Universität Basel

Research Project

Characterization of resistance to tyrosine kinase inhibition as a basis for novel therapeutic approaches in myeloid malignancies

Third-party funded project

Project title Characterization of resistance to tyrosine kinase inhibition as a basis for novel therapeutic approaches in myeloid malignancies
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Myeloid leukemias show dysregulated hematopoiesis often driven by constitutively activated tyrosine kinases as JAK2 in myeloproliferative neoplasms (MPN) or FLT3 in certain forms of acute myeloid leukemia (AML). JAK2 and FLT3 inhibitors show suboptimal efficacy and loss of response. Thus, insight into resistance mechanisms is key to inform sustainable therapies. I will study resistance focusing on JAK2 and FLT3 inhibition in MPN and AML. Resistance after initial response (resistance“) and suboptimal initial response (resistance“) will be addressed along with novel therapeutic strategies.MPN are chronic leukemias with excess of mature myeloid cells, transformation to AML and propensity to thromboses, characterized by constitutively activated JAK2 signaling. JAK2 activates STAT3/5, PI3K/AKT and the MAPK pathway with MEK and ERK kinases. JAK2 inhibitors blocking the active kinase (type I inhibition) loose effect in ~50% of patients. Resistance mutations have been detected in cell lines but not in patients. We have shown resistance via JAK family heterodimer formation in MPN cells, but insight into mechanisms in patients is scarce. Given these limitations, I characterized the novel type II JAK2 inhibition blocking inactive JAK2 with high efficacy. Little is known whether type II JAK inhibition also evokes acquired resistance. In addition, JAK2 inhibition cannot suppress MAPK activation in MPN in vivo, as compensatory MAPK activation via PDGFRa signaling mediates intrinsic resistance to JAK2 inhibition. Combined JAK2/MEK inhibition showed superior effects, but knowlege is scarce about the significance of other MAPK pathway components as ERK and whether MAPK activation may contribute to resistance in other myeloid leukemias as FLT3-mutant AML. In AM with acute expansion of blasts, mutations in FLT3 are most frequent. FLT3 activates MAPK and PI3K signaling as well as STAT5 and FLT3 inhibitors have limited activity. As we observe superior effects of combined FLT3/MEK inhibtion in FLT3-mutant AML cells, we hypothesize MAPK activation could contribute to FLT3 inhibitor resistance. I will characterize intrinsic and acquired resistance to tyrosine kinase inhibition in these myeloid leukemias and respective therapeutic approaches.Specific research aims: 1. We will study intrinsic resistance in MPN/AML focusing on MAPK activation as mediator and therapeutic target. We will address the significance of targeting ERK1/2 to overcome resistance in MPN with genetic and pharmacologic approaches and study the role of MAPK activation for FLT3 inhibitor resistance in AML.2. We will study acquired resistance with a focus on type I and II JAK2 inhibitors in MPN. We aim to understand whether and how the novel type II JAK inhibition evokes resistance and how it can be abrogated. We will study incidence, dynamics and mechanism of resistance to type I JAK inhibitors in MPN patients.3. As a further perspective, we will study thrombosis formation in MPN focusing on the role of platelet activation and turnover in the setting of activated JAK2 and MAPK signaling, resistance and interventions.Hypotheses:

We expect combined JAK/ERK inhibition to increase therapeutic efficacy in MPN given ERK's essential role for hematopoiesis and distal position, and we anticipate a role of compensatory MAPK activation in FLT3-inhibitor resistance (Aim 1). For acquired resistance to JAK2 inhibitors, we expect adaptive rather than genetic processes given the observed reversibility (Aim 2). In addition, we hypothesize platelet activation in the setting of JAK2 and MAPK activation to promote thromboses in MPN (Aim 3).Relevance: These studies will enhance our insight into the biology and therapeutic targeting of intrinsic and acquired resistance to tyrosine kinase inhibition and innovatively relate to new aspects of thrombosis formation in these myeloid malignancies.

Keywords JAK2; Acute myeloid leukemia; Resistance; FLT3 ; Tyrosine kinase inhibition; Myeloid malignancies; Myeloproliferative neoplasms
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