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Scientific comment

Does angiogenesis matter in primary myelofibrosis?☆

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Primary myelofibrosis (PMF) is a clonal hematopoietic disorder characterized by an initial prefibrotic proliferative phase that over time progresses to bone marrow fibrosis, extramedullary hematopoiesis, peripheral blood cytopenias and an increased risk of developing acute myeloid leukemia (AML). In recent years, the molecular mechanisms that cause PMF have been extensively studied and the genomic changes that cause the disease have been widely elucidated.[1]

A unique feature of PMF is a systemic inflammatory reaction that manifests, among other things, through high serum levels of inflammatory cytokines and chemokines, and a stromal bone marrow reaction involving collagen deposition and increased vascular proliferation.[2,3] There is now convincing evidence that megakaryocytes play a major role in this stromal reaction.[4,5] More specifically, megakaryocytes from patients with PMF produce high levels of inflammatory cytokines including transforming growth factor-beta 1 (TGFβ1).[6] Recently, PMF systemic inflammatory reaction has taken center stage after a suggestion that a possible mechanism by which ruxolitinib, a JAK1 and JAK2 inhibitor, increases overall survival, is through its anti-inflammatory effect, as this medication only marginally decreases the disease burden.[7]

While the diagnosis of advanced PMF is not a major challenge, the differential diagnosis between prefibrotic PMF and essential thrombocythemia (ET), a related neoplastic disease, is not always easy,[8] since both diseases are characterized by high platelet counts, increased bone marrow cellularity, and increased number of atypical megakaryocytes in the bone marrow. The importance of making such differentiation is fundamental, since most patients with ET have a benign disease while PMF patients have a substantial decrease in overall survival.[9,10]

In this issue of the Revista Brasileira de Hematologia e Hemoterapia (RBHH), Ponce et al. evaluated the expression of anti-latency-associated peptide (LAP) human TGFβ1 in bone marrow megakaryocytes as well as the microvascular density (MVD) in bone marrow biopsies from patients with ET and PMF.[11] Although the number of patients was small, one of the main findings of the study was that MVD is significantly increased in prefibrotic PMF compared to ET. Since there is no objective way of histologically differentiating prefibrotic

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PMF from ET, the addition of a novel diagnostic tool that may contribute to this differentiation is welcomed. If the finding of increased MVD observed predominantly in patients with prefibrotic PMF in this study can be reproduced by other authors, it could serve as another diagnostic marker, with the potential to improve the pathologist's ability to differentiate between these two conditions. Recently, immunostaining for nuclear factor, erythroid-derived 2 (NF-E2) on bone marrow biopsies has shown to be a promising technique to help differentiate between prefibrotic PMF and ET.[12]

Another finding of the study of Ponce et al. was the relationship between megakaryocyte TGFβ1 expression, MVD and bone marrow fibrosis, suggesting a possible mechanism by which increased levels of TGFβ1 produced by megakaryocytes can induce an inflammatory reaction that culminates in new vessel formation and fibrosis.[11] Although no causal relationship can be determined, this finding adds to the literature, pointing to a role for TGFβ1 on the process of neo-angiogenesis and fibrosis in human and animal models of PMF.[6,13]

In conclusion, these findings may contribute to improve our ability to differentiate patients with prefibrotic PMF and ET and also reaffirms a possible role of TGFβ1 in neo-angiogenesis in PMF.

Conflicts of interest

The author declares no conflicts of interest.

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