The Development and Use of Janus Kinase 2 Inhibitors for the Treatment of Myeloproliferative Neoplasms

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KEYWORDS

• JAK2V617F mutation • Myeloproliferative neoplasms • JAK2 inhibitors
• JAK-STAT signaling • Myelofibrosis • Polycythemia vera • Mutant calreticulin

KEY POINTS

- Janus kinase (JAK) 2 inhibitors were developed as rationally designed therapy in myeloproliferative neoplasms (MPNs) following the discovery of the activating JAK2V617F mutation.
- The oral JAK1/JAK2 inhibitor ruxolitinib is approved by the Food and Drug Administration for the treatment of intermediate and advanced phase myelofibrosis and in certain cases of polycythemia vera.
- Activated JAK-signal transducer and activator of transcription (STAT) signaling is a central feature of MPN and, as a result, JAK2 inhibitors have clinical efficacy regardless of the type of MPN phenotypic driver mutation.
- Although providing clinical benefit to MPN patients, JAK2 inhibitors are not strongly clonally selective for either JAK2V617F-mutant or *CALR*-mutant MPN cells.
- Despite an absence of clonal selectivity for MPN cells and no difference in the rate of leukemic transformation, ruxolitinib seems to improve overall survival in myelofibrosis.

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INTRODUCTION

The discovery of the JAK2V617F mutation in patients with myeloproliferative neoplasms (MPNs) launched a new era of rationally designed molecularly targeted therapy in *BCR-ABL* negative MPN. The JAK2V617F mutation, which activates Janus kinase (JAK)-2 signaling, is present in more than 95% of patients with polycythemia vera (PV), approximately 65% of patients with myelofibrosis (MF), and 55% of patients with essential thrombocythemia (ET).[1] Improved understanding of the molecular biology of MPN has established activated JAK-signal transducer and activator of transcription (STAT) signaling, driven by JAK2V617F, MPLW515L/K, or mutant calreticulin (*CALR*) at the center of MPN pathogenesis,[2] establishing the JAK-STAT pathway as a key therapeutic target in these diseases (**Fig. 1**). The thrombopoietin receptor, *MPL* is mutated in between 1% and 5% of MPN cases, leading to cytokine independent growth and activated JAK-STAT signaling.[3] More recently, somatic mutations were discovered in the gene calreticulin (*CALR*) in 20% to 25% of ET and MF patients.[4,5] Calreticulin is a calcium-binding chaperone protein that localizes to the endoplasmic reticulum (ER) under normal conditions. More than 30 different

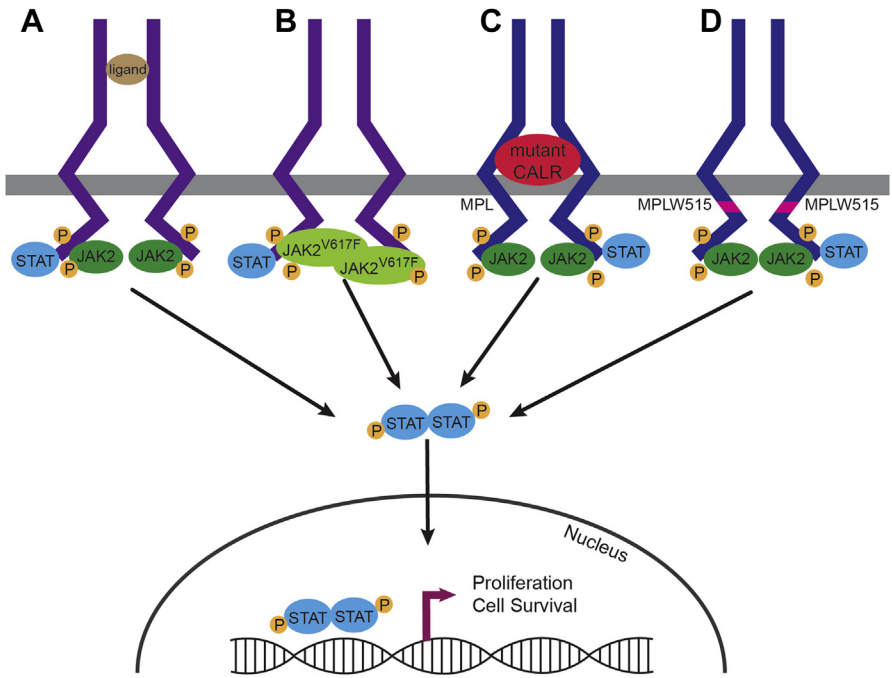

Fig. 1. JAK2-STAT signaling pathway activation in MPN. (*A*) Normally, JAK2-STAT signaling pathway activation occurs through ligand binding to and active dimerization of type 1 cytokine receptors (eg, MPL, EPOR, or GM-CSFR). Activated STAT translocates to the nucleus, where it binds promoters upregulating proliferation and cell survival genes. (*B*) The activating mutation V617F in JAK2 leads to constitutive activation of JAK2-signaling independent of ligand binding. (*C*) Mutant CALR physically interacts with MPL to activate the MPL signaling pathway in a thrombopoietin-independent manner. (*D*) Mutation to MPL at amino acid 515 causes constitutively active MPL signaling. Note: Purple receptor denotes any type 1 cytokine receptor; blue receptors denote MPL.