haematologica
Journal of the Ferrata Storti Foundation

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Received: December 4, 2024.
Accepted: December 18, 2024.

Citation: Lucas Wadley and Angela Fleischman.
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Haematologica. 2025 Jan 2. doi: 10.3324/haematol.2024.286665 [Epub ahead of print]

Primary myelofibrosis progression: a game of cellular telephone

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

In this issue of *Haematologica,* Jung and colleagues utilise single-cell RNA sequencing (scRNA-seq) on 33 MPN patient BM biopsies, including 12 overt and 5 pre-fibrotic PMF, to dissect deep into immune, myeloid, haematopoietic stem and progenitor cell (HSPC) subpopulation functions and interactions. Jung *et al.* elucidate PMF-specific and progression-dependent inflammatory and fibrotic signatures, and unique cell-to-cell communications.[10]

One of PMF's trademarks is the proliferation and activity of abnormal MKs, so it was no surprise that in overt PMF, Jung found a significant rise in the MK population compared to pre-PMF, as well as a bias for MK differentiation of their HSPCs.[3] Moreover, this MK's were enriched further in patients with peripheral blood blast cells ≥1%, at the expense of mature cells such as monocyte and dendritic cells. Probing deeper into the MK subpopulations, differentiation, fibrosis, TGF-β, and inflammatory cytokine signalling was substantially increased in the overt PMF patients. Unsurprisingly, overt PMF was associated with another MK subset highly expressing genes known be key players in fibrosis, like *CXCL2* and *LTBP1* in comparison to non-fibrotic MPN and pre-PMF.[6,7] Additionally, a MK subset significantly associated with epithelial-mesenchymal transition (EMT)-related genes was the star of the overt PMF MKs. Inflammatory stress cooperates with EMT pathways in the initiation and progression of organ fibrosis. And with bone marrow fibrosis striking fear of inevitable bone marrow failure in patients, cooperative organ fibrosis is not a bump in the road, but highway pile-up. [8] The same subset had similar population upheavals in post essential thrombocythemia (ET) and post-polycythaemia vera (PV) myelofibrosis. This reiterates the current model of MKs as the inciters of fibrosis in myelofibrosis. [10]

Jung *et al*. continued the 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 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 find that myeloid derived suppressor cell monocyte variant (M-MDSC) was greatly increased in over-PMF patients compared to all others. With immune cells minding their own business, and no regulations on malignant growth creates a great neighbourhood for these MPN clones to build chaos within the BM; but not great for current and future residents as inevitably homes will crumble on the fibrotic ground. [9,10]

Unique ligand-receptor (LR) interactions were bioinformatically assessed with 90 interactions identified with 38 being significantly associated in overt-PMF, with those interactions being

between HSPCs, MKs and T-cells. The interactions enriched in overt-PMF further complemented Jung *et al.*'s cellular subset analysis by being correlated with MK differentiation, inflammatory and fibrotic signalling, immune dysfunction and tumour-associated signalling. With overt-PMF MKs being the more prominent source of fibrosis mediation, and markers for T-cell exhaustion and dysfunction being associated in a more diverse array of T-cells in overt-PMF than in pre-PMF. With these increased and diversified cellular interactions suggests that fibrotic progression in MPN subtypes is due to an accumulation of differing and compounding events rather than a single or singular style 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 for PMF progression, was precluded in this study. Additionally, given the small sample size owing to the rarity of the disease, the study is limited in the complexity of treatment plans for each patient. Frequent longitudinal BM aspirates in this disease are a challenge to acquire. Regardless, 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 is disease modification is unclear. Bone marrow fibrosis (BMF) is a pathological feature of myelofibrosis, with higher grades associated with poor prognosis. Limited data exist on the association between outcomes and BMF changes. With past studies showing inflammation being a key driver for disease progression accompanying Jung *et al*.'s novel findings support precedence for drug discovery targeting immune alterations and MK subsets, which are indeed on the horizon.[9] Jung *et al.*'s molecular findings provide a map to navigate the cellular landscape of PMF and may help inform rationale drug combinations. [10]

