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Preview

Message in a platelet: decoding platelet transcriptomes in myeloproliferative neoplasms

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Platelets are anucleate but contain a rich repertoire of mRNAs. In this issue of *Cell Reports Medicine*, Shen and colleagues[1] present platelet transcriptomes from patients with myeloproliferative neoplasms to study disease mechanisms and generate a predictive algorithm for fibrotic progression.

Many patients are diagnosed with cancer at an early or chronic phase. The ability to predict progression to advanced disease and likelihood of complications including thrombosis is crucial for optimal management. In this issue of *Cell Reports Medicine*, Shen and colleagues[1] demonstrate that the platelet transcriptome can differentiate between clinically distinct subtypes of myeloproliferative neoplasms (MPNs), a group of chronic blood cancers. They identify key features of the platelet transcriptome that, when combined with basic clinical predictors, can predict advanced stage disease.

MPNs arise following acquisition of a mutation in a hematopoietic stem cell that leads to a proliferation advantage, clonal expansion, and excess production of blood cells and bone marrow progenitors, especially of the megakaryocyte lineage. The vast majority of cases are due to one of three mutations affecting Janus Kinase 2 (*JAK2V617F*), calreticulin (*CALR*), or *MPL*, the gene encoding the thrombopoietin receptor. All three mutations result in constitutive activation of MPL-JAK-STAT signaling.[2]

Although they share the same molecular drivers, three distinct clinical phenotypes can occur: polycythaemia vera (PV) and essential thrombocythaemia (ET), representing chronic-phase MPNs, and myelofibrosis (MF), a more severe MPN.[3] People may live with an MPN for many years, and rates of progression are highly variable. Both ET and PV may progress to secondary MF, and all three MPNs carry a risk of transformation to secondary acute myeloid leukemia (sAML), which has a dismal prognosis despite best available therapy. MPNs also carry a substantially increased risk of thrombosis, a major cause of morbidity and mortality.

Fortunately, only a minority of patients with ET/PV will develop fibrosis. In addition to the driver mutations, the majority of patients harbor additional mutations in a wider range of genes that contribute to heterogeneity in clinical subtype and risk of progression. This had led to the development of models for genetic risk stratification and personalized prognosis assessment.[4] Gene mutations are not, however, the only determinant of progression: these act in the context of a complex interplay of cell-extrinsic factors. A major challenge remains capturing these factors in a model that can help predict disease progression and risk of thrombosis to identify patients who may benefit from early intervention with potentially disease-modifying therapies or more intensive thromboprophylaxis.

A dramatic increase in atypical megakaryocytes is a cardinal feature of MPNs, and they are key drivers of bone marrow fibrosis. Platelets are released from megakaryocytes as anucleate "cell fragments" and circulate in the blood for 3–7 days. In addition to a substantial protein cargo, they contain a wealth of RNA: messenger RNAs (mRNAs), unspliced pre-mRNAs, rRNAs, and tRNAs.[5] The platelet transcriptome is modified during circulation, due to altered splicing[6] or uptake of mRNAs transferred from other cells,[7,8] and specific platelet transcriptome signatures have been reported in cardiovascular diseases and solid tumors.[9] Examination of the platelet transcriptome in MPNs should therefore be very revealing, as it reflects the transcriptional state of parent megakaryocytes at the time of platelet release, as well as stimuli encountered during peripheral circulation (Figure 1). Surprisingly, platelet transcriptomics in MPN is a relatively understudied area.

Shen et al.[1] analyzed 120 purified platelet samples from healthy controls and two cohorts of patients with MPN (24 ET, 33 PV, and 40 primary or secondary MF), generating the largest dataset of platelet transcriptomes in MPNs reported to date. Each clinical subtype showed differential gene expression signatures as compared to healthy controls, with the most pronounced changes observed in MF (> 6600 differentially expressed genes). A core set of genes were differentially expressed in all MPNs versus controls, and a set of genes were progressively differentially expressed from chronic phase (ET/PV) to advanced stage MPN (MF). Interrogation of the core gene set suggested that perturbed interferon signaling, and immune cell activation pathways are core to MPN pathophysiology, while increased expression of fibroblast growth factor receptor genes, matrix metalloproteinases, and cell cycle regulators were enriched in MF. Their data also identified potential mediators of thrombo-inflammation in ET and PV, including interferon inducible transmembrane genes (IFITM2, IFITM3), solute carrier family genes (SCL16A1, SCL2A), and coagulation factor V.

