Cytokine 82 (2016) 52–57

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

TC-PTP and PTP1B: Regulating JAK–STAT signaling, controlling lymphoid malignancies

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ARTICLE INFO

Article history:
Received 4 November 2015
Received in revised form 28 December 2015
Accepted 29 December 2015
Available online 23 January 2016

Keywords:
Leukemia and lymphoma
JAK–STAT
Tyrosine phosphatase
PTP1B
TC-PTP

ABSTRACT

Lymphoid malignancies are characterized by an accumulation of genetic lesions that act co-operatively to perturb signaling pathways and alter gene expression programs. The Janus kinases (JAK)–signal transducers and activators of transcription (STATs) pathway is one such pathway that is frequently mutated in leukemia and lymphoma. In response to cytokines and growth factors, a cascade of reversible tyrosine phosphorylation events propagates the JAK–STAT pathway from the cell surface to the nucleus. Activated STAT family members then play a fundamental role in establishing the transcriptional landscape of the cell. In leukemia and lymphoma, somatic mutations have been identified in JAK and STAT family members, as well as, negative regulators of the pathway. Most recently, inactivating mutations in the protein tyrosine phosphatase (PTP) genes *PTPN1* (PTP1B) and *PTPN2* (TC-PTP) were sequenced in B cell lymphoma and T cell acute lymphoblastic leukemia (T-ALL) respectively. The loss of PTP1B and TC-PTP phosphatase activity is associated with an increase in cytokine sensitivity, elevated JAK–STAT signaling, and changes in gene expression. As inactivation mutations in *PTPN1* and *PTPN2* are restricted to distinct subsets of leukemia and lymphoma, a future challenge will be to identify in which cellular contexts do they contributing to the initiation or maintenance of leukemogenesis or lymphomagenesis. As well, the molecular mechanisms by which PTP1B and TC-PTP loss co-operates with other genetic aberrations will need to be elucidated to design more effective therapeutic strategies.

1. Introduction

Lymphoid malignancies are diverse, categorized by structural genetic alterations and sequence mutations. Independently, these lesions are typically not sufficient for transformation but rather act co-operatively to promote leukemia or lymphoma.

Despite the wide range of genetic alterations associated with lymphoid malignancies, certain signaling pathways are repeatedly targeted. Cytogenetic and gene profiling strategies have identified recurrent alterations to transcription factor networks, antigen receptor signaling, cytokine receptor signaling and Ras signaling. In addition, to directly influencing cell proliferation, survival and metabolism, "re-wiring" of such signaling networks can initiate cell transformation by modifying gene expression programs.

Advancements in second-generation sequencing technology such as whole-genome, exome and transcriptome sequencing, have allowed for a more detailed characterization of the genomic landscapes of lymphoid malignancies [1]. Future challenges lie in linking perturbed signaling networks to changes in gene profiles. For example, failure to shut down the pre-thymic gene program in thymic progenitors blocks differentiation and promotes leukemogenesis [2]. Yet, the signaling pathways responsible for maintaining the pre-thymic gene program and consequently promoting lymphoid malignancies, remain ill-defined.

A signaling pathway deregulated in multiple lymphoid malignancy subtypes, is the Janus kinases (JAK)–signal transducers and activators of transcription (STATs) pathway. In leukemia and lymphoma, elevated phosphorylation of JAK and STAT molecules has been associated with pro-survival and drug resistance gene programs [3].

Protein tyrosine phosphorylation is a reversible post-translational modification controlled by protein tyrosine kinases (PTK) and protein tyrosine phosphatases (PTP). Activating and deactivating mutations within PTK and PTP genes often result in enzymes which can either promote or suppress oncogenesis. The oncogenic capacity of dysregulated kinases has been discussed at length in previous reviews. Herein we focus on the emerging role of two phosphatases, PTP1B (gene *PTPN1*) and TC-PTP (gene *PTPN2*) in regulating JAK–STAT signaling in hematological diseases.

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http://dx.doi.org/10.1016/j.cyto.2015.12.025
1043-4666/

2. The JAK–STAT pathway

Intercellular communication contributes to immune cell homeostasis by regulating cell proliferation, differentiation, survival and metabolism. Cytokines are critical soluble mediators of such communication, activating signaling networks capable of promoting or suppressing gene expression. Within this network, the canonical JAK–STAT pathway is a direct link from cytokine receptors at the cell surface to the nucleus. Following binding of a cytokine to its cognate receptor, associated JAK molecules phosphorylate each other and the cytoplasmic tail of the receptor. The phosphorylated tail then provides docking sites for SH2-containing STAT molecules. Recruited STAT molecules are phosphorylated by JAK molecules and dissociate from the receptor, translocate into the nucleus, and bind DNA as either hetero- or homodimers (Fig. 1). The differential use of 4 JAK (JAK1, JAK2, JAK3 and TYK2) and 6 STAT (STAT1, STAT2, STAT4, STAT5a/b, STAT6) molecules by the large array of cytokine receptors contributes to the diverse transcriptional profiles induced by cytokine–JAK–STAT pathways.