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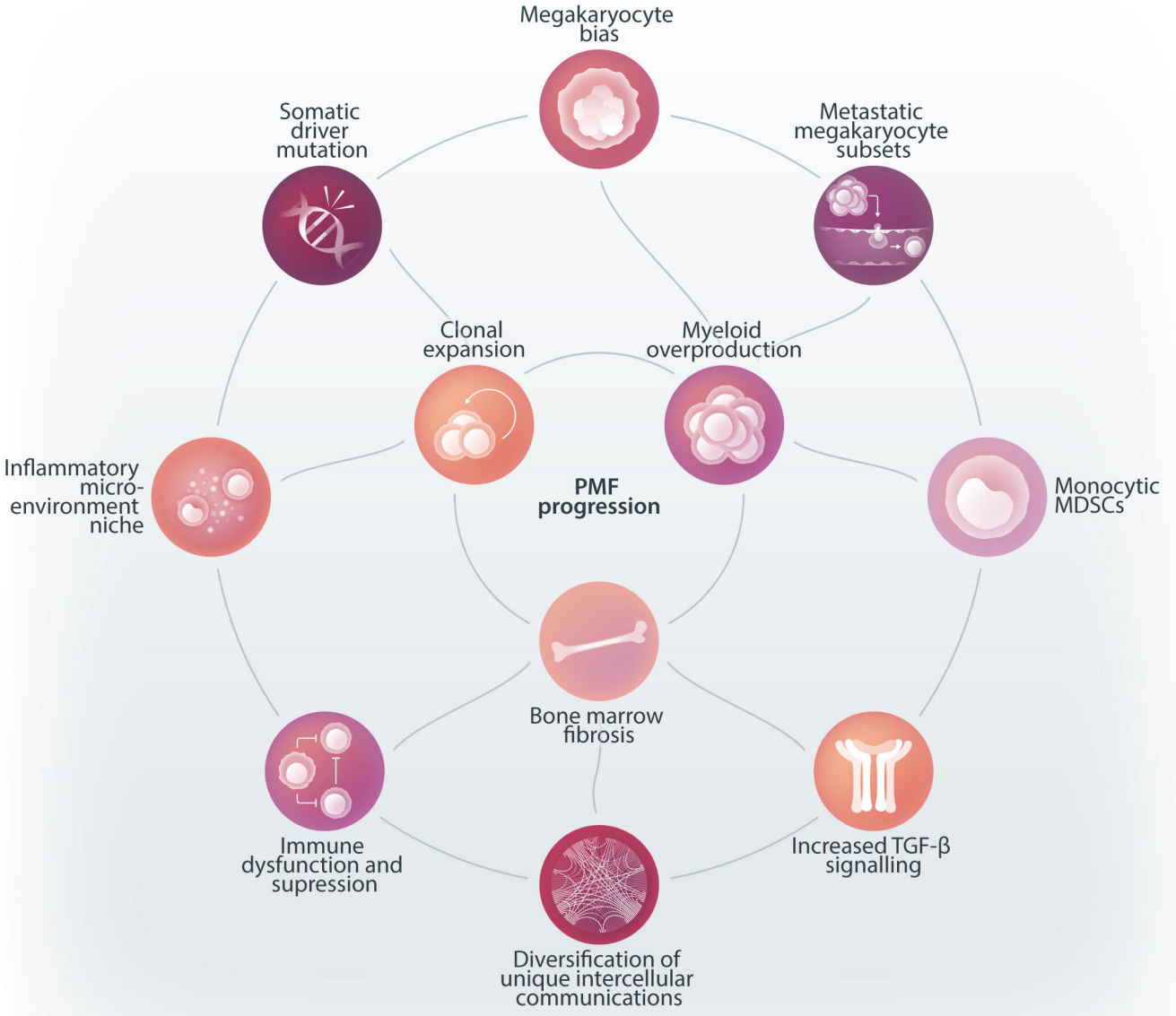
Figure 1. Key factors driving primary myelofibrosis (PMF) progression.


Megakaryocyte bias
Somatic driver mutation
Metastatic megakaryocyte subsets
Clonal expansion
Myeloid overproduction
Inflammatory micro-environment niche
PMF progression
Monocytic MDSCs
Bone marrow fibrosis
Immune dysfunction and supression
Increased TGF-β signalling
Diversification of unique intercellular communications