Primary myelofibrosis and its paraneoplastic stromal effects
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During its most recent meeting (November 2006), the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) recommended the use of the name primary myelofibrosis (PMF) for the clinicopathologic entity otherwise known as chronic idiopathic myelofibrosis, agnogenic myeloid metaplasia, or myelofibrosis with myeloid metaplasia.\(^{1}\) The deliberations of the expert panel took into account the fact that the key pathogenetic process in PMF is no longer idiopathic or agnogenic; PMF is now known to constitute a clonal stem cell disease with recurrent molecular markers (e.g. JAK2V617F, MPLW515L/K) and/or cytogenetic markers (e.g. del(13q), del (20q), +8, +9, and abnormalities involving chromosome 1, 7, and 12).\(^{2}\)

The PMF designation also underscores the characteristic, albeit neither invariant nor specific, association of the underlying clonal myeloproliferation with overt myelofibrosis.\(^{3}\) However, the bone marrow and splenic stromal changes in PMF, including angiogenesis, are reactive in nature and completely reversible with effective treatment of the primary clonal process.\(^{4,5}\) Such has been the case also with other myeloid neoplasms that are sometimes associated with similar histological changes.\(^{6-9}\) This, however, does not undermine the possibility of a direct detrimental effect from these paraneoplastic features on both effective hematopoiesis and the tempo of clonal myeloproliferation.

For operational purposes, one can consider two interdependent pathogenetic mechanisms in PMF; a primary megakaryocyte-weighted clonal myeloproliferation and a secondary (paraneoplastic) stromal reaction that includes bone marrow fibrosis, osteosclerosis, angiogenesis, and extramedullary hematopoiesis (EMH). As stated above, current evidence strongly supports the stem cell origin of the clonal myeloproliferation in PMF and this decades-long contention has recently been validated by the demonstration of both cytogenetic and molecular markers of clonality in lymphocytes and myeloid progenitors of patients with PMF.\(^{10-22}\) What remains at large is the primary clonogenic mutation although both JAK2V617F and MPLW515L/K are now considered serious candidates in this regard.\(^{10-20}\) For the record, JAK2V617F induces a polycythemia vera-like disease in mice whereas MPLW515L causes a PMF phenotype.\(^{12,21-23}\) Regardless, about half of the patients with PMF do not display either mutation and the precise pathogenetic role of these mutations, when they are present, remains to be clarified. Other molecular alterations in PMF include decreased expression of the tumor suppressor retinoic acid receptor (RAR)-β2 gene as a result of abnormal promoter methylation,\(^{24}\) and reduced megakaryocyte/platelet surface expression of MPL.\(^{25}\) Additional insight into the molecular pathogenesis of PMF is currently being pursued through global gene expression analysis.\(^{26,27}\)

The second component of the pathogenetic process in PMF constitutes the bone marrow stromal changes (i.e. collagen fibrosis, angiogenesis, osteosclerosis) that often accompany the disease as well as EMH that occurs in the spleen, liver, and other non-hepatosplenic sites.\(^{28}\) These paraneoplastic histological changes are believed to be mediated by clonal cell-derived cytokines as well as autoimmune reactions to the altered bone marrow stroma. Consistent with this notion, bone marrow fibroblasts in PMF have repeatedly been shown to be polyclonal whereas both cellular and extracellular levels of various cytokines are often altered in patients with the disease.\(^{3}\) It is generally hypothesized that, in humans, an abnormal cellular interaction between megakaryocytes and neutrophils contributes to their release of nosogenic cytokines: transforming growth factor-β (TGF-β), platelet-derived growth factor, basic fibroblast growth factor, and tumor necrosis factor-α.

A similar scenario is considered to occur in experimentally induced myelofibrosis in mice in which either systemic over-expression of thrombopoietin (TPO) or megakaryocyte lineage restricted under-expression of the transcription factor GATA-1\(^{38,39}\) results in PMF-like stromal changes. Similar experiments in mice have also suggested a primary fibrogenic role for hematopoietic cell-derived TGF-β\(^{40}\) and an osteogenic role for stromal cell-derived osteoprotegerin.\(^{29}\) Finally, there is a current consensus that both circulating progenitor cell trapping and abnormal cytokine stimulation of embryonic hematopoietic sites are implicated as mechanisms of hepatosplenic EMH in PMF.\(^{24,40}\) Such a contention is supported by the high concordance between cytogenetic findings in bone marrow and splenic tissue in PMF.

In the current issue of the journal, Zetterberg et al.\(^{41}\) describe microvascular density, morphology, and pericyte coverage in the bone marrow of patients with PMF and of mice with experimental myelofibrosis. In both instances, compared to controls, angiogenesis was increased and morphologically aberrant, and the vessels often covered with pericytes. These observations are largely confirmatory; both increased angiogenesis and abnormal vessel structure have previously been reported in the context of both bone marrow and spleen in...
patients with PMF. Similarly, vascular endothelial growth factor expression by bone marrow cells in such patients has previously been looked into, with similar or different findings. What was novel in the study by Zetterberg et al. was the demonstration of pronounced pericyte coverage of the bone marrow microvasculature in PMF; increased pericyte coverage was also noted in normal bone marrow on vessels with a larger perimeter. Furthermore, the authors demonstrated similar changes in the bone marrow and spleen of mice with experimental myelofibrosis. On the other hand, the informative sample sizes in the study were not large enough to support the authors’ suggestion regarding the effect of either JAK2V617F or secondary myelofibrosis on bone marrow angiogenesis.

It is unlikely that the above-mentioned observations are unique to PMF and instead probably represent common changes associated with tumor-associated neoangiogenesis, albeit with some tissue-specific differences. Furthermore, the precise pathogenetic contribution of angiogenesis in PMF has not been clarified and its prognostic value remains dubious. Nevertheless, these limitations do not undermine the potential value of angiogenesis-directed therapy in PMF although proof-of-principle is lacking in this regard. In other words, cytokine and immune modulation rather than direct anti-angiogenic activity might underlie the therapeutic efficacy of thalidomide and/or lenalidomide in PMF; increased pericyte coverage was also noted in normal bone marrow on vessels with a larger perimeter.

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