

Role of JAK2 Beyond Myeloproliferative Neoplasms (MPNs): Rationale for Targeting the JAK-STAT Pathway in Other Hematological Malignancies and Solid Tumors

Theresa M. McDevitt and Matthew V. Lorenzi
Oncology Drug Discovery,
Bristol-Myers Squibb
USA

1. Introduction

Janus kinases (JAKs) are a family of receptor-associated tyrosine kinases which are crucial for the survival and proliferation of immune and hematopoietic-derived cells. There are four mammalian JAKs identified to date: JAK1, JAK2, JAK3 and TYK2 (Lopez et al., 2010). JAKs are responsible for mediating the intracellular signaling of numerous growth factors and cytokines (Murray et al., 2007 & O'Shea et al., 2002). Once activated JAKs directly phosphorylate and activate the transcription factors signal transducers and activators of transcriptions (STATs) which transduce JAK signaling by translocating to the nucleus to modulate a subset of genes that are critical for cell proliferation and survival (Aaronson et al., 2002 & Levy et al., 2002). Dysregulated JAK signaling has been implicated in the pathogenesis of several blood-borne cancers but most notably in myeloproliferative neoplasms (MPNs) (Nelson et al., 2006; Lucia et al., 2011 & Patnaik et al., 2009). MPNs are hematological malignancies defined by the excessive proliferation of one or more myeloid-derived cells. MPNs are classified into two clinical categories either BCR-ABL-positive (BCR-ABL (+)) or BCR-ABL-negative (BCR-ABL (-)) based on the presence of the BCR-ABL fusion protein. The major BCR-ABL (-) MPNs include polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF). The specific pathogenic role that JAK2 has in driving some of these MPNs is highlighted by the recent seminal discovery of the JAK2^{V617F} mutation (Baxter et al., 2005; James et al., 2005; Kralovics et al., 2005; & Levine et al., 2005). The JAK2^{V617F} mutation is a somatic, gain-of function point mutation which leads to constitutive activation of JAK2 and subsequent downstream activation of STATs (Baxter et al., 2005 & James et al., 2005). Current data demonstrates that JAK2 is a disease associated gene involved in the pathogenesis of BCR-ABL (-) MPNs. However, it remains unclear if JAK2 pathway mutations are the primary drivers of sustained disease progression. New data is emerging that suggests that targeting the JAK-STAT pathway may have implications beyond the treatment of MPN and can be useful for the treatment of other hematological and non-hematological cancers. This review will summarize the pathogenic role of JAK-STAT signaling in BCR-ABL (-) MPNs and introduce the potential broader implications by

which JAK-STAT pathway inhibition may have in treating hematological malignancies as well as solid tumors.

2. Janus Kinase Family (JAKs)

2.1 Function

Janus kinases are a family of cytoplasmic receptor associated tyrosine kinases responsible for integrating the signaling of numerous growth factors and cytokines that are critical for hematopoiesis and immune function. There are four JAK family members; JAK1, JAK2, JAK3 and TYK2. JAK1, JAK2 and TYK2 are ubiquitously expressed while JAK3 expression is restricted to myeloid and lymphoid tissue (Valentino et al., 2006 & Ward et al., 2000). Various cytokines and growth factor receptors rely on JAKs to propagate their intracellular signaling cascades since many of these receptors lack intrinsic kinase activity. JAKs can be differentially or coordinately activated in response to various growth factor or cytokine stimuli (Murray, 2007). Targeted disruption of individual JAKs have been generated in an effort to better understand the biological non-redundant roles that JAKs have in development. JAK1 knock-out mice have been generated and present with a perinatal lethal phenotype that is characterized by severe defects in lymphopoiesis and neuronal development (Rodrig et al., 1998). JAK3 mutations in humans have been described in patients with severe combined immunodeficiency (SCID), an immune disorder where major defects in T- and B- cell development are observed. This clinical phenotype is recapitulated in JAK3 knock-out models where these mice manifest with SCID-like features characterized by impaired lymphocyte production (Nosaka et al., 1995 & Park et al., 2000). TYK2 deficiencies although rare have been reported, and these patients usually present with severe dermatitis and hyper-IgE syndrome-like symptoms (HIES). Genetic disruption studies involving TYK2 have presented with severe defects in IL-12 signaling and impaired Th1 and Th2 mediated immune responses (Karaghiosoff et al., 2003). Genetic inactivation of JAK2 in mice is embryonically lethal due to severe anemia, confirming the critical role that JAK2 is thought to have in erythropoiesis (Parganas et al., 1998).

