Assessing the Role of Constitutive JAK/STAT Signaling in Jak2V617F-p53 Post-MPN Leukemia Using a Novel Knock-in/Knock-out Mouse Model of Jak2V617F

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Activating mutations of JAK2V617F are present in the majority of patients with myeloproliferative neoplasms (MPNs), diseases that are at significant risk of acute myeloid leukemia (AML) transformation. Past mouse modeling has shown that combined JAK2V617F and p53 loss alone is sufficient to induce AML, highlighting the importance of this high-risk genotype. Current JAK inhibitor therapy is ineffective for the treatment of JAK2/p53 double-mutant leukemia suggesting either inadequate target inhibition or loss of oncogenic JAK-STAT signaling dependency. To further explore this, a novel Jak2V617F mouse model allowing for sequential knock-in followed by knock-out of the Jak2V617F oncogene using dual, orthogonal Dre/Cre recombinase systems has been developed. The main objectives were to validate this knock-in/knock-out mouse model in the context of p53 loss and to assess Jak2V617F dependency in Jak2V617F/p53 leukemia. It was demonstrated that Jak2V617F knock-in by Dre recombination combined with p53 nullizygosity results in a potent AML phenotype consistent with prior studies. Furthermore, we demonstrate that deletion of Jak2V617F via Tamoxifen in Dre-rox Cre-lox (Dre-Cre) cells in vivo suggests improvement in peripheral blood mutant cell fraction. Meanwhile, attempts for validation and mechanistic studies by deletion of Jak2V617F using 4-OHT (active conformation of Tamoxifen) in vitro in Dre-Cre cells was unsuccessful suggesting Cre silencing. These data demonstrate the feasibility of this model and suggest that Jak2V617F/p53 mutant cells remain reliant on constitutive JAK/STAT signaling for leukemic cell maintenance. We hope further mechanistic insights gained by this model will aid in the development of novel therapies.