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Targeting the SHP2 phosphatase enhances therapeutic effects of the JAK2 inhibitor ruxolitinib in myeloproliferative neoplasms by inhibiting the MAPK pathway

Experimental Hematology / Oncology

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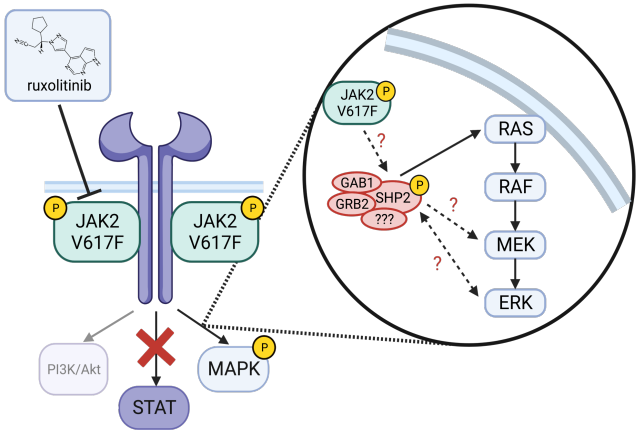
1 Introduction and Methods

Myeloproliferative neoplasms (MPN) are haematologic malignancies with mutations in JAK2, CALR or MPL that result in constitutive JAK2 activation and STAT3/5, MAPK and PI3K/Akt signalling.

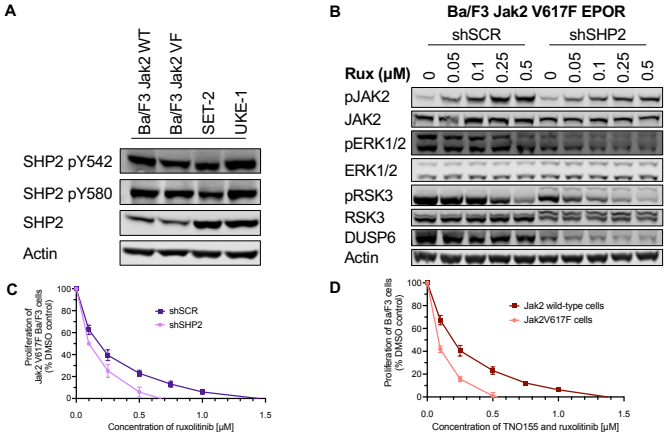
JAK2 inhibitors like ruxolitinib inhibit the JAK-STAT axis, but sustained MAPK pathway signalling in vivo limits therapeutic efficacy[1,2,3]. The tyrosine phosphatase SHP2, has been implicated in JAK2-MAPK pathway signal transduction and RAS activation and plays an important function in haematopoiesis.

Hyperactive SHP2 is implicated in various cancers, but its role in MPN has not been fully investigated. We target SHP2 genetically and pharmacologically in MPN cell lines to study its role in MAPK pathway activation and investigate the therapeutic potential of dual SHP2/JAK2 inhibition in MPN cell lines, mouse models, patient samples and a ex vivo bioreactor system.

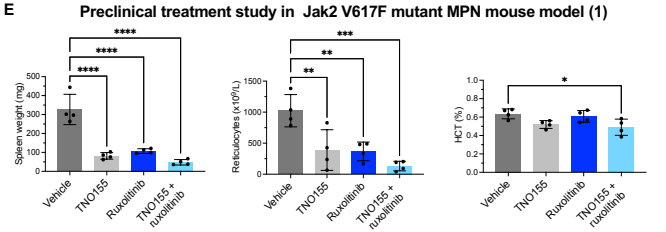


Overview of JAK2 signalling in MPN after JAK2 inhibition in vivo including proposed involvement of SHP2 in JAK2-MAPK signal transduction.

