Evaluating the Role of the Epo Axis in a Murine Model of Jak2V617F Mediated MPN

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Erythropoietin in JAK2V617F MPN

• EPO signaling reported to be the fundamental defect in PV (Prchal, NEJM 1974; Vainchenker, Nature 2005)

• Epo-/- and EpoR-/- mice develop BFU-E and CFU-E progenitors. EpoR+/- mice no phenotype (Lodish, Cell 1995)

• JAK2V617F mutant CD34+CD38-CD90+Lin- cells demonstrate enhanced erythroid colony formation in methylcellulose culture (Jamieson, PNAS 2006)

• JAK2V617F mutant CD34+CD38+ cells demonstrate enhanced erythroid colony formation in methylcellulose containing SCF, IL3 and EPO at concs < 0.5 U/mL (Delhommeau, Blood 2007)
The MPN-initiating cell population is contained within the HSC compartment.

45.2 DONOR

45.1 RECIP

11 Gy

2° bone marrow recipients

Hematocrit (%)

Weeks Post Bone Marrow Transplant
MPN-initiating cells are contained within the long-term HSC compartment (CD150+CD48-LSK)
Jak2V617F HSCs achieve clonal dominance over time
What role (if any) does erythropoietin play in the initiation and maintenance of Jak2V617F mediated MPN?
Expressing Jak2V617F in erythroid lineage only

Jak2 WT

jak2 G1849T
Erythroid-lineage restricted Jak2V617F expression results in elevated hematocrit

All mice aged 8-12 weeks
Erythroid-lineage restricted Jak2V617F expression results in suppressed serum Epo levels

![Graph showing serum Epo levels](image)

- \( p = 0.0001 \)
- \( p = 0.0007 \)
Erythroid-lineage restricted Jak2V617F expression results in an attenuated MPN phenotype
Jak2V617F EpoRCre mice do not have expanded HSCs or myeloid progenitors.
Conclusions

• The LT-HSC population maintains Jak2V617F MPN in vivo

• Erythroid lineage restricted Jak2V617F expression results in a markedly attenuated MPN phenotype

• Cytokine receptors that employ Jak2 signaling and are expressed in HSCs (e.g. TpoR) may mediate clonal dominance and could represent therapeutic targets in JAK2V617F MPN
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EpoR maximally expressed on committed erythroid progenitors

Walkley, Blood 2001