ELSEVIER

Blood 142 (2023) 937–938

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Mechanisms and Therapeutic Strategies to Reverse TET2 Mutant Clonal Hematopoiesis and the Risk of MDS, AML, and Atherosclerotic Cardiovascular Disease

Nicole Prutsch, PhD[1,2], Amélie Vromman, PhD[3,2], Brittaney Leeper, BS[4], Mengyu Chen, BS[3], Shuning He, PhD[1], Siyang Ren, MS[5], Christopher J. Walker, PhD[6], Mark W. Zimmerman, PhD[1], Mariana Janini Gomes, PhD[3], Eduardo J. Folco[3], Philipp J. Rauch, MD[7,8], Prafulla C. Gokhale, PhD[4], Brian J. Abraham, PhD[9], Donna S. Neuberg, ScD[5], Benjamin L. Ebert, MD PhD[8,10,7], Peter Libby, MD[3,2], A. Thomas Look, MD[1,2]

[1] Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA
[2] equal contribution, Boston
[3] Department of Medicine, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
[4] Experimental Therapeutics Core and Belfer Center for Applied Cancer Science, Dana-Farber Cancer Institute, Boston, MA
[5] Department of Data Science, Dana-Farber Cancer Institute, Boston, MA
[6] Karyopharm Therapeutics Inc., Newton, MA
[7] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA
[8] Broad Institute of MIT and Harvard University, Cambridge, MA
[9] Department of Computational Biology, St. Jude Children's Research Hospital, Memphis, TN
[10] Howard Hughes Medical Institute, Boston, MA

Inactivating mutations of the epigenetic modifier *TET2* are frequent in myeloid malignancies and clonal hematopoiesis of indeterminate potential (CHIP). These mutations in hematopoietic stem and progenitor cells (HSPCs) impart a clonal advantage with increased self-renewal. CHIP is associated with an increased risk of hematological malignancies and, surprisingly, with atherosclerotic cardiovascular disease, supported by studies in mice and humans. The heightened cardiovascular risk in CHIP patients may result from a pro-inflammatory slant of the mutant HSPC progeny, particularly monocytes and macrophages, independent from the risk imparted by elevated LDL cholesterol levels. Targeting molecules like IL-1β may provide a strategy to lower the risk of cardiovascular morbidity in patients with CHIP. However, as an alternative strategy, administration of drugs that selectively suppress the growth of mutant CHIP clones in the bone marrow (BM) might reduce the risk of both i) progression to MDS or hematologic malignancy and of ii) atherosclerotic cardiovascular disease. This study focused on identifying drugs that reverse the inflammatory and atherosclerotic properties of TET2-mutant macrophages. Our previous investigations demonstrated that the nuclear export inhibitor eltanexor selectively kills *Tet2*-mutant HSPCs in zebrafish embryos and reduces the number of mutant colonies in murine colony formation assays. A murine competitive repopulation model of CHIP tested the *in vivo* efficacy of eltanexor. We found that eltanexor selectively reduces *Tet2*-mutant circulating monocytes while having no effect on overall total white blood cell counts. Moreover, a second trial using *Ldlr-/-* atherosclerosis-prone mice consuming a high-cholesterol diet, showed that treatment with eltanexor selectively reduces the amount of aortic atherosclerotic plaque formation as well as spleen weight in mice injected with *Tet2+/-* (mutant) BM cells, whereas eltanexor had no significant effect in mice injected with *Tet2+/+* (wild-type) BM cells. Single-cell CITE-seq analysis of *Ldlr-/-* mice injected with a mix of *Tet2+/-* and *Tet2+/+* BM cells showed that eltanexor selectively reduces the percentage of *Tet2+/-* HSPCs. Additionally, CITE-seq analysis revealed a significant reduction in pro-inflammatory macrophages in the arterial wall after eltanexor treatment, along with a decrease in IL-1β expression by these cells. As TET2 functions in mechanistically regulating gene regulation through epigenetic DNA methylation, we employed ChIP-seq and CUT&RUN-Seq technologies to investigate the mechanisms underlying enhancer dysregulation caused by loss of *Tet2*. Enhancer profiling of bone marrow-derived macrophages showed that the negative regulator of the macrophage inflammatory response, ATF3, is associated with a super-enhancer. Notably, the ATF3 super-enhancer emerged as the largest super-enhancer in wild-type macrophages but was reduced in *Tet2*-mutant macrophages. Our investigation also revealed that ATF3 binds with IL-1β at H3K27ac modified regions, and this binding was significantly diminished in *Tet2*-mutant macrophages. Remarkably, treatment with eltanexor restored the binding of ATF3 to IL1β, providing a mechanism to explain the anti-inflammatory effect of eltanexor concordant with our *in vivo* results. In sum-

mary, this study proposes eltanexor treatment as a novel therapeutic approach to specifically target *TET2*-mutant cells in individuals with CHIP and sheds light on the underlying mechanisms of the pro-inflammatory slant of *TET2*-mutant macrophages. These findings offer potential new avenues for precise therapies in humans with CHIP and associated cardiovascular risks from atherosclerosis.