2.2 Structure

JAK proteins share seven homologous structural domains (JH1-JH7) each of which elicit distinct functional features within JAK proteins. The JAK homology domains consist of the C-terminus JH1 domain which is the kinase-active domain, the auto-regulatory JH2 pseudokinase domain, the SH2-like JH3 domain and the N-terminus FERM (four-point-one, ezrin, radixin, and moesin) domain (JH4-JH7). Although the JH3 domain possesses a SH2-like sequence it is unable to bind and interact with phospho-tyrosine residues and therefore its precise function remains unclear while the FERM domain is responsible for mediating the interactions of JAKs with their cognate receptors (Huang et al., 2001 & Radtke et al., 2005). The JH2 pseudokinase domain is a unique structural feature of the JAKs that is otherwise absent in other kinase families. The JH2 pseudokinase domain bears high sequence identity to the JH1 kinase domain but is devoid of any catalytic activity and is thought to act as a regulatory domain through catalytic auto-inhibition (Saharinen et al., 2000). Moreover, key activating point mutations have been identified in the JH2 pseudokinase domain of JAK2 that are critically involved in the pathogenesis of some myeloproliferative neoplasms (MPNs).

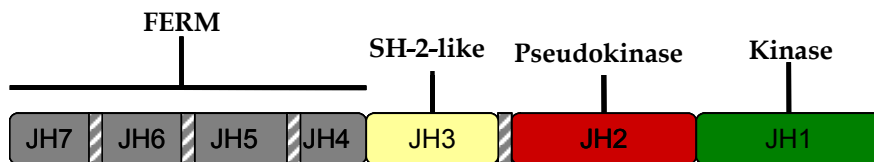


Fig. 1. **JAK Protein Domain Structure.** The seven homologous JAK domains (JH1-JH7) conserved throughout the JAK kinase family.

2.3 JAK-STAT signaling

In the absence of ligand, JAKs are pre-associated with receptor monomers, upon ligand binding receptor dimerization ensues leading to trans-phosphorylation and auto-activation of JAKs. Once activated, JAKs proceed to phosphorylate specific tyrosine residues within the cytoplasmic domains of growth factor receptors creating docking sites for downstream mediators of JAK signaling. JAKs can activate classical signaling pathways such as PI-3-kinase and MAPK but JAKs also directly activate STATs as described above. STATs are latent transcription factors that are activated and phosphorylated by JAKs at specific tyrosine residues (Darnell J, 1997 & Benekli et al., 2003). Once phosphorylated, STAT monomers can then homo/hetero-dimerize through reciprocal Src homology 2 (SH2) interactions and translocate to the nucleus to modulate the transcription of key genes which promote cell growth and survival.

