National Human Genome Research Institute

The Forefront of Genomics

Development of hematologic malignancies in *Runx1/Tet2* deficient mice

Poster L4

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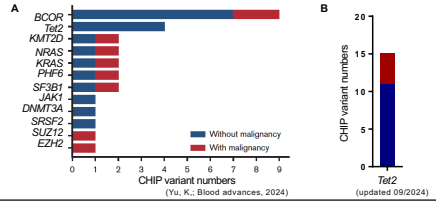
Oncogenesis and Development Section

Abstract

Familial platelet disorder with associated myeloid malignancies (FPDMM) is caused by germline *RUNX1* mutations and characterized by thrombocytopenia and increased risk of hematologic malignancies. Based on our recent longitudinal natural history study for patients with FPDMM, a large number of FPDMM patients have at least one somatic mutation in clonal hematopoiesis of indeterminate potential (CHIP) or AML driver genes, with *Tet2* being one of the most frequently mutated genes. These clinical findings suggest that *RUNX1* and *TET2* mutations/deficiency may cooperate in clonal hematopoiesis and hematologic malignancies in patients with FPDMM. To test this hypothesis, we generated *Runx1$^{f/f}$Mx1-CreTet2$^{f/f}$* mice, in which both *Runx1* and *Tet2* would be deleted in hematopoietic cells upon Cre induction with poly (I:C). After poly (I:C) treatment, *Runx1$^{f/f}$Mx1-CreTet2$^{f/f}$* mice displayed hematopoietic alterations primarily attributable to *Runx1* deficiency. In addition, *Runx1$^{f/f}$Mx1-CreTet2$^{f/f}$* mice exhibited lower platelet counts, increased percentage of c-Kit$^+$ cells in peripheral blood, compared to *Runx1$^{f/f}$Mx1-Cre* mice or those with other genotypes. Importantly, among the 11 *Runx1$^{f/f}$Mx1-CreTet2$^{f/f}$* mice, 5 were analyzed prior to death, and 4 of them developed leukemia, as demonstrated by flow cytometry and histological analysis. As expected, following transplantation of spleen cells from these 5 *Runx1$^{f/f}$Mx1-CreTet2$^{f/f}$* mice, recipients receiving cells from 4 leukemia donors developed myeloid leukemia with variable median survival. In contrast, hematologic malignancies were not observed in *Tet2$^{f/f}$Mx1-Cre* mice. Interestingly, the gene expression profile of leukemia cells from one of these mice differed markedly from the others, likely due to differences in leukemia cell phenotype and additional mutations. DNA sequencing of the three AML samples revealed somatic mutations orthologous to established human AML driver mutations, including predicted loss-of-function variants in *Tet3* and *Gata1*, and gain-of-function variants in c-*Kit* and *Kras*. These results suggest that *RUNX1* and *TET2* mutations/deficiency cooperate for hematologic malignancies. Additionally, the transplantable leukemia model can be a useful system to explore drug efficacy in vivo for FPDMM.

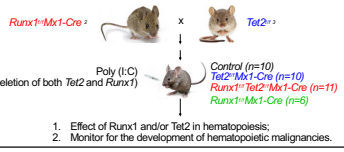
1. Background

Somatic mutations in *TET2* are frequently found in FPDMM patients



2. Study design:

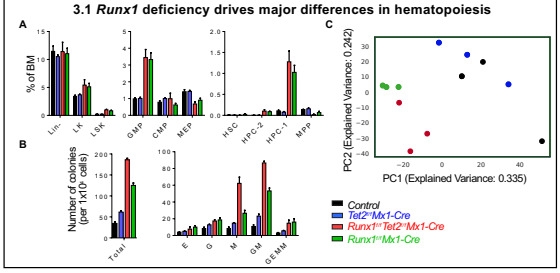
Do mutations in *RUNX1* and *TET2* cooperate for malignant transformation?



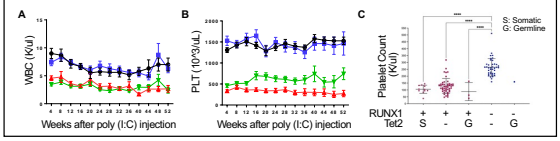
1. Effect of Runx1 and/or Tet2 in hematopoiesis;
2. Monitor for the development of hematopoietic malignancies.