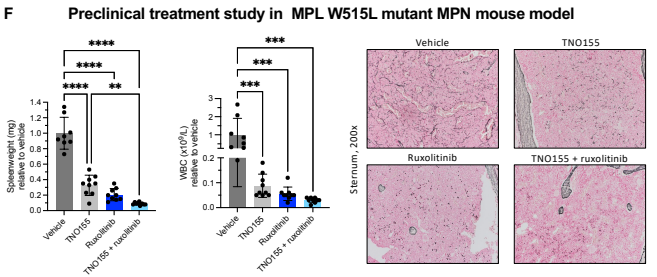
2 Results



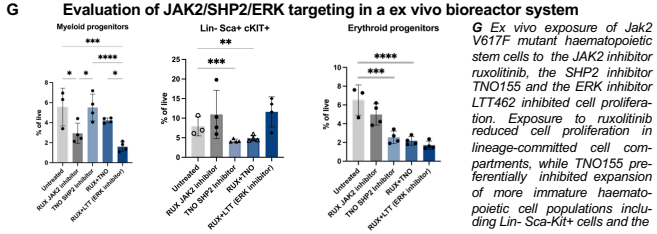
A *SHP2 is expressed and phosphorylated at two tyrosine phosphorylation sites (Y542/Y580) in isogenic (Ba/F3 Jak2 EpoR) and JAK2 V617F mutant human (SET-2, UKE-1) MPN cell lines.* ***B*** *shRNA-mediated knock-down of SHP2 suppresses MAPK pathway effectors including pERK1/2, pRSK3, and DUSP6 in Jak2 V617F Ba/F3 cells.* ***C*** *shRNA-mediated knock-down of SHP2 sensitizes Jak2 V617F Ba/F3 cells to ruxolitinib.* ***D*** *Proliferation is more strongly inhibited by combined JAK2/SHP2 inhibition with ruxolitinib and TNO155 in Jak2 V617F mutant vs Jak2 wild-type Ba/F3 cells.*



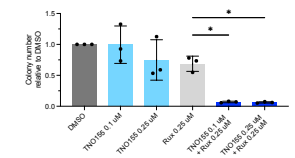
E *Combined ruxolitinib/TNO155 treatment enhances corrective effects in a Jak2 V617F mutant competitive transplantation mouse model characterized by splenomegaly and erythrocytosis compared to either drug as single agent.*



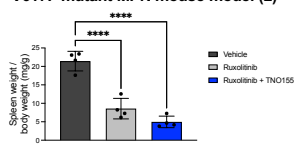
F *Combined ruxolitinib/TNO155 treatment enhances corrective effects in a MPL W515L mutant retroviral mouse model characterized by splenomegaly, leucocytosis and early bone marrow fibrosis compared to either drug as single agent.*



G *Ex vivo exposure of Jak2 V617F mutant haematopoietic stem cells to the JAK2 inhibitor ruxolitinib, the SHP2 inhibitor TNO155 and the ERK inhibitor LTT462 inhibited cell proliferation. Exposure to ruxolitinib reduced cell proliferation in lineage-committed cell compartments, while TNO155 preferentially inhibited expansion of more immature haematopoietic cell populations including Lin- Sca-Kit+ cells and the erythroid cell production as reflected by significantly reduced numbers of Ter119 progenitor population.*



H *Ex vivo exposure of primary MPN patient PBMCs to TNO155 and ruxolitinib shows significantly reduced colony formation after 14 days.*



I *Combined ruxolitinib/TNO155 treatment is also effective in a Jak2 V617F mutant competitive transplantation mouse model using a 50% reduced dose of ruxolitinib.*

3 Conclusions and Outlook

We show a relevant role of SHP2 in different MPN models. We observed enhanced MAPK pathway suppression after combined SHP2/JAK2 targeting and sensitization of Jak2 V617F mutant but not Jak2 wild-type MPN cell lines to ruxolitinib by targeting of SHP2. Combined SHP2/JAK2 inhibition showed enhanced corrective effects of the phenotype in two MPN mouse models and reduced colony growth in primary MPN patient cells. Future efforts will focus on consolidating the significance of SHP2 as a therapeutic target in MPN.

4 References

[1] Stivala et al., JCI 2019
[2] Brkic et al., Leukemia 2021
[3] Jayavelu et al., Nature 2020

5 Acknowledgements

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The figures in sections 1 was created with BioRender.com.

6 Contact

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