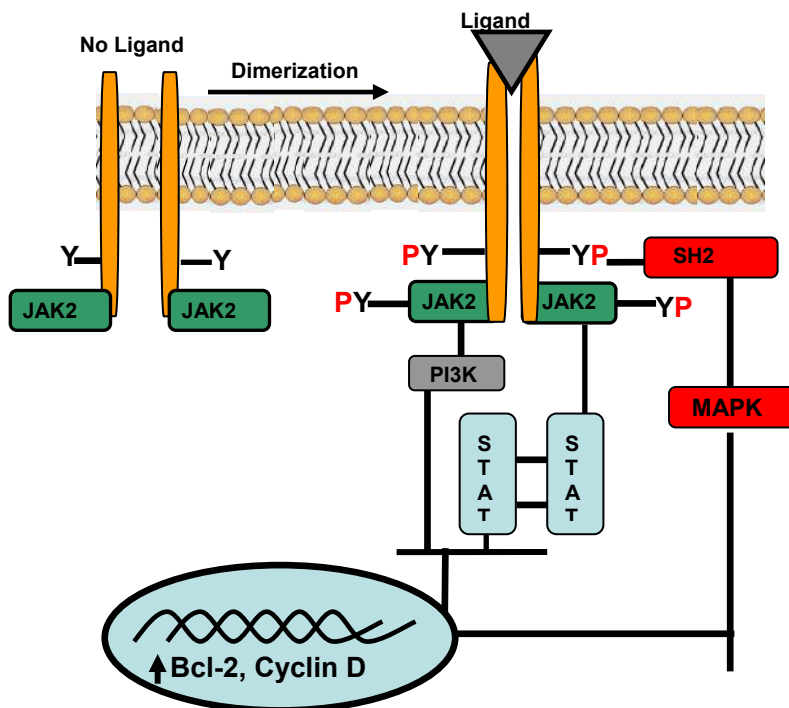


Fig. 2. **Ligand-Induced JAK-STAT Activation**

3. Myeloproliferative Neoplasms (MPNs)

3.1 Clinical biology

MPNs are hematopoietic malignancies characterized by excessive growth of one or more myeloid derived cell lineages such as erythrocytes, platelets and/or granulocytes. MPNs are clinically grouped into either BCR-ABL (+) or BCR-ABL (-) based on the presence of the BCR-ABL protein, as seen in CML patients. Dysregulated JAK-STAT signaling has been implicated in the pathogenesis of these BCR-ABL (-) MPNs. The three most common BCR-ABL (-) MPNs include polycythemia vera (PV), essential thrombocythemia (ET) and idiopathic myelofibrosis (IMF) with an estimated annual cumulative incidence of 130,000 patients in the United States which translates into an estimated prevalence of 6.2 per 100,000 cases (Ma et al., 2008; Mesa et al., 1999 & Ania B et al., 1994). The major clinical features of PV include uncontrolled growth of multiple myeloid-derived lineages with the dominating lineage being erythrocytes which is often reflected by an increased hematocrit and splenomegaly, while minor features include trilineage myeloproliferation of the bone marrow (Wadleigh & Tefferi, 2010). ET is characterized by an increase in both platelet size and number while hematocrit is unchanged. IMF is the most severe of the three MPNs and the major clinical criteria for diagnosis usually includes megakaryocytic proliferation accompanied by severe fibrosis of the bone marrow or hypercellularity of the bone marrow that is characterized by granulocyte proliferation (Wadleigh & Tefferi, 2010). IMF can manifest on its own or it can be preceded by PV or ET, post-PV or post-ET IMF has a variable evolution rate of roughly 25 evolutions per 1000 patients ET/PV patients (Passamonti et al., 2008 & Gangat et al., 2007). Furthermore, each one of these MPNs has the potential to progress to acute myelogenous leukemia (AML). In an unselected BCR-ABL (-) MPN population the overall leukemic transformation (LT) rate registered at 4.0% with MF having the highest transformation rate: 11.4%-MF, 4.3%-PV & 1.75% for ET (Cervantes et al., 1991). Aberrant tyrosine kinase signaling has been implicated in the pathogenesis in the majority of MPNs, most notably with CML where the product of a chromosomal translocation results in the production of constitutively active tyrosine kinase known as the BCR-ABL (Druker et al., 1996). The discovery of the BCR-ABL tyrosine kinase led to the development of the clinically successful small molecule inhibitor, imatinib, which predominately targets BCR-ABL in addition to PDGF-R and KIT kinases (O'Brien et al., 2003). The initial observation that altered tyrosine kinase signaling could single-handedly drive the entire pathogenesis of a disease as seen with BCR-ABL and CML hinted at the possibility that other altered tyrosine kinase signaling could be involved in the pathogenesis of these BCR-ABL (-) MPNs.

3.2 Pathogenic role of JAK2 in BCR-ABL-negative MPNs

Mutations in JAK2 have been implicated as a key genetic factor responsible for driving BCR-ABL (-) MPNs and several lines of evidence highlight this finding. The major hematopoietic growth factors erythropoietin (Epo) and thrombopoietin (Tpo) that give rise to the myeloid derived cells that often over-populate PV and ET patients such as erythrocytes and platelets signal exclusively through JAK2. Loss of heterozygosity (LOH) on chromosome 9, where JAK2 is localized is observed in roughly 30% of PV patients (Kralovics et al., 2002), moreover, progenitor cells isolated from PV patients have routinely demonstrated an increased sensitivity to hematopoietic growth factors such as Epo and Tpo in ex vivo colony growth assays. Additionally, multiple animal models involving targeting expression of

JAK2 including transgenic and retroviral transduction methods leads to a MPN-like phenotype *in vivo*, further supporting a causal role for JAK2 in the pathogenesis of these diseases (Wernig et al., 2006)

