

Eliminative Signaling by Janus Kinases: Role in the Downregulation of Associated Receptors

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ABSTRACT

Activation of cytokine receptor-associated Janus kinases (JAKs) mediates most, if not all, of the cellular responses to peptide hormones and cytokines. Consequently, JAKs play a paramount role in homeostasis and immunity. Members of this family of tyrosine kinases control the cytokine/hormone-induced alterations in cell gene expression program. This function is largely mediated through an ability to signal toward activation of the signal transducer and activator of transcription proteins (STAT), as well as toward some other pathways. Importantly, JAKs are also instrumental in tightly controlling the expression of associated cytokine and hormone receptors, and, accordingly, in regulating the cell sensitivity to these cytokines and hormones. This review highlights the enzymatic and non-enzymatic mechanisms of this regulation and discusses the importance of the ambidextrous nature of JAK as a key signaling node that integrates the combining functions of forward signaling and eliminative signaling. Attention to the latter aspect of JAK function may contribute to emancipating our approaches to the pharmacological modulation of JAKs. *J. Cell. Biochem.* 115: 8–16, 2014. © 2013 Wiley Periodicals, Inc.

KEY WORDS: CYTOKINE; DOWNREGULATION; JAK; KINASE; RECEPTOR

Members of the Janus kinases (JAKs) family play a key role in immunity and hormone signaling. These kinases' function is instrumental in numerous important physiological processes. Tight regulation of JAK-dependent mechanisms is therefore essential for homeostatic integrity of many tissues, as well as for their ability to cope with environmental challenges. Both loss and abnormal increase in JAK activity is often responsible for diverse diseases (reviewed in Costa-Pereira et al. [2011], Kerr et al. [2003], and Stark and Darnell [2012]). Accordingly, tremendous medical significance of JAK is reflected by a growing number of research programs developed to identify and characterize pharmacologic agents that target these kinases [Wilks, 2008].

Tight association of JAKs with cognate cytokine receptors plays a key role in the mechanism of their activation and functions. This characteristic also positions JAKs as a unique group of protein kinases that, at least initially anchored to the cell membrane (unlike cytosolic and nuclear tyrosine kinases, such as Src and Abl), yet do not have their own transmembrane domain for the membrane recruitment (unlike the receptor tyrosine kinases such as epidermal growth factor receptor). Four members of this family of tyrosine kinase (JAK1, JAK2, TYK2, and JAK3) have been discovered and extensively characterized [Wagner and Schmidt, 2011]. All these proteins harbor

several common protein domains. The interaction of JAKs with the intracellular domain of diverse cytokine receptors is mediated by the four-point-one, ezrin, radixin, and moesin (FERM) domain. Additional common motifs include the Src homology domain 2, the pseudokinase domain (initially considered to mediate the serine/threonine kinase activity), and the tyrosine kinase domain (reviewed in Costa-Pereira et al. [2011], Kerr et al. [2003], Stark and Darnell [2012], and Strobl et al. [2011]). JAKs are often co-translated and subsequently largely remain tightly associated with intracellular domains of the cytokine receptors. This association per se might play an important role in receptor trafficking, presence on the cell surface and function. Specific examples of such regulation are outlined in the subsequent sections.

JAK AT THE CROSS-ROADS OF CYTOKINE SIGNALING

Activation of JAK represents the most proximal and often essential step in the signaling elicited by a given cytokine (Fig. 1). JAK activity is required for majority of events that occur upon cytokine receptor activation. A few notable exceptions (often limited to a particular tissue or cell type) include JAK activity-independent activation of

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JAK: THE JANUS KINASE, AFTER ALL...

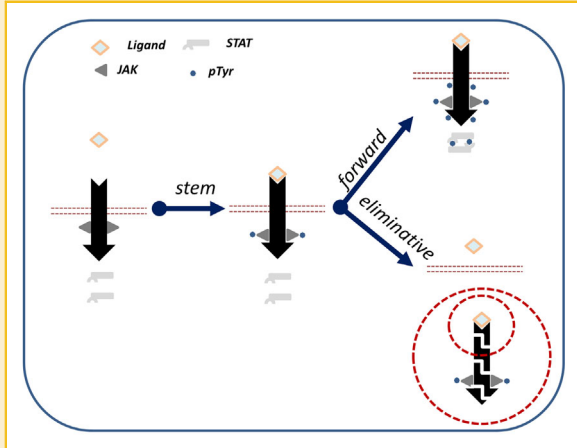


Fig. 1. Interaction of a cytokine ligand with the extracellular domains of its cognate receptor initiates the cytokine signaling. Common elements of this signaling ("stem signaling") are represented by the activation of JAKs resulting in their own phosphorylation. Activated JAKs then signal "forward" to phosphorylate the intracellular domains of the receptor and recruited STAT proteins that become activated and alter the transcriptional program of a cytokine-exposed cell. Concurrently, the "eliminative" signaling mediated by JAKs promotes downregulation of associated receptors often coupled with their proteolytic degradation via lysosomal or/and proteasomal pathway.

