Mechanisms and targeting of oncogenic signaling in myeloproliferative neoplasms

Myeloproliferative neoplasms (MPNs) are chronic leukemias with excessive proliferation of mature myeloïd cells. They present as essential thrombocythemia (ET) with thrombocytosis, polycythaemia vera (PV) with erythrocytosis, or myelofibrosis (MF) with expansion of megakaryocytes and bone marrow fibrosis. They lead to bone marrow failure or may transform to acute myeloïd leukaemia (AML). Hema-topoïetic stem cell transplantation is the sole curative therapy, but is limited to a subset of patients. It is the goal of our studies to contribute to novel therapeutic approaches for MPN patients by targeting the molecular signaling driving these diseases. MPN are characterized by hyperactive signaling of the JAK2 kinase due to acquired mutations in the JAK2 signaling pathway. JAK2 is an intracellular non-receptor tyrosine kinase essential for hematopoiesis representing the exclusive mediator of signaling from the thrombopoietin receptor MPL, the erythropoietin and GM-CSF receptors. JAK2 activates several signaling pathways including STAT transcription factors, the phosphoinositide-3-kinase (PI3K) pathway and the mitogen-activated protein kinase (MAPK) pathway. The central role of JAK2 signaling in MPN has led to the development of JAK2 inhibitors which act as ATP mimetics and stabilize JAK2 in the activated conformation (type I inhibition, e.g. ruxolitinib). However, type I JAK2 inhibitors have not met the expectations. They fail to reduce the mutant clone suggesting limited curative potential, and induce resistance. To improve therapeutic targeting of JAK2 signaling in MPN, we are pursuing several approaches:

More effective targeting of JAK2

A new mode of JAK2 inhibition has recently been reported which stabilizes the inactive form of JAK2 (type II inhibition). We found high potency of type II JAK inhibition in preclinical MPN models. We observed decreased mutant allele burden due to preferential inhibition of mutant JAK2 suggesting type II inhibition could lead to a class of agents with curative potential. Resistance to type I JAK inhibitors is also abrogated. We are continuing our studies on type II JAK inhibition, which appears to herald the development of mutant-selective inhibitors, as a basis for improved therapeutic options.

Resistance mechanisms to JAK2 inhibitors

Response to type I JAK inhibitors is often lost upon prolonged exposure. JAK2 resistance mechanisms occur in vitro, but have not been observed in patients. It has been shown that MPN cells functionally adapt and reactivate JAK2 signaling through formation of JAK2 heterodimers with other JAK family members such as JAK1 and TYK2. We found that this escape mechanism extends to type I JAK2 inhibitors in clinical development, and observed cross-resistance. These molecular studies of resistance mechanisms to JAK inhibitors may reveal new therapeutic targets, while studies on patient samples will provide insight into clinical JAK2 inhibitor resistance.

JAK2 signaling network

JAK2 induces activation of STAT-, PI3K- and MAPK signaling. Therapeutic targeting of these pathways in other malignancies was impeded by feedback or cross-talk signaling revealing intricate signaling networks. We identified signaling networks which could show that combined inhibition of several targets such as JAK2 and Bcl-2/Bcl-xl can provide superior benefit in JAK2-driven leukemias. We are investigating the signaling network downstream of JAK2 to delineate the mechanisms limiting efficacy of JAK2 inhibitors and to inform novel therapeutic strategies. We aim to extend these studies to other myeloid malignancies with substantial clinical benefit of tyrosine kinase inhibitors.

JAK2 signaling in thrombopoiesis

Efficacy of therapeutic targeting with JAK2 inhibitors can be limited by off-target toxicities. Thrombopoiesis is a significant side effect of JAK2 inhibition. We have shown that JAK2 regulates megakaryocyte-biased stem cells, and are interested in differential effects of JAK2 inhibitors on thrombopoiesis.

Selected Publications


Characteristics of oncogenic signaling, therapeutic response and resistance in MPN patients

Our studies on oncogenic signaling and targeted therapeutic approaches in MPN are in close collabora-tion with Prof. R. Skoda who has established a long-term MPN patient cohort at University Hos-pital Basel, and Prof. J. Passweg, Head of the Di-vision of Hematology at University Hospital Basel. We are studying clinical isolates of MPN patients with different mutational setup or at different stag-es of the disease for characteristics of oncogenic signaling and functional capacity of hematopoietic stem/progenitor cells. We are interested in the sig-naling dynamics in response to different therapies and upon development of resistance to conven-tional JAK2 inhibitors such as ruxolitinib. Collaborative studies with Prof. R. Levine based on the MPN cohort at Memorial Sloan Kettering Cancer Center New York, support these efforts. We aim to corre-late the molecular findings with clinical characteris-tics of response or resistance to therapy in these MPN patients. These translational studies will fa-cilitate potential clinical studies on improved tar-geting of JAK2 signaling in MPN in the longer term.


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