

A System Biology Perspective to Overcoming the Challenges of JAK Inhibition Monotherapy for Myeloproliferative Neoplasms: An Overview

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Abstract

The JAK-STAT pathway mediates signals that are involved in hematopoiesis. Aberrant JAK-STAT signaling has been identified in myeloproliferative neoplasm making the pathway a novel therapeutic target for myeloproliferative neoplasms through the application of JAK inhibitors. A major limitation to therapy with the current JAK inhibitors is a lack of selectivity which results in toxicity to patients. It is thought that increasing the selectivity of inhibitors will reduce toxicity observed with JAK inhibition therapy. System biology is a novel technology that holds great potentials for increasing the selectivity of JAK inhibitors. Its application to drug designing can broaden the spectrum as well as repurpose the available JAK inhibitors for improved clinical outcome and possible cure for myeloproliferative neoplasms. This review presents an overview on the role of system biology in JAK inhibition therapy for myeloproliferative neoplasms.

Keywords: JAK-STAT pathway • JAK inhibitors • Therapy • Myeloproliferative neoplasm • System biology

About the Study

System biology provides a good analytical tool to understand, predict, and control of biological processes particularly for blood cell production as well as hematological malignancies such as myeloproliferative neoplasms [1,2]. Myeloproliferative neoplasms are heterogeneous hematopoietic stem cell disorders that involve mutations which activate the physiological signal-transduction pathways associated with activated JAK-STAT signaling [3,4]. The current World Health Organization classification of Myeloproliferative neoplasms have identified Chronic Myeloid Leukaemia, Chronic Neutrophilic Leukaemia, Polycythemia Vera, Primary Myelofibrosis, Essential Thrombocythemia, Chronic Eosinophilic Leukaemia and other unclassified neoplasms [5]. They are classified into three groups of (i) Neoplasms with Philadelphia positive chromosome such as Chronic Myeloid Leukaemia (ii) Neoplasms with Philadelphia negative chromosome such as Polycythemia Vera, Essential Thrombocytopenia, Primary Myelofibrosis and (iii) other uncommon myeloid neoplasms including Chronic Eosinophilic Leukaemia,

Chronic Myelomonocytic Leukaemia and Systemic Mastocytosis [6]. Studies identified three main mechanisms of pathophysiology which include (iv) somatic driver mutations that stimulate activation of JAK-STAT pathway (v) cooperating driver mutations in myeloid genes and (vi) uncommon genetic factors that initiate different clinical neoplastic phenotypes.

The Role of JAK-STAT Pathway

In 2005, the activating V617F mutation in the exon 14 of the JAK 2 gene (JAK2V617F) was identified in 50% of myeloproliferative neoplasm patients. Following this, other JAK 2 mutations such as mutation in the exon 9 gene encoding for calreticulin (CALR) were identified in 25% of cases and in a minority of about 5% a mutation in MPL exon 10 was identified [7,8]. The discovery in myeloproliferative neoplasm patients of mutations affecting JAK 2 signaling led to the identification of deregulated signaling through the JAK-STAT pathway as a major pathogenic mechanism of clonal proliferation and the development of drugs targeting JAK 2 [9]. Ruxolitinib was the first

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Received: August 24, 2021; Accepted: September 07, 2021; Published: September 14, 2021

JAK 2 inhibitor approved for therapy of myeloproliferative neoplasms [10]. Several other JAK 2 inhibitors have been developed for patients with myeloproliferative neoplasms but have been discontinued due to toxicity.

JAK inhibition therapy

Following the identification of activating mutations in the JAK-STAT pathway, there was considerable effort put into the development of substances that can target the kinase activity of JAK 2. These are commonly referred to as the JAK inhibitors. JAK inhibitors could be classified into two groups of allosteric and non-allosteric inhibitors depending on their mechanism of action and region targeted for therapy.

Non-allosteric inhibitors

There are two types namely the type I inhibitors and type II inhibitors. While type I inhibitors target the ATP-binding site of JAK2 in the active conformation of the kinase domain, the type II inhibitors target the ATP-binding site of its kinase domain in the inactive conformation. Type I inhibitors have been prominent in the management of myeloproliferative disorders. Ruxolitinib, a Type I inhibitor has been recently approved for the treatment of myeloproliferative disorders by the US food and Drug Administration. Though at the early stages of clinical trials, type II inhibitors are more effective and powerful than type I inhibitors. Two type II inhibitors (NVP BBT594 and NVP-CH2868) have been developed. The NVP – BBT594 was effective in myeloproliferative neoplasm cellular models while NVP-CH2868 has been effective in preclinical mouse myeloproliferative models [11,12].

Allosteric inhibitors

These are inhibitors which bind to other sites different from the ATP-kinase binding active sites. There are two types namely type III inhibitors which bind to a site close to the ATP-binding site (e.g. LS104) and type IV inhibitors which bind to an allosteric site far from the ATP-binding Site (e.g. ONO44580). Targeting regions outside the ATP-binding site provides an advantage of higher selectivity and the possibility to overcome drug resistance by targeting two different sites in a combinatorial therapy model [13,14]. There are currently no JAK allosteric inhibitor in clinical use.

The Challenges of JAK Inhibition Therapy

The aim of JAK 2 inhibition therapy for myeloproliferative neoplasms has not been achieved. There are limitations with respect to limited efficacy, selectivity and dose-limited toxicities [15]. There is need for new inhibitors or combination therapies which will not only ameliorate symptoms but could arrest clonal proliferation of the myeloid stem cells. New generation of JAK 2 inhibitors such as allosteric inhibitors targeting unique sequences in JAK 2 are needed to be developed. Such inhibitors will be less toxic and will target the clonal complexities of the disease [16].

Perspective for a System Biology Framework

System biology provides a network analysis of disease related genes and drug targeting of signaling pathways which could enable the discovery of drugs with the potential desired effects for a given disease [17,18]. Proteomics enables integrated view of biological systems by studying all the transduced proteins in a cell [19]. This can be applied to enhance our understanding of the complexity of multiple molecular mechanisms implicated myeloproliferative neoplasms with respect to JAK inhibitor interactions. Integrated proteomics technologies are currently being explored for various cancer phenotypes to identify common mechanisms that drive the clonal proliferation of cells including aberrant metabolomics [20].

Conclusion

JAK inhibition remains a novel therapeutic target for myeloproliferative neoplasms. System biology presents a dynamic tool that could be strategically applied in JAK inhibition for designing dose regimens, drug repurposing and combination therapies for future interventions on patients with myeloproliferative neoplasms.

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How to cite this article: Ogbuabor, Alphonsus Ogbonna,Achukwu Uwadiegwu Peter, Ufelle Anayo Silas,et al. "A System Biology Perspective to Overcoming the Challenges of JAK Inhibition Mon Therapy for Myeloproliferative Neoplasms : An Overview." *J Blood Lymph* 11 (2021) : 260.