2.1. Mutations of the JAK–STAT signaling axis and hematological malignancies

Genetic alterations to cytokine driven JAK–STAT signaling are prevalent in leukemia and lymphoma. Gain-of-function mutations in the IL-7R that result in receptor dimerization and constitutive JAK1 activation occur in 9% of cases of T-ALL [4,5]. Likewise, gain-of-function mutations have been detected in JAK1, JAK2 and JAK3 in ALL subsets with varying frequencies [3,6]. Mutations among the STAT genes are less frequent in cancer, but gain-of-function STAT3 and STAT5 mutations have been reported in both B and T cell malignancies [7–11]. Such mutations typically induce prolonged STAT phosphorylation, causing profound changes in gene expression that enable cell survival and proliferation independent of growth factors and cytokines.

Under physiological conditions, the amplitude and duration of JAK–STAT signaling are regulated by multiple molecular mechanisms. These include the internalization and degradation of cytokine receptors by the lysosome or proteasome pathways, the recruitment of cytokine-induced SH2-containing protein 1 (CIS1) and suppressors of cytokine signaling proteins (SOCS 1–7), and

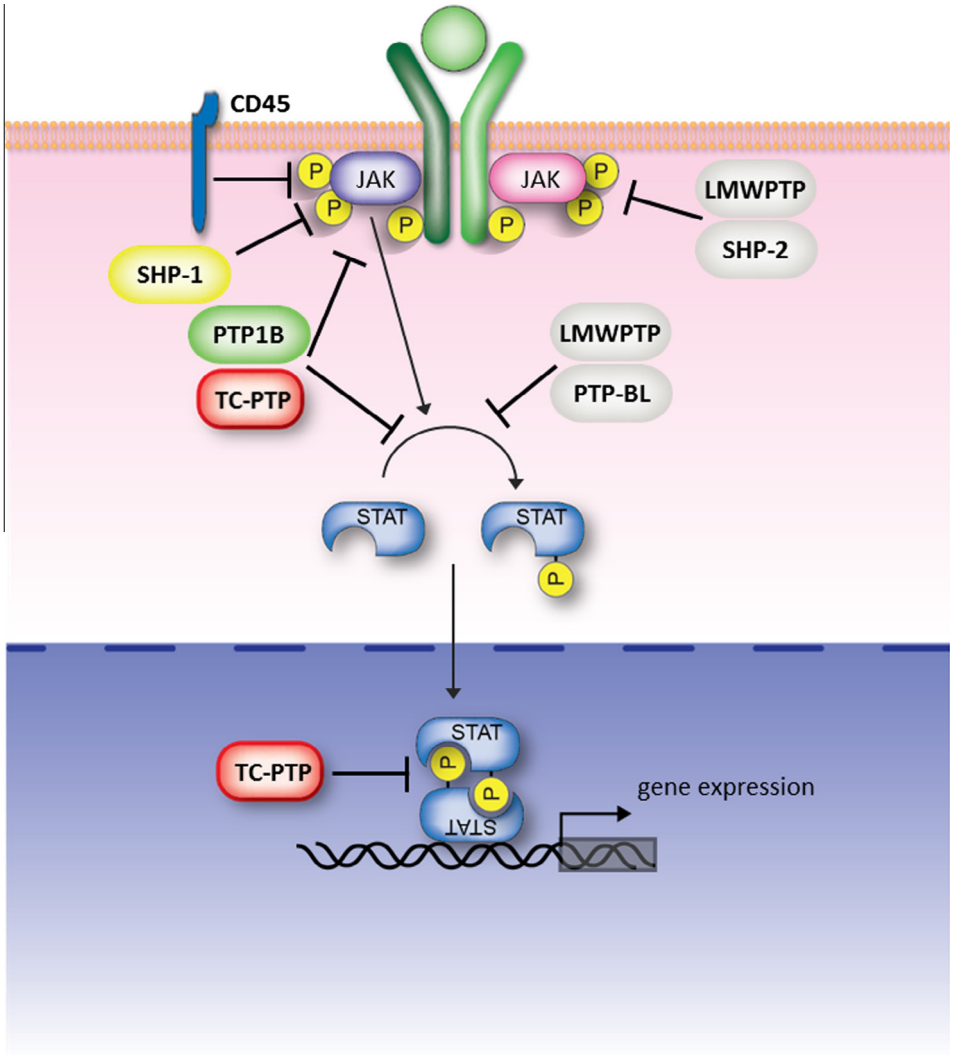

Fig. 1. Protein tyrosine phosphatases regulate cytokine receptor–JAK–STAT signaling. A schematic representation of JAK–STAT signaling downstream of cytokine receptors. Protein tyrosine phosphatase identified as negative regulators of JAK–STAT signaling are depicted. PTPs reported to be mutated or repressed in leukemia or lymphoma are shown in color. A given PTPs substrate is identified by a bar-headed line.