3.3 V617F and other JAK2-associated mutations in MPNs

In 2005, several independent laboratories identified a unique somatic activating point mutation in the JAK2 gene (V^{617F}). The JAK2 V^{617F} mutation occurs in the JH2 pseudokinase domain of JAK2 in exon 14 at position 617 where a valine is replaced with a phenylalanine which leads to constitutive activation of JAK2. The mechanism of activation of the V617F mutation is believed to be due to the removal of the auto-inhibitory function of the JH2 pseudokinase domain present in JAK2. The incidence of the JAK2 V^{617F} mutation is highly prevalent within the BCR-ABL (-) MPN patient population particularly within PV cohorts where more than 95% (Wernig et al., 2006) of PV patients are positive for it while 50% of ET and IMF patients are positive for it (Pikman et al., 2006). Although the JAK2 V^{617F} mutation represents a major genetic event underlying the pathogenesis of these MPNs there is still a fraction of PV patients (~5%) and ET/IMF patients (~50%) that present with these MPNs but yet are negative for the V617F JAK2 mutation. The existence of V617F-negative MPNs highlights the need to identify additional JAK2 signaling components that may be involved in the pathogenesis of these V617F-independent MPNs. Several gain-of-function mutations comprised of deletions, insertions and frame-shifts have been indentified in exon 12 of JAK2 in a small subset of V617F-negative PV patients (~3%) (Scott et al., 2007). Interestingly, exon 12 JAK2 mutations are mutually exclusive from V617F JAK2 mutations and to date have only been described in V617F-negative PV patients. Expression of exon 12 JAK2 mutations results in a PV-like phenotype *in vivo* that is characterized by erythrocytosis. Alternatively, activating point mutations in the thrombopoietin receptor (Tpo-R/c-MPL) have been identified in a subset of V617F-negative ET and IMF patients (5-10%). The mechanism of action for the MPLW515L mutation is similar to that of the V617F mutation since it also results in the removal of an auto-inhibitory sequence thought to be located within the transmembrane region of the Tpo receptor which causes spontaneous activation of downstream JAK2-STAT signaling (Pikman et al., 2006). The relative frequencies of these JAK-related mutations are summarized in figure 3 (Paradanani et al, 2011). The oncogenic potential of these mutations in MPN is further highlighted by their ability to induce MPN-like phenotypes in murine bone marrow reconstitution studies. JAK2 V^{617F} expression induces a PV-like phenotype that presents with erythrocytosis and splenomegaly while (Wernig et al., 2006) MPLW515L promotes a more aggressive MF-like phenotype characterized by marked thrombocytopenia and severe fibrosis of the bone marrow (Pikman et al., 2006). Collectively, these results highlight a strong selective pressure to activate JAK-STAT signaling in BCR-ABL(-) MPNs and thus therapies designed to target the JAK-STAT signaling may be beneficial for the treatment of MPN.

4. JAK inhibitors in clinical development

Since the discovery of the JAK2 V^{617F} mutation in 2004 remarkable scientific progress has been made from bench to bedside with the first JAK inhibitors being tested in humans by mid 2007. Currently there are 36 clinical trials in the US underway evaluating various treatments for MPNs or investigating the molecular pathobiology underlying MPNs. The current JAK inhibitors are typically small molecule ATP competitive inhibitors of both wild-type and

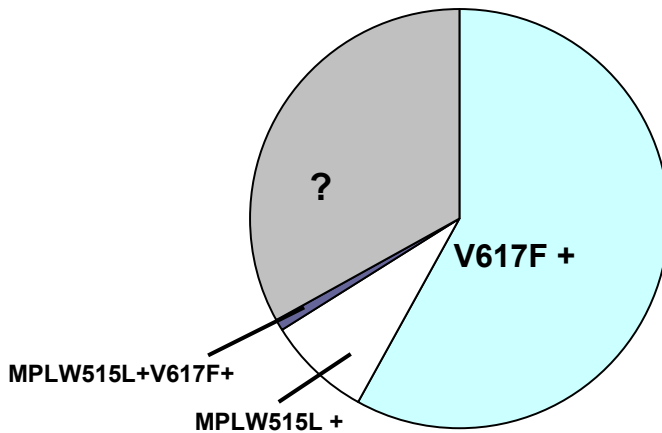


Fig. 3. **Allele Frequency in IMF Cohort**, adapted from Chaligne R, et al. *Leukemia* (2008). Relative mutation frequency in a IMF cohort (n =603), V617F; 58%, MPLW515L; 8.1% and MPLW515L/V617F <1%