The authors tested the ability of differentially expressed genes in platelets to

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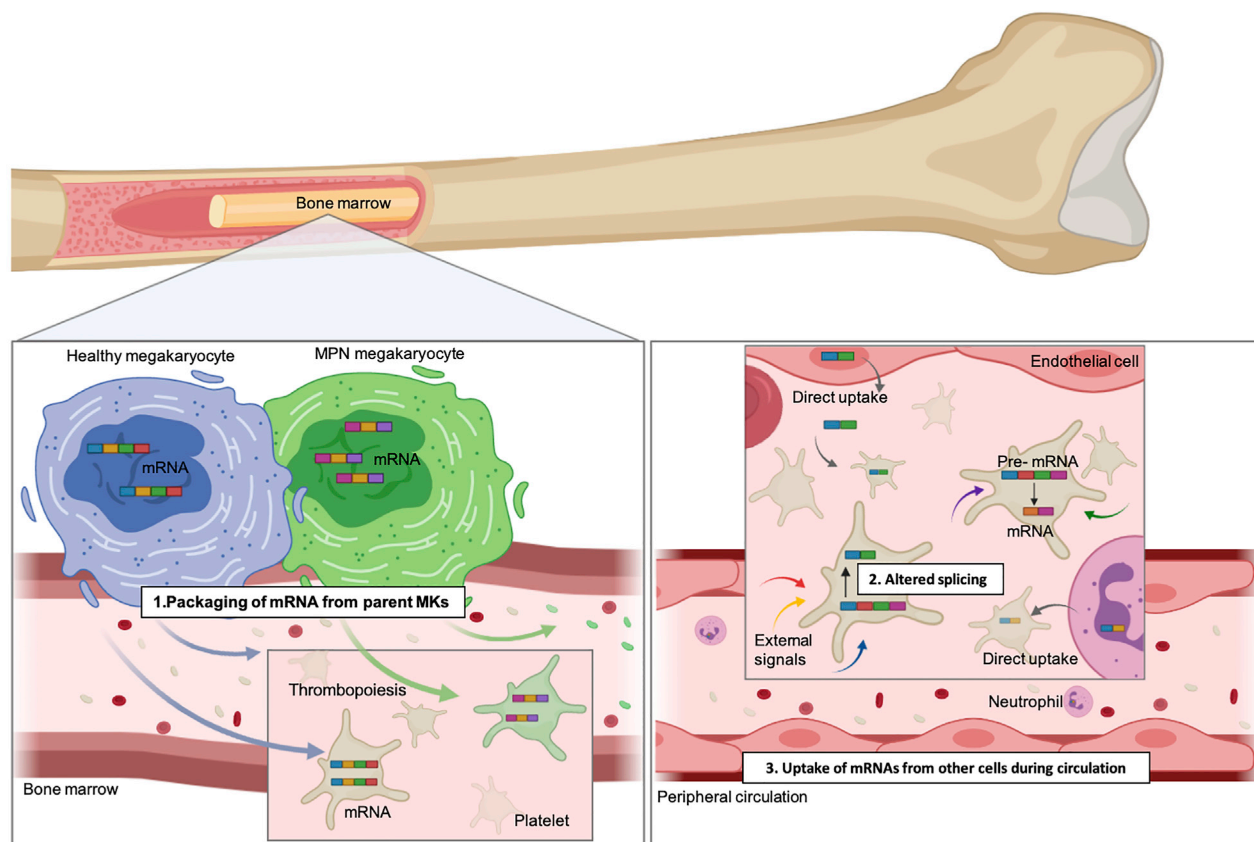

Figure 1. Factors influencing the platelet transcriptome
Platelets are produced from megakaryocytes in the bone marrow. During thrombopoiesis, megakaryocytes package mRNAs into developing platelets. (1) The platelet transcriptome reflects the transcriptional state of the parent megakaryocytes. In myeloproliferative neoplasms (MPNs), platelets derived from the MPN clone (green) may harbor a unique transcriptional signature. The platelet transcriptome is also modified during peripheral circulation due to (2) external signals inducing specific splicing of the platelet pre-mRNA) and (3) platelet uptake of mRNAs transferred other cells. Figure created with BioRender.com (2021).

predict which patients had myelofibrosis versus ET/PV. Incorporating the top 20 most differentially expressed transcripts in MF together with widely available clinical parameters (age, sex, driver mutation status, platelet count, and hemoglobin) outperformed prediction of myelofibrosis based on the clinical parameters alone. This limited gene set could potentially be assayed in a targeted, cost-effective approach in a clinical diagnostic setting.

It is important to note that this study used snapshots of the clinical subtypes to infer clinical progression and serial samples from patients were not studied. Relatively limited clinical/molecular information was available on the study cohort, and therefore it was not possible to confirm whether these 20 transcriptomic markers added value to routinely employed, mutationally enhanced risk score models. Also, whether the transcriptomic signatures were specific to platelets or also detectable in whole blood or granulocytes that may be easier to isolate by a routine diagnostic lab was not explored. Worthwhile future studies include analysis of ribosomal RNA (which was depleted in this study) and functional and proteomic studies to confirm a link between changes in gene/protein expression with clinical outcomes including fibrosis and thrombosis.

Overall, this study contributes a wealth of data to the field and draws attention to the wider potential of the transcriptome of this intriguing anucleate cell type in other disease contexts—acting as little messengers or sentinels containing information about the transcriptional state of their parent megakaryocytes and the hematopoietic microenvironment as well as altered signals encountered in during peripheral circulation.

DECLARATION OF INTERESTS

S.S., L.M., and B.P. indicate no relevant conflicts of interest.

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