Disclosures Prutsch: *Karyopharm Therapeutics:* Research Funding. **Walker:** *Karyopharm Therapeutics Inc.:* Consultancy, Current Employment, Current equity holder in publicly-traded company. **Zimmerman:** *Foghorn Therapeutics:* Current Employment, Current holder of *stock options* in a privately-held company. **Neuberg:** *Madrigal Pharmaceuticals:* Current equity holder in private company. **Ebert:** *Exo Therapeutics:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy; *Neomorph Inc.:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Skyhawk Therapeutics:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *TenSixteen Bio:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Calico:* Research Funding; *Novartis:* Research Funding. **Libby:** *Novo Nordisk:* Research Funding; *Novartis:* Research Funding; *Genentech:* Research Funding; *Soley Therapeutics:* Current holder of *stock options* in a privately-held company; *XBiotech:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *iRhythm:* Current holder of *stock options* in a privately-held company; *TenSixteen Bioscience:* Current holder of *stock options* in a privately-held company. **Look:** *Karyopharm Therapeutics:* Research Funding.

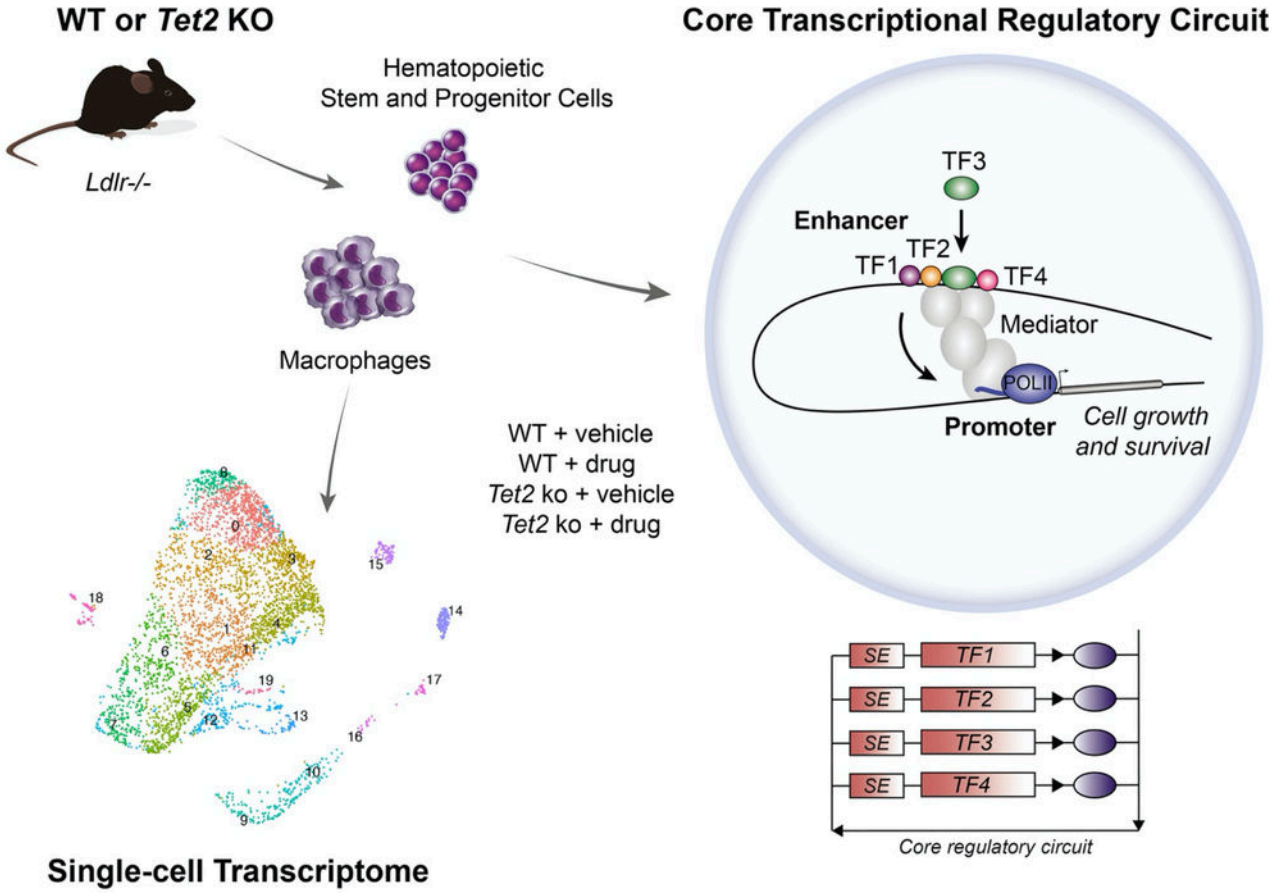

Figure 1

https://doi.org/10.1182/blood-2023-181149