ELSEVIER

Blood 142 (2023) 4515

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

631.CHRONIC MYELOID LEUKEMIA: BIOLOGY AND PATHOPHYSIOLOGY, EXCLUDING THERAPY

PPIL2 Is a Target of the JAK2-STAT5 Pathway and Mediates p53 Polyubiquitination and Degradation

Pan Wang, PhD[1], *Xu Han, PhD*[1], *Kehan Ren*[1], *Ermin Li, PhD*[1], *Honghao Bi, PhD*[2], *Inci Aydemir*[2], *Peng Ji, MD PhD*[1]

[1] Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago, IL
[2] Northwestern University, Chicago, IL

The activated JAK2-STAT pathway is characteristic of myeloproliferative neoplasms (MPNs). We previously revealed that Plek2, a downstream target of the JAK2/STAT5 pathway, functions as a scaffold protein to activate Akt and plays an important role in the pathogenesis of JAK2 ^{V617F}-induced MPNs. To further explore the mechanisms of the Plek2 signalosome, we performed a comprehensive proteomic analysis of Plek2 interacting proteins and found peptidylprolyl isomerase-like 2 (PPIL2) as a potential novel effector of the signalosome. As a U-box E3 ubiquitin ligase, PPIL2 was reported to be involved in cancer metastasis. However, its role in normal and malignant hematopoiesis remains unknown. We found that PPIL2 is required for human and murine erythropoiesis in vitro. Knockout of PPIL2 through CRISPR/Cas9 significantly reduced cell proliferation and differentiation and led to marked apoptosis. Mechanistically, PPIL2 interacts with and catalyzes p53 polyubiquitination at lysine 24 to promote proteosome-mediated p53 degradation, thereby preventing p53-dependent cell cycle inhibition and apoptosis. We further revealed that PPIL2 is a downstream target of the JAK2/STAT5 pathway and is upregulated in a JAK2 ^{V617F}-positive MPN mouse model and in patients with MPNs. Loss of Ppil2 ameliorated JAK2 ^{V617F}-induced myeloproliferative phenotypes including erythrocytosis, neutrophilia, thrombocytosis, and splenomegaly in JAK2 ^{V617F}-knockin mice. The same findings were also observed when the JAK2 ^{V617F}-knockin mice were treated with cyclosporin A, an inhibitor of PPIL2. Our findings reveal PPIL2 as an effector of the JAK2/STAT5 pathway and Plek2 signalosome. PPIL2 plays an important role in normal erythropoiesis and the pathogenesis of JAK2 ^{V617F}-induced MPNs by degrading p53, pointing to PPIL2 as a potential therapeutic target for the treatment of MPNs.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-177677