mutant JAK enzymes that can be either selective JAK2 inhibitors or non-selective JAK2 inhibitors with the latter having additional activity against other kinases besides JAK2. Initial clinical trials with JAK inhibitors were designed to recruit only IMF patients based on the biological severity of IMF compared to ET or PV, however more recently, clinical trials have expanded to include testing of JAK inhibitors in both PV and ET cohorts. The most advanced JAK inhibitor in the clinic to date is ruxolitinib (INCB018424), a pan-JAK inhibitor which demonstrates potent activity against JAK2 and JAK1 (Quintas-Cardama et al., 2010). A recent phase I/II trial (n=153) has commenced evaluating ruxolitinib for the treatment of IMF. While on ruxolitinib, a significant number of patients demonstrated a favorable clinical response including a reduction in spleen size, improvement in constitutional symptoms and normalization of pro-inflammatory cytokine levels. The suppression of inflammatory cytokines is thought to be linked to the pan inhibitory effects of ruxolitinib on both JAK1 and JAK2 (Verstovsek et al., 2010). Given the clinical response of ruxolitinib in the treatment of IMF, trials have begun to evaluate the safety and efficacy of ruxolitinib in the treatment of PV and ET. Interestingly, these clinical responses did not correlate with JAK2V617F status and molecular remission of the mutant allele was absent even after two years of continued therapy (Verstovsek et al., 2008). The lack of effect on mutant allele burden could be due to direct loss of the mutant allele itself also known as “V617F-independence” that is reported to occur in some patients throughout the evolution of MPN (Passamonti et al., 2010). TG101348 is small molecule inhibitor of JAK 2 in clinical development. Results from a phase I/II multicenter study in IMF patients revealed that >45% of patients on TG101348 observed a >50% reduction in spleen size which was evident by five months but could be detected early two months and more than 70% of patients that presented with elevated white blood cell counts prior to treatment normalized (Pardananani et al., 2009). Unlike ruxolitinib, there was no significant decrease in serum levels of inflammatory cytokines while on therapy although the majority of patients did report a resolution of IMF-associated constitutional symptoms.

Compound	Company	Indication	Phase	NCT Trial #
INCB18424	Incyte	PV/ET/MF	I/II/III	NCT01445769
TG101348	TargeGen	MF	I/II	NCT00631462
SB1518	S*BIO	PV/ET/MF	I/II	NCT00745550
CYT387	YM BIOSCIENCES	MF	I/II	NCT00935987
AZD1480	Astra Zeneca	MF	I/II	NCT00910728
LY2784544	Eli Lilly	PV/ET/MF	I	NCT01134120
BMS-911543	Bristol Myers-Squibb	MF	I	NCT01236352

Table 1. Current JAK Inhibitors in the Clinic

5. Implications for targeting JAK-STAT signaling in additional hematological cancers and solid tumors

Activating mutations in JAK2 (V617F and exon 12) in BCR-ABL (-) MPNs appear to be the primary mechanism by which these cells preferentially activate JAK-STAT signaling, however there are additional mechanisms available for cells to activate JAKs. Cells can also undergo chromosomal rearrangements which also lead to constitutive activation of JAKs. Chromosomal translocations activate JAKs by causing constitutive dimerization through replacement of amino terminal sequences with a fusion partner. In non-MPN hematological malignancies such as acute leukemias and lymphomas chromosomal rearrangements involving JAK2 represent another mechanism for activating JAK2. There have been seven fusion partners identified for JAK2, most of which lead to constitutive activation of JAK2 signaling, these are summarized in table 2.

Fusion Partner	Cancer	Oncogenic	Reference
TEL (ETV6)	T-ALL, aCML,B-ALL	Yes	Lacronique, 1997
PCM1	ALL, aCML	Yes	Reiter, 2005
BCR	aCML	Yes	Greisinger, 2005
SSBP2	B-ALL	Yes	Poitras, 2008
STRN3	ALL	Yes	Mullighan, 2009
PAX5	ALL	No	Bousquet, 2007
SEC31-A	cHL	Yes	VanRoosbroeck, 2011

Table 2. Summary of JAK2 fusion partners due to chromosomal translocations involving chromosome 9p24. Abbreviations include:- T-ALL = T-cell acute lymphoblastic leukemia, aCML= atypical chronic myelogenous leukemia, B-ALL = B-cell acute lymphoblastic leukemia, ALL = acute lymphoblastic leukemia and cHL = classic Hodgkin lymphoma.

