Molecular pathogenesis of myeloproliferative neoplasms

Myeloproliferative neoplasms (MPN) are a group of blood diseases characterized by aberrant proliferation of precursors of the myeloid, erythroid and megakaryocytic lineages. Theories regarding the origin of these disorders involve a tendency towards leukemic transformation. Currently, no curative therapy is available. MPNs comprise 3 entities: polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). The goal of our studies is to advance the understanding of the molecular events that initiate MPN and influence its progression to leukemia. A recurrent mutation Janus kinase 2 (JAK2) gene that substitutes a valine to a phenylalanine at position 617 (JAK2-V617F) is present in a majority of patients with MPN, in particular PV. This mutation leads to activation of the JAK2 tyrosine kinase and represents a driver for the proliferation of hematopoietic cells. Activating mutations of calreticulin (CALR) and the thrombopoietin receptor (MPL) represent other frequent driver events. Despite this progress, several questions remain unsolved including how a single JAK2 mutation causes three different MPN phenotypes, what other genes might be involved and what determines the progression to acute leukemia. We are examining these questions by combining three approaches: molecular studies in patients with sporadic MPN, genetic analysis of familial MPN and transgenic mouse models that mimic the human disease.

Analysis of clonal progression in MPN

Using next generation sequencing, we determined the mutational profiles of MPN patients and analyzed correlations with clinical outcome and prognosis. We found that increasing number of somatic mutations per patient was associated with higher risk of transformation to acute leukemia and with reduced survival. Some gene mutations, e.g. TP53 had a particularly bad prognostic impact. By examining individual colonies grown from patient’s peripheral blood, the clonal architecture can be precisely determined. In a subset of patients with sporadic MPN additional somatic mutations can either precede or occur after the acquisition of JAK2-V617F. We are examining the impact of the clonal architecture on outcome and response to therapy.

Familial predisposition for MPN

Familial syndromes resembling MPN can be grouped into two classes: 1. Inherited disorders with high penetrance and polycythaemic hematopoiesis. 2. Hereditary predisposition to true MPN, with low penetrance, clonal hematopoiesis and occurrence of somatic mutations, e.g. in JAK2-V617F.

We identified mutations in the thrombopoietin (THPO) gene as the cause for an inherited form of thrombocythemia in several families with a “class 1” phenotype. In another family we found a previously described mutation in MPL. However, in the majority of families neither THPO nor MPL is mutated. The search for these disease genes is ongoing. Families with “class 2” phenotype are more common than generally assumed. These germ-line mutations increase the likelihood of acquiring a somatic JAK2-V617F mutation. We are using genetic methods to map the locus for these pre-disposing mutations.

Mouse models for MPN

We generated JAK2-V617F transgenic mice that express the human JAK2-V617F. This conditional construct can be activated by Cre-recombinease. Depending on the mode of Cre-mediated activation, these mice developed a phenotype resembling ET with strongly elevated platelet counts or a PV-like phenotype with increased hemoglobin, thrombocytoysis and neutrophilia. A major focus of our research is to examine the nature of the MPN initiating stem cells and their interactions with the bone marrow microenvironment. We demonstrated that MPN can be initiated by transplanting single hematopoietic stem cells that carry JAK2-V617F as the sole genetic alteration and that loss of function mutations in Etv2 promoted disease initiation from single cells and accelerated disease towards myelofibrosis. We are dissecting the contributions of additional genes to the pathogenesis using conditional knockout models. We are also using our mouse models for pre-clinical screening of JAK inhibitors and other potential therapeutic agents.

Selected Publications


Fig. 1: Model of MPN disease evolution and risk stratification in correlation to mutational events.

Fig. 2: Frequency and distribution of mutations in patients with MPN. (A) Number of patients with mutations in the genes as indicated. Red bars and red text indicate chromosomes abnormalities. (B) Circos plot illustrating co-occurrence of somatic mutations in the same individual. The length of the arc corresponds to the frequency of the mutation, while the width of the ribbon corresponds to the relative frequency of co-occurrence of two mutations in the same patient.

Experimental Hematology

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