3. Results

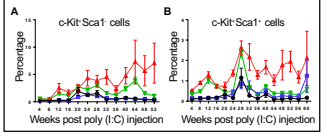
3.1 *Runx1* deficiency drives major differences in hematopoiesis



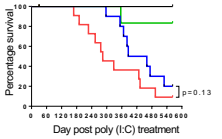
3.2 Platelet levels are consistently lower in *Runx1$^{f/f}$Tet2$^{f/f}$Mx1-Cre* mice



3.3 c-Kit$^+$ cells were increased in *Runx1$^{f/f}$Tet2$^{f/f}$Mx1-Cre* mice



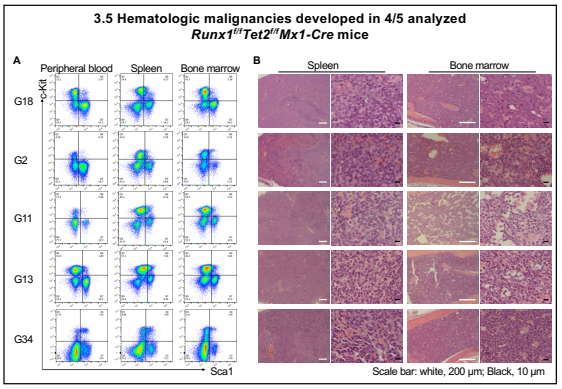
3.4 Overall survival



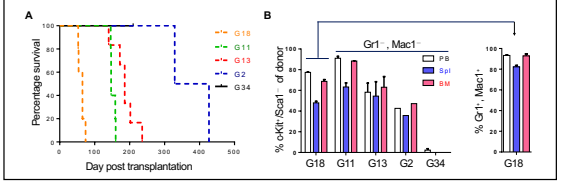
Conclusion and Future direction

- *RUNX1* and *TET2* mutations/deficiency cooperate for hematologic malignancies.
- The transplantable leukemia model can be a useful system to explore drug efficacy in vivo for FPDMM.
- Multiomic, immunologic, and mechanistic studies of this mouse model are ongoing.

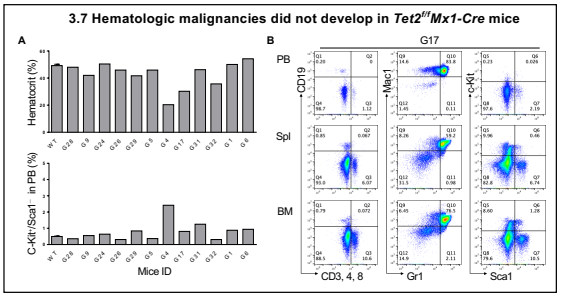
3.5 Hematologic malignancies developed in 4/5 analyzed *Runx1$^{f/f}$Tet2$^{f/f}$Mx1-Cre* mice



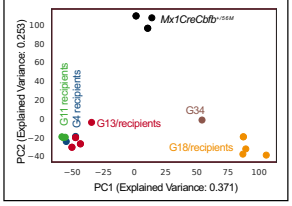
3.6 Hematologic malignancies developed in *Runx1$^{f/f}$Tet2$^{f/f}$Mx1-Cre* mice were transplantable



3.7 Hematologic malignancies did not develop in *Tet2$^{f/f}$Mx1-Cre* mice



3.8 Gene expression profile of analyzed *Runx1$^{f/f}$Tet2$^{f/f}$Mx1-Cre* mice



3.9 Mutations likely contribute to leukemia pathogenesis in *Runx1$^{f/f}$Tet2$^{f/f}$Mx1-Cre* mice

ID	Gene	Allele frequency	Mutation
G13	Grid1	0.424615385	p.Glu790Lys
	Kit	0.210300429	p.Asp814Tyr
	Kras	0.209150327	p.Gly12Val
G18	Tet3	0.985221675	p.Lys1244*
G11	Gata1	0.978448276	p.Arg293His

Reference

1. Yu, K., et al., Blood Adv, 2024. **8**(2): p. 497-511.
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3. Moran-Crusio, K., et al., Cancer Cell, 2011. **20**(1): p. 11-24.

There are no relevant conflicts of interest to disclose.

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