5.1 Role of JAK-STAT signaling in non-MPN hematological malignancies

Evidence is accumulating indicating dysregulated JAK-STAT signaling in various types of lymphomas. In classical Hodgkin lymphoma (cHL) and primary mediastinal B cell lymphoma (PMBL) several different mechanisms appear to be involved in the preferential activation of the JAK-STAT signaling network. An estimated 30% cHL patients and 35%-45% of PMBL patients (Joos et al., 2003, 2000; Meier et al.,2009) present with genetic gains in chromosome band 9p24, the region where JAK2 is localized. Recently, several tumorigenic functions have been associated with this amplicon including JAK2-mediated increases in

programmed cell death 1 ligand 1 (PD-L1) expression. PD-L1 is also localized to band 9p24 and therefore cells positive for this genetic gain can also demonstrate increased PD-L1 expression in addition to elevated JAK 2 content. PD-L1 inhibits antitumor cytotoxic T lymphocyte (CTL) responses by activating its cognate inhibitor PD-1 receptor located on T-cells, therefore PD-L1-/PD-1 interactions can promote tumorigenesis by mediating tumor evasiveness. A recent study showed elevated expression of PD-L1 and JAK2 in a subset of cHL and PMBL cell lines that were positive for the 9p24 amplicon and went on to show that PD-L1 expression could be augmented upon JAK2 inhibition suggesting a regulatory role for JAK2 in PD-L1 expression (Green et al., 2010 & Rui et al., 2010). In another study, alternative oncogenic functions were implicated for the 9p24 amplicon based on STAT-independent epigenetic functions of JAK2. In this study, JAK2 was shown to cooperate with the epigenetic modifier JMJD2C in several lymphoma cell lines positive for the 9p24 gain to induce epigenetic remodeling of the oncogene MYC locus leading to altered expression of MYC (Rui et al., 2010). The cooperative interplay between JAK2 and JMJD2C was further demonstrated when the anti-proliferative effects induced by loss of JMJD2C were exaggerated upon JAK inhibition. In addition, inactivating mutations in SOCS-1, a negative regulator of JAK-STAT signaling are observed in 40% of cHL patients (Weniger et al., 2006 & Mottok et al., 2007). Increased expression of activated STATs, namely STAT 3 and STAT6 are often observed in cHL patients and this is thought to be due to sustained signaling loops perpetuated by chronic IL-13 stimulation (Skinnider et al., 2002) furthermore, loss of STAT3 or STAT6 in cHL cell lines results in diminished proliferative capacity and induction of apoptosis (Baus, 2009 & Kube et al., 2005). To further validate a role for abnormal JAK-STAT signaling in lymphoma-type cancers is the more recent study in which an inverse relationship between the inhibitory microRNA-135a and JAK2 was observed in cHL patients. Interestingly, low levels of miR-135a expression were strongly correlated with disease relapse and shorter disease-free survival in a cohort of cHL patients. The regulatory role of miR-135a on JAK2 was confirmed when over-expression of miR-135a led to an increase in JAK2 expression (25%-55%) in lymphoma cell lines (Navarro et al., 2009).

5.2 Role of dysregulated JAK-STAT signaling in multiple myeloma

Altered JAK-STAT signaling has also been implicated in the progression of multiple myeloma (MM). MM is an aggressive hematological malignancy characterized by excessive proliferation of clonal plasma B-cells that accumulate in the bone marrow (Anderson et al., 1999). The maintenance of MM is highly dependent on the interaction of myeloma cells with resident bone marrow stromal cells (BMSC) both of which secrete various cytokines and growth factors that promote myeloma cell growth. IL-6 is recognized as a critical cytokine that's essential for the survival and proliferation of myeloma cells (Bommert et al., 2006). Elevated serum levels of IL-6 are frequently observed in MM patients who fail to respond to conventional chemotherapies and IL-6 levels also correlate with poor prognosis of MM (Niesvizky et al., 1995). IL-6 signals through JAK1/JAK2/TYK2 leading to downstream activation of STAT3 to promote proliferation and survival of myeloma cells (Murray et al., 2007). Interestingly, elevated levels of activated STAT3 have been observed in more than 50% of myeloma patient samples (Bharti AC et al., 2004). Pre-clinical studies have shown that JAK inhibition can induce apoptosis, inhibit proliferation and block constitutive and IL-6 induced activation of STAT3 in several MM cell-based models. Furthermore, JAK inhibition also enhanced the anti-tumorigenic effects of bortezomib, a current therapy

