibit aberrant expression and regulation of inflammatory genes and cytokines (Fig. 1). Tet2-deficient macrophages upregulated inflammatory genes at steady state, and failed to resolve inflammation, as evidenced by increased and sustained arginase levels following activation. Consequently, Tet2 deficient mice exhibited an aberrant cytokine profile associated with sustained inflammation. Together, these data suggest that, in addition to altering the trajectory of differentiation from the stem cell, Tet2 mutations may also impact disease pathogenesis by promoting an inflammatory environment from the mature macrophage.

Reasons you should read this paper:
Given the recent heightened focus on the role of the inflammatory microenvironment in driving hematopoietic dysfunction and disease, the timing and relevance of this paper is spot on. Since its initial publication in Experimental Hematology in August of 2017, this paper has

been cited by over twenty papers investigating topics ranging from sepsis, heart failure, atherosclerosis, and, of course, clonal hematopoiesis. Ongoing work by the same group expands on examination of Tet2-associated inflammation in humans, with the aim of understanding how mutations in CHIP drive susceptibility to many different diseases with aging. I look forward to the next installment!

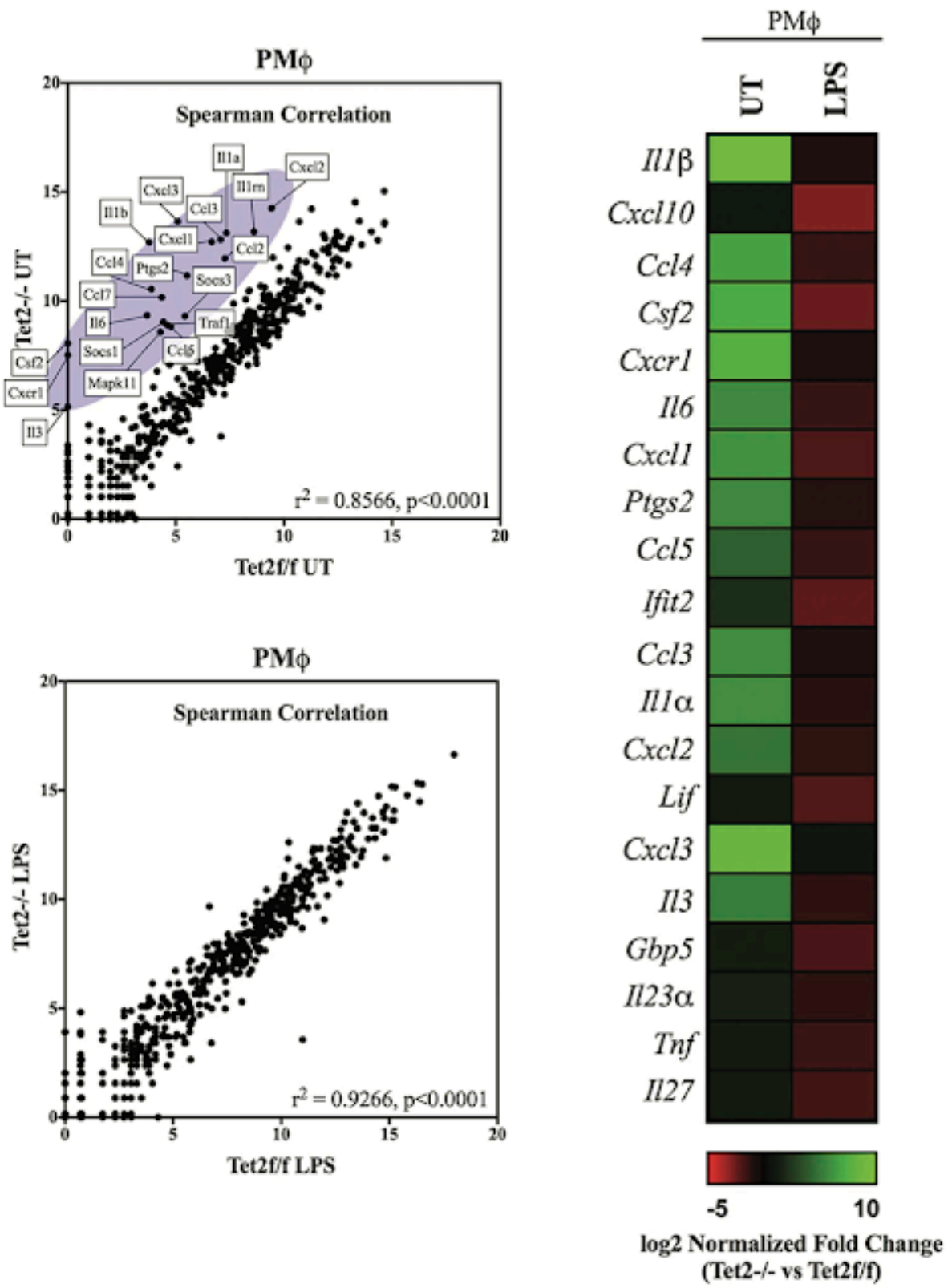

Figure 1 depicts the aberrant inflammatory response in Tet2-deficient macrophages. [Figure 4C&D from manuscript]

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In this issue of Simply Blood, Anna Beaudin is **Exploring *Experimental Hematology*** and highlighting and deconstructing one of her favorite manuscripts from the ISEH society journal: *"Tet2 restrains inflammatory gene expression in macrophages*" By Cull et al.