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POSTER ABSTRACTS

301.VASCULATURE, ENDOTHELIUM, THROMBOSIS AND PLATELETS: BASIC AND TRANSLATIONAL

ATRA Can Correct Impaired Proplatelet Formation By Regulating HIF-1α/SPHK2/S1P Axis in ITP

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Introduction

Under normal physiological conditions, the bone marrow (BM) niche is hypoxic, and sustained and consistent oxygen gradients result in stable physiological hypoxia. Hypoxia inducible factor (HIF) is central to mediating the cellular response to hypoxia. Whether hypoxia gradients regulate megakaryocyte (MK) differentiation and maturation and the possible mechanisms of these actions remain unknown. Our previous data showed that impaired proplatelet formation (PPF) contributed to the development of thrombocytopenia in ITP. Recent studies suggest that the S1P signaling pathway in MKs plays a critical role in PPF (*Blood*, 2013; *J EXP MED*, 2012). To further explore the underlying mechanism of impaired PPF in ITP, we found that HIF-1α/SPHK2/S1P axis-mediated cytoskeletal reorganization was defective in the PPF of ITP. All-trans retinoic acid (ATRA), which has been shown to be a promising treatment option for ITP patients in our clinical studies (*Blood*, 2021; *Lancet Haematology*, 2017; *Lancet Haematology*, 2021), could restore cytoskeletal reorganization and correct impaired PPF.

Methods

Thirty patients with newly diagnosed ITP and 30 healthy donors were included in our study. The 30 ITP patients received ATRA at a dose of 10 mg orally twice daily for 12 weeks. Bone marrow samples were taken before the first medication (Day 0) and after 12 weeks of ATRA therapy (Day 85). We employed an imaging cytometry platform to perform a comprehensive quantitative analysis of MK distribution and hypoxic status in the bone marrow microenvironment of ITP. Targeted and untargeted metabolomic profiling through metabolomic analysis was performed to explore the relationship between the metabolome and ITP.

Results

We analyzed the hypoxic status of MKs in the endosteal niche and perivascular niche. In healthy controls, MKs in the perivascular niche exhibited a hypoxic profile, defined by robust HIF-1α expression and strong retention of pimonidazole. MKs in the endosteal region were less hypoxic. These results reflect a spatial hypoxia gradient in the bone marrow microenvironment. In contrast, we found that, irrespective of their location, ITP MKs displayed less hypoxia with no defined spatial gradients.

ITP-MKs in the perivascular niche displayed altered cytoskeletal reorganization and impaired proplatelet formation (PPF). Metabolomics data revealed a decreased S1P level in ITP patients. Downregulated sphingosine kinase 2 (SPHK2) in MKs suppressed S1P production. S1P was essential for cytoskeletal reorganization and PPF regulation. In addition, we demonstrated that hypoxia inducible factor-1α (HIF-1α) mediated SPHK2 activation and S1P production. These data suggested that a disrupted hypoxia gradient contributed to impaired PPF via the HIF-1α/SPHK2/S1P axis.

We then investigated the effect of ATRA on PPF. The ITP patients received ATRA at a dose of 10 mg orally twice daily for 12 weeks. For patients who received ATRA, S1P levels, HIF-1α and SPHK2 expression levels were increased compared with the pretreatment levels. And ATRA corrected impaired PPF and restored cytoskeletal reorganization by upregulating HIF-1α.

Conclusions

A disrupted hypoxia gradient contributed to impaired PPF in the ITP bone marrow environment via the HIF-1α/SPHK2/S1P axis. The ATRA-induced correction of impaired PPF is a potential mechanistic explanation for the clinical efficacy of ATRA in ITP.

Disclosures No relevant conflicts of interest to declare.

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