POSTER 30: Impact of heterochromatin alterations and retrotransposon expression on HSC functional changes and clonal selection in the context of TET2 loss

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Clonal hematopoiesis of indeterminate potential (CHIP) refers to the stress or age-related expansion of mutated hematopoietic stem cells (HSCs) eventually increasing the risk of leukemia. CHIP is mainly driven by mutations in epigenetic factors such as TET2. Heterochromatin, notably by the trimethylation of lysine 9 of histone H3 (H3K9me3), plays a major role in repressing retroelements (RTEs). RTEs, such as long interspersed elements (LINE-1/Ll) or endogenous retroviruses (ERV) are major contributors of gene regulatory networks.

We previously showed increased RTE expression in HSCs upon aging and irradiation (IR) stress, a model of premature aging. This is associated with a loss of H3K9me3. We also showed that RTE derepression upon IR is associated with changes in HSC gene expression. TET2 was shown to repress RTE through H3K9me3 in embryonic stem cells. Derepressed RTE may rewire the transcriptome and act as the driving force behind HSC functional changes. However, if TET2 represses RTE in HSCs, and whether H3K9me3 changes and RTE derepression upon aging and stress play a role in clonal expansion of TET2 mutated HSCs is unknown.

Using H3K9me3 CUT&Tag experiments performed in HSCs sorted from Tet2-1-mice or WT littermates, we show that TET2 loss leads to a gain ofH3K9me3 at gene promoters, but to the loss ofH3K9me3 at RTE, mainly L!Md, the young subfamilies of Lis, and ERVs. RNA-seq experiments showed a gain of the HSC signatures in Tet2$^{-/-}$ HSCs, which correlates with an increased number and frequencies of HSCs as observed by F ACS. An enrichment in inflammatory pathways was also found in Tet2$^{-/-}$ as compared to WT HSCs

Gene deregulation is not associated with H3K9me3 changes at gene promoters but rather with H3K9me3 changes at intronic L1Md.

We further show that irradiating Tet2$^{-/-}$ -mice leads to an exacerbated loss ofH3K9me3 at RTEs in HSCs. This is associated with expression a higher number of RTEs.

These results show that TET2 controls RTEs through H3K9me3 in HSCs. Our results also suggest that LlMd derepression following TET2 loss may be involved in transcriptomic deregulation in HSCs. Whether the synergistic deregulation ofRTEs in Tet2HSCs is involved in their clonal expansion is currently under investigation.