mitogen-activated protein kinase by erythropoietin in vascular smooth muscle cells [Ammarguella et al., 2001], activation of this kinase as well as of Src by prolactin [Sakamoto et al., 2007], stimulation of the recruitment of protein kinase D2 (PKD2) to the interferon receptor [Zheng et al., 2011a], induction of CCL20 chemokine expression by interleukin (IL)-17 [Kao et al., 2005], and others.

Most of the "forward" signaling, by which JAK enables the effects of the cytokines functions, is mediated via tyrosine phosphorylation and ensuing activation of the signal transducer and activator of transcription proteins (STAT). However, diverse STAT-independent effects of JAK activation include phosphorylation and cross-activation of unrelated signaling (e.g., insulin receptor substrate [Wang et al., 1997]) and activation of additional signaling branches dependent on unrelated kinases (such as PI3K [Kaur et al., 2005], p38 kinase [Katsoulidis et al., 2005], and others) are documented in the literature. Given how many excellent reviews have been dedicated to the "forward" signaling via JAK, we decided not to focus on this topic in this review.

Instead, we wish to highlight and discuss the eliminative functions of JAKs, that is, the role of these kinases in rapid and irreversible downregulation of cytokine receptors that limits the ability of a cell to respond to the subsequent encounters with a given cytokine (Fig. 1) [HuangFu and Fuchs, 2010; Fuchs, 2012, 2013]. Here we provide specific examples as per how the JAK-activating cytokines (e.g., type 1 interferons) or hormones (e.g., growth hormone) utilize the activation of JAK for decreasing receptor levels and terminating the signal. These examples suggest that JAK activation represents an important step in eliminating the cognate receptors and in ensuing restriction of the magnitude and duration of cytokine-elicited effects.

Historical excursion into JAKs naming and characterization is abundant on irony [Stark and Darnell, 2012]. Being convinced of importance of tyrosine kinases in diverse biological function, Andrew Wilks carried out a series of elegant, daring, and largely successful studies to identify the novel members of this family. Two of cloned genes were named *Just Another Kinase* (JAK1 and JAK2). Being fond of the abbreviation JAK and having noticed a putative serine/threonine kinase motif in addition to a characteristic tyrosine kinase domain, Wilks proposed that JAK may have both tyrosine and serine/threonine kinase activities. Understandable analogy with a two-faced Roman god Janus shaped the acronym "JAK" to be representative of Janus kinase [Wilks and Oates, 1996; Wilks, 2008].

Years of subsequent biochemical characterization carried out by many investigators (regrettably, too many for each to be properly cited within the space constraints) convincingly demonstrated that all four members of JAK family do not possess an appreciable serine/threonine kinase activity. Yet, the name persisted, and, as we hope to demonstrate in the following section, for a very good reason. Indeed, Janus is the God of Gates and Doors; conversely, JAKs as signaling mediators are functioning right at the gateway of cytokine signaling (Fig. 1). Janus, the God of beginnings and endings, has two faces to simultaneously look to the future and the past. Very appropriate of this allegory, JAKs mediate both positive (STAT activation) and negative regulatory (receptor downregulation) events elicited by cytokines and hormones. Therefore, JAKs should be considered the true Janus kinases in their ability to shape both the starting the cytokine signaling and terminating it by elimination of cytokine receptors and desensitization of the cell to additional ligand exposure (Fig. 1).

ROLE OF JAK IN ELIMINATIVE SIGNALING BY SPECIFIC RECEPTORS

TYPE 1 INTERFERON RECEPTOR

This receptor is composed by two diverse chains: IFNAR1 associated with TYK2 and IFNAR2 associated with JAK1 (reviewed in Uze et al. [2007]). Maintenance of the basal levels of IFNAR1 on cell surface in human cells directly depends on its association with TYK2 [Gauzzi et al., 1997], which impedes its ligand-independent constitutive endocytosis [Ragimbeau et al., 2001, 2003; Payelle-Brogard and Pellegrini, 2010]. When bound to IFNAR1, this kinase masks the linear endocytic motif [Kumar et al., 2008], whose exposure to the cellular endocytic machinery could be further regulated by tyrosine phosphorylation and activity of protein tyrosine phosphatase PTP1B [Carbone et al., 2012]. Mouse IFNAR1 contains a different endocytic motif; as a result, the plasma membrane levels of mouse IFNAR1 do not depend on either TYK2 status [Karaghiosoff et al., 2000] or PTP1B activities [Carbone et al., 2012].

