EDITORIAL

Primary myelofibrosis progression: a game of cellular telephone

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Received: December 4, 2024.
Accepted: December 18, 2024.
Early view: January 2, 2025.

https://doi.org/10.3324/haematol.2024.286665

Primary myelofibrosis (PMF) is characterized by the overproduction of atypical megakaryocytes with bone marrow fibrosis.[1-4] While JAK inhibitors are utilized in PMF to reduce spleen size and address symptoms, their impact on fibrosis and disease progression is less clear. The World Health Organization has classified two sequential categories of PMF, pre-fibrotic (pre-PMF) and overt (overt PMF), as symptoms and pathology progressively worsen over time and result in poorer outcomes.[2] While transcriptomic studies have identified gene signature differences between pre-fibrotic and overt PMF, the precise mechanisms that map the conversion from pre-PMF to overt PMF is uncharted territory and warranted further in-depth exploration.[5]

In this issue of *Haematologica*, Jung and colleagues describe their research utilizing single-cell RNA sequencing on bone marrow biopsies from 33 patients with myeloproliferative neoplasms, including 12 with overt PMF and five with pre-PMF, to dissect deep into immune, myeloid, hematopoietic stem and progenitor cell (HSPC) subpopulation functions and interactions.[6] Jung *et al.* elucidated PMF-specific and progression-dependent inflammatory and fibrotic signatures, and unique cell-to-cell communications (Figure 1).

One of the hallmarks of PMF is the proliferation and activity of abnormal megakaryocytes,[3] so it was no surprise that in overt PMF Jung *et al.* found a significant rise in the megakaryocyte population compared to that in pre-PMF, as well as a bias to megakaryocyte differentiation of the HSPC. Moreover, these megakaryocytes were enriched further in patients with peripheral blood blast cells ≥1%, at the expense of mature cells such as monocytes and dendritic cells. Probing deeper into megakaryocyte subpopulations, differentiation, fibrosis, transforming growth factor-β, and inflammatory cytokine signaling were substantially increased in the patients with overt PMF. Unsurprisingly, overt PMF was associated with another megakaryocyte subset highly expressing genes known be key players in fibrosis, such as *CXCL2* and *LTBP1*, in comparison to non-fibrotic MPN and pre-PMF.[7,8] Additionally, a megakaryocyte subset significantly associated with epithelial-mesenchymal transition (EMT)-related genes was the star of the overt PMF megakaryocytes. Inflammatory stress cooperates with EMT pathways in the initiation and progression of organ fibrosis. Since bone marrow fibrosis raises the fear of inevitable bone marrow failure in patients, cooperative organ fibrosis is not a bump in the road, but a highway pile-up.[9] The same subset had similar population upheavals in post-essential thrombocythemia and post-polycythemia vera myelofibrosis. This reiterates the current model of megakaryocytes as the inciters of fibrosis in myelofibrosis.

Jung *et al*. continued their analysis to identify 15 subsets of T and NK cells in patients: while not drastically different in their distributions, bioinformatic functional analysis showed gradual increases in cytotoxicity and dysfunction in the said T-cell populations from non-fibrotic MPN to pre-PMF to overt PMF. While informative at a surface level, Jung and colleagues pulled back the cellular curtain to show that the myeloid-derived suppressor cell monocyte variant (M-MDSC) was greatly increased in patients with overt PMF compared to all others. The combination of immune cells minding their own business and the absence of regulation of malignant growth provides a great neighborhood in which the MPN clones can create chaos within the bone marrow, although this is not great for current and future residents as inevitably homes will crumble on the fibrotic ground.[6,10]

Unique ligand-receptor interactions were bioinformatically assessed: 90 interactions were identified with 38, between HSPC, megakaryocytes and T cells, being significantly associated in overt PMF. The interactions enriched in overt PMF further complemented the cellular subset analysis of Jung *et al*. by being correlated with megakaryocyte differentiation, inflammatory and fibrotic signaling, immune dysfunction and tumor-associated signaling. Overt PMF megakaryocytes were the most prominent source of fibrosis mediation, and markers of T-cell exhaustion and

