mutant cell proliferation. This finding might explain the competitive advantage of mutant HSCs over WT HSCs in *Jak2V617F* mice (Dunbar et al., 2017). Thus, mutant, Mk-primed HSCs and elevated IFN signaling are of importance in onset and progression of *JAK2V617F*$^{+}$ ET. We propose a model in which *JAK2V617F* mutation occurs in Mk-primed HSCs, leading to expansion of this population and hypersensitivity to IFN signaling, which promotes Mk lineage differentiation. An alternative mechanism cannot be ruled out where the bone marrow microenvironment (e.g., enhanced IFN signaling) is altered to preferentially promote Mk differentiation with subsequent acquisition of *JAK2V617F* in Mk-primed HSCs, which further accelerates Mk production (Figure S4G).

The association between stem cell heterogeneity and therapeutic effects in ET was studied further here. We found that the *JAK2V617F*$^{+}$ Mk-primed HSC compartment was reduced in individuals with ET after treatment. Prior studies in MPN mice (predominantly manifesting PV phenotypes) have demonstrated that IFNα can directly target *Jak2V617F*$^{+}$ HSCs through pro-apoptosis or proliferation-associated exhaustion (Austin et al., 2020; Hasan et al., 2013; Mullally et al., 2013). We observed this pro-apoptotic effect in HET mutant HSCs in individuals with ET after treatment, whereas cell cycling was enhanced only moderately enhanced. Interestingly, HOMO cells seemed to re-enter quiescence through restoration of the TSC-mTOR signaling pathway or TP53 activation, implying that these mutant, quiescent cells are preserved and serve as residual disease-initiating stem cells. Molecular remission can be achieved by IFNα treatment (Hasselbalch and Holmström, 2019); however, rapid molecular relapse occurs in some individuals after IFNα discontinuation (Ishii et al., 2007). Our findings imply that relapsing cells might originate from quiescent mutant HSCs in individuals with T-ET. Thus, our results suggest that transient, low-dose IFN stimulation promotes proliferation and differentiation of *JAK2V617F*$^{+}$ Mk-primed HSCs during disease onset, whereas, upon treatment (including a chronic, therapeutic dose of IFNα), the mutant Mk-primed HSC population was reduced by promoting apoptosis or quiescence of mutant cells.

Because HSC heterogeneity underlies the disparate phenotypes of MPNs harboring the same initiating mutation, malignant transformation of neoplasms might involve a specific subset of stem cells within a heterogeneous stem cell population. This concept might inform pathogenic mechanisms and potential therapeutic strategies for various cancer stem cell heterogeneities.

Limitations of Study

This study is limited by the small number of samples collected and the complexity of the therapies received by these individuals, which remains to be investigated further. Additionally, the cellular and molecular basis of the changes in HSCs of individuals with PV upon treatment remains to be established.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.stem.2021.01.018.

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AUTHOR CONTRIBUTIONS

J.T., T.S., S.M., Y.Z., M.J., Y.G., P.T., Ding Wang, Di Wang, and A.Z. performed the research and analyzed the data. P.Z., R.F., Z.X., J.Z., and R.Y. analyzed the data. Dong Wang, L.S., T.C., and L.Z. designed the experiments, analyzed the data, and wrote the paper. S.J.L., J.L., A.R.G., and E.H.B. designed the experiments and wrote the paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.