Downregulation of the entire receptor is driven by unmasking of IFNAR1 endocytic motifs mediated by the phosphorylation-dependent ubiquitination of IFNAR1 [Kumar et al., 2003, 2004]. This ubiquitination facilitated by the β -Trcp E3 ubiquitin ligase accelerates receptor internalization and stimulates its post-internalization trafficking toward the lysosomal degradation [Kumar et al., 2007].

The recruitment of β -Trcp to IFNAR1 relies on IFNAR1 phosphorylation on serine residues within a specific phospho-degron [Kumar et al., 2004]. This phosphorylation (and ensuing IFNAR1 ubiquitination, endocytosis, and degradation) could be mediated by cross-eliminative stimuli that do not require JAK activity [Liu et al., 2008, 2009a]. These stimuli include tobacco smoking products [HuangFu et al., 2008], non-ligand cytokines and growth factors [HuangFu et al., 2010, 2012; Zheng et al., 2011b], pathogens [Qian et al., 2011], activity of oncogenic proteins [Bhattacharya et al., 2011b], and stress conditions [Liu et al., 2009b; Bhattacharya et al., 2010, 2011a, 2012].

Nevertheless, the ligands (i.e., type 1 interferons) elicit a different specific pathway leading to the downregulation of IFNAR1. This pathway is largely dependent on activities of TYK2 and JAK1 [Marijanovic et al., 2006; Liu et al., 2008]. Activated JAKs signal toward IFNAR1 downregulation via stimulating the recruitment of β -Trcp as a result of increased serine phosphorylation within the IFNAR1 phospho-degron [Kumar et al., 2004; Marijanovic et al., 2006]. As neither TYK2 nor JAK1 possess the serine kinase activities, their effect is indirect. In the interferon-stimulated cells, another kinase—PKD2—is recruited to IFNAR1. This kinase becomes activated as a result of JAK-mediated tyrosine phosphorylation within the plekstrin homology domain of PKD2 [Zheng et al., 2011a]. As a result, activated PKD2 phosphorylates the serines within IFNAR1 degron, stimulates the recruitment of β -Trcp and ensuing ubiquitination and degradation of IFNAR1 as well as attenuation of cellular responses to type 1 interferons [Zheng et al., 2011c].

ERYTHROPOIETIN RECEPTOR

Erythropoietin activates its homodimeric JAK2-associated receptor (EpoR) to and promote erythropoiesis and elicit other important physiological effects, such as regulating renal function and plasma volume, angiogenesis, and cognitive effects, etc. (reviewed in Constantinescu et al. [1999]). Post-translational mechanisms dominate the regulation of the cell surface EpoR levels [Sinclair et al., 2008], the latter determine responsiveness of cells to Erythropoietin. Since the first demonstration of an essential role of associated JAK2 in erythropoietin-induced signaling and transcriptional activation [Witthuhn et al., 1993], important studies gained the insight into the relationship between EpoR and JAK2 and their mutual regulation. Although early results were suggestive that ligand promotes the interaction between these two proteins [Miura et al., 1994], subsequent work strongly supports the notion that JAK2 is already associated with EpoR in naïve cells. Evidence for the latter paradigm include demonstrated ability of JAK2 to phosphorylate immature EpoR in the endoplasmic reticulum [Cohen et al., 1997] and important role of associated JAK2 in delivering the de novo synthesized EpoR to the cell surface [Huang et al., 2001].

EpoR homodimers are pre-formed prior to their interaction with the ligands [Livnah et al., 1999; Constantinescu et al., 2001]; the latter trigger activation via inducing a conformational change leading to JAK2 activation [Remy et al., 1999]. This dimerization is required even for enhanced signaling mediated by a constitutively active JAK2^{V617F} oncogene found in patients with diverse myeloproliferative diseases and present in almost all patients with polycythemia vera [Lu et al., 2008]; accordingly, the integrity of the FERM domain in this mutant is essential for its high intrinsic activity [Wernig

et al., 2008]. It would be expected that the latter activity should promote receptor elimination. Indeed, EpoR expression is reduced on early erythroblasts in mice expressing constitutively active JAK2^{V617F} [Bumm et al., 2006].