available for MM, in tumor models of myeloma. In summary, JAK inhibition may not be sufficient as a mono-therapy for the treatment of MM but studies that combine JAK inhibitors with the current treatments available for MM like bortezomib may prove beneficial for MM patients. Of note, the pan-JAK inhibitor, INCB18424, currently being tested for the treatment of MPN is also being evaluated in a phase I study for the treatment of MM.

5.3 Implications for abnormal JAK-STAT signaling in solid tumors

Dysregulated JAK-STAT signaling has also been implicated in the pathogenesis of solid tumors primarily due to elevated levels of constitutively activated STATs. Among the STATs, STAT3 and STAT5 are the most studied and well characterized regarding their oncogenic potential. Activated STATs possess multiple oncogenic traits which promote tumorigenesis including tumor cell proliferation, induction of anti-apoptotic and immune cell responses. A defined role has been established for STAT5 in driving some hematological malignancies, including some MPNs where STAT5 expression leads to a MPN-like phenotype, while STAT3 appears to be more involved in solid tumor progression (Germain, 2007). In solid tumors, increased STAT activation is thought to be due to sustained cytokine stimulation via autocrine/paracrine signaling loops rather than increased activity in upstream activators of STATs such as JAKs. Elevated levels of activated STAT3 are observed in multiple solid tumors including breast, prostate, colon, pancreatic, head and neck and ovarian cancers (Song et al, 2006 & Frank., 2003) Recently, an extensive profiling study was done that identified a subset of solid tumor cell lines that expressed high levels of constitutive and IL-6 inducible activated STAT3 and when these cells were treated with specific JAK inhibitors both constitutive and inducible STAT3 activation was suppressed (Hedvat et al., 2009). In a panel of pancreatic cell lines, elevated activated STAT3 levels were found to correlate with gp130 expression, an IL-6 receptor, reinforcing the idea that STAT activation in solid tumors is related to sustained cytokine stimulation (Corcoran et al., 2011)

6. Conclusion

Emerging clinical data on a variety of JAK2 inhibitors support a role of these agents in the symptomatic relief of MPN patients. However, there are still unresolved issues associated with these inhibitors including the inability of most inhibitors to reduce the amount of mutant allele burden. The numerous mechanisms that blood-derived cancer cells have acquired to preferentially activate JAK-STAT signaling (point mutations, translocations & chromosomal gains) demonstrates the importance of this pathway in promoting hematological malignancies. The use of JAK inhibitors for the treatment of other non-MPN hematological cancers such as lymphomas and multiple myelomas are intriguing but require additional pre-clinical studies to determine which JAKs underlie these findings. In this regard, lymphomas with a high frequency of the 9p24 gain (30%) coupled with the recent identification of the novel JAK2-SEC31-A fusion protein implicates a preference for these cells to also activate JAK-STAT signaling. In multiple myeloma, a reliance of these cells on IL-6 for their survival and growth suggests that these patients could benefit from JAK inhibition therapies. For the role of JAK2-STAT signaling in solid tumors, it remains unclear of the potential of pathway inhibition but is likely to require rational combination strategies with other agents in clinical development to unmask the full therapeutic potential of JAK inhibitors.

7. Conflict of Interest

Matthew Lorenzi & Theresa McDevitt are employees of Bristol-Myers Squibb.

8. References

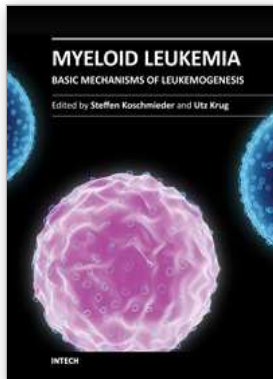
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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Phone: +86-21-62489820
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