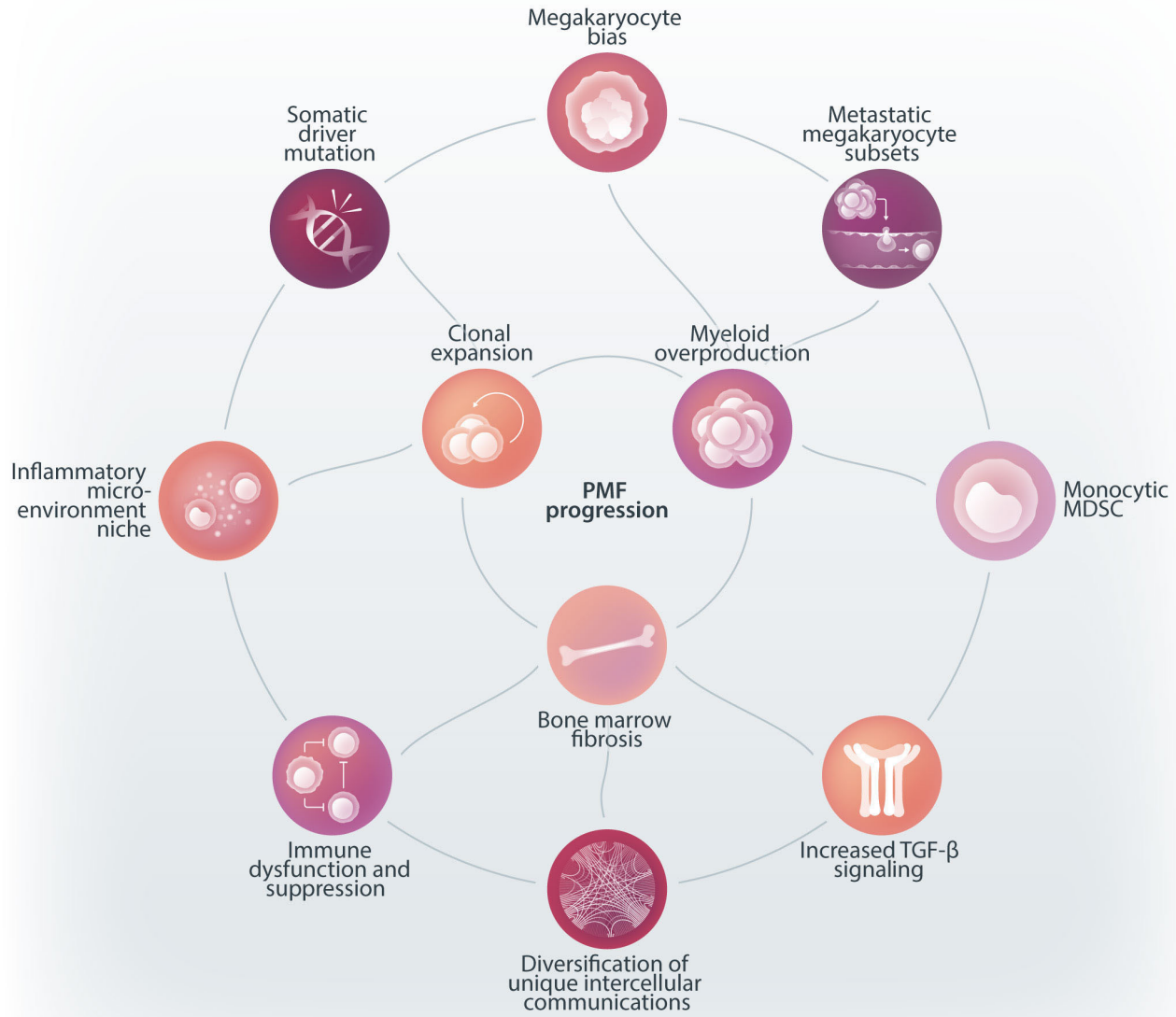

Figure 1. Key factors driving the progression of primary myelofibrosis. PMF: primary myelofibrosis; MDSC: myeloid-derived suppressor cells; TGF-β: transforming growth factor-beta.

dysfunction were associated in a more diverse array of T cells in overt PMF than in pre-PMF. These increased and diversified cellular interactions suggest that fibrotic progression in MPN subtypes is due to an accumulation of differing and compounding events rather than a single or single type of event.[7-9]

Important limitations of the study are acknowledged by the authors. Evaluation of non-hematopoietic cells, such as fibroblasts and myofibroblasts which are also likely integral to PMF progression, was precluded in this study. Additionally, given the small sample size consequent to the rarity of the disease, the study is limited by the complexity of treatment plans for each patient. Frequent longitudinal bone marrow aspirates in this disease are a challenge to acquire. Nevertheless, Jung and colleagues revealed intra- and intercellular communications that strongly correlate with PMF progression as well as fibrotic development in other classical MPN subtypes.

While a mainstay of therapy for PMF is the use of JAK inhibitors, their role in disease modification is unclear. Bone marrow fibrosis is a pathological feature of myelofibrosis, with higher grades being associated with poor prognosis. There are limited data on the association between outcomes and changes in bone marrow fibrosis. Past studies showing that inflammation is a key driver of disease progression together with the novel findings of Jung *et al*. support giving precedence to drug discovery strategies targeting immune alterations and megakaryocyte subsets, which are indeed on the horizon. Jung *et al*.'s molecular findings provide a map to navigate the cellular landscape of PMF and may help inform rationale drug combinations.

Disclosures

No conflicts of interest to disclose.

Contributions

LW wrote the first draft of this editorial. AF made additions and edits to this draft.

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