MEGAKARYOCYTOPOIESIS IN MYELOPROLIFERATIVE NEOPLASMS

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In the chronic myeloproliferative neoplasms (MPN) the involvement of a hematopoietic stem cell manifests itself with a global myeloproliferative process involving all three myeloid cell lines, that variably predominate in the different clinical entities. A prominent proliferation of megakaryocytes is found in essential thrombocytemia (ET) and primary myelofibrosis (PMF), but while in ET megakaryocytes appear morphologically normal and maturing, dysmegakaryocytopenia occurs in PMF. In this disorder, megakaryocytes have a typical morphological appearance and topographical distribution that help making diagnosis, according to the WHO criteria. Small to large megakaryocytes are present displaying an aberrant nuclear/cytoplasmic ratio with hyperchromatic, plump lobulated or irregularly folded nuclei, and are clustered tightly; the process of proplatelet formation is abnormal in terms of proplatelet density and size. Clonal, dysplastic megakaryocytes are the source of growth factors locally released in abnormal quantities, which on turn stimulate polyclonal fibroblasts to produce fibers contributing to the derangement of bone marrow microenvironment; emperipolesis is one of the mechanisms for intramedullary megakaryocyte death. However, stimulation of fibroblasts caused by megakaryocytic fibrogenic and inflammatory cytokines finally results in a pathological microenvironment that participates in the development of the hematopoietic clone. The role of abnormal megakaryocytopenia in the pathogenesis of myelofibrosis is illustrated by murine models in which over-expression of TPO or abnormalities of the transcription factor GATA-1 result in abnormal deposition of extracellular matrix proteins, neoangiogenesis and osteogenesis, closely mimicking human disorder. Transforming growth factor is probably the major cytokine involved in this process. It is of interest that an N-terminal truncation of GATA-1 due to somatic mutations in Down syndrome children with the transient myeloproliferative disorder induces extensive proliferation of dysplastic murine fetal megakaryocytes, reinforcing the involvement of downstream GATA-1 targets; however, until now, no genetic abnormality in GATA-1 has been demonstrated in PMF, although the content and cellular compartmentalization are defective. On the contrary,
GATA-1 mRNA was overexpressed in bone marrow aspirates of ET or polycythemia vera (PV) patients.

The JAK2V617F mutation is a critical event in the pathogenesis of MPNs, occurring in a HSC which shows skewing towards the erythroid differentiation, at least in PV. Retroviral transplant studies demonstrated that the JAK2V617F mutation can produce a myeloproliferative phenotype with erythrocytosis and variable leukocytosis, while thrombocytosis was not generally observed, notwithstanding progressive abnormalities of megakaryocyte maturation finally accompanied myelofibrosis. On the other hand, transgenic mice displayed a variable phenotype that correlated with the transgene copy number; mice presenting relatively low number of transgenes manifested thrombocytosis while both erythrocytosis and thrombocytosis developed in the presence of high transgene copy number. These observations suggest that different V617F allele burden correlates at least partially with MPN phenotypes; according, most patients with PV harbor homozygous V617F clones compared to very few in ET, and inverse correlation between V617F allele burden and platelet count exists. To gain better insight into the role of JAK2V617F mutation in lineage decision, three knock-in mouse models have been recently described. In all the models, a MPN phenotype developed; it was characterized by erythrocytosis and thrombocytosis with evolution to myelofibrosis in two models expressing a mouse JAK2V617F allele, and a ET-like phenotype with thrombocytosis and moderate polycythemia but not splenomegaly or myelofibrosis in the model expressing a conditional mutated human gene. Quite unexpectedly, in one murine-JAK2 model, homozygosity for mutated allele resulted in further increase of platelet count. Thus, these studies confirm the essential role of JAK/STAT pathway in the pathogenesis of MPNs, but additional factors must intervene in the preferential proliferation of maturing or dysplastic megakaryocytic lineage in ET and PMF, respectively, as compared to the expansion of erythroid lineage in PV. Signals originated from the PI3K/Akt and/or downstream preferential activation of STAT3 versus STAT5 could be one of these variables. Finally, mice expressing MPLW515L mutation developed extensive proliferation of megakaryocytes and an acute myelofibrosis phenotype. Insights into the abnormal regulation of megakaryocyteopoiesis in ET derived from a whole-genome expression analysis highlighting a resistance to apoptosis with down-regulation of proapoptotic genes. However, we must acknowledge that a comprehensive picture that could explain the complex and unique involvement of the megakaryocytic lineage in ET and PMF is still lacking.
REFERENCES