Inactivation of EpoR-associated JAK2 and ensuing termination of erythropoietin-induced signaling is attributed to the effects of tyrosine protein phosphatases, including SH-PTP1 [Klingmuller et al., 1995] and PTP1B [Cohen et al., 2004], as well of SOCS proteins that could target JAK2 and/or its association with the receptor [Sasaki et al., 2000]. Other regulators such as Spry1 [Sathyanarayana et al., 2012] or an adaptor protein Lnk also function as negative regulators of JAK2 signaling and downstream effects of erythropoietin [Tong et al., 2005]. It remains to be seen whether these mechanisms directly participate in regulating the EpoR turnover.

A C-terminal truncation in EpoR found in patients with primary familial and congenital polycythemia has been reported [Furukawa et al., 1997; Arcasoy et al., 1999; Watowich et al., 1999; Forget et al., 2000]. This alteration results in an impaired downregulation of EpoR [Sulahian et al., 2009] and sustained JAK2 activation and signaling [Furukawa et al., 1997; Arcasoy et al., 1999; Watowich et al., 1999; Forget et al., 2000]. Given that this mutant lacks the phospho-degron motif needed for the recruitment of β -Trcp E3 ubiquitin ligase, which has been shown to play a key role in EpoR downregulation and degradation [Meyer et al., 2007], it is plausible that sustained activation of JAK2 results from dissociation of its ability to signal forward from JAK2-mediated elimination of EpoR [Verdier et al., 2000; Walrafen et al., 2005]. A dominant nature of this mutation has been reported [Watowich et al., 1999] suggesting that the loss of degron (along with the loss of distal tyrosine residues [Arcasoy and Karayal, 2005] implicated in recruitment of PI3K elements [Sulahian et al., 2009]) renders this receptor constitutively active.

In line with this possibility, JAK-stimulated ubiquitination of EpoR by β -Trcp may stimulate elimination of receptor via diverse mechanisms including involvement of lysosomal and proteasomal activities [Verdier et al., 2000; Walrafen et al., 2005]. Ubiquitination of EpoR plays a key role not only in receptor elimination but also in its signaling [Bulut et al., 2011]. Whereas a central role of β -Trcp E3 in the elimination of EpoR has been firmly established [Meyer et al., 2007], a potential role of other ubiquitin ligases such as p33^{RUL} cannot be ruled out [Friedman et al., 2003]. The role of JAK2 in the function of these ligases remains to be elucidated.

THROMBOPOIETIN RECEPTOR

Thrombopoietin receptor (TpoR) is capable of activating both JAK2 and TYK2. This activation in response to the ligand plays a key role in the differentiation of megakaryocytes, formation of platelets, and renewal of the hematopoietic stem cells (reviewed in Kaushansky [2009]). Association of TpoR with both JAK2 and TYK2 ensures a proper plasma membrane localization of the receptor in the absence of the ligand. Whereas, unlike for EpoR, a large fraction of the TpoR is processed to the mature Endo H-resistant form and reaches the cell surface even in the absence of JAK2, this association stabilizes the mature form of the receptors and protects it from internalization and other modes of degradation that may involve proteasomal activity [Royer et al., 2005; Tong et al., 2006].

TpoR is known to be downregulated in cells exposed to the ligand [Sato et al., 1998]. TpoR-dependent activation of JAK2 and TYK2 within the context of thrombopoietin signaling is negatively regulated by the presence of a unique amphipathic motif at the junction between the transmembrane and cytoplasmic domains [Staerk et al., 2006]. Either the role of this domain in receptor stability or the function of JAK2 and TYK2 in the ligand remains to be determined. However, consistent with a hypothesis that JAKs contribute to TpoR elimination, this receptor is robustly downregulated in cells that harbor constitutively active JAK2^{V617F} [Pecquet et al., 2012]. Constitutively active mutant forms of TpoR have been reported in some myeloproliferative neoplasms [Kota et al., 2008; Marty et al., 2009], the exact effect of these mutations on the rate of receptor downregulation remains to be elucidated.

GROWTH HORMONE RECEPTOR

Growth hormone receptor (GHR) is tightly associated with JAK2 and relies on JAK2 for mediating most, if not all, of its signaling pathways (reviewed in Frank [2002] and Frank and Fuchs [2008]). Association of the GHR with JAK2 ensure proper GHR maturation [He et al., 2003, 2005] and plays a paramount role in enabling the trafficking of de novo synthesized receptor to the cell surface [He et al., 2005; Loesch et al., 2007]. The fate of already matured GHR is also influenced by JAK2 interaction given that the proteolytic turnover rate for this receptor is grossly accelerated in cells lacking JAK2 even in the absence of the ligand [He et al., 2005]. Studies that examined the role of catalytically active JAK2 in the ligand-inducible ubiquitination, endocytosis, and degradation of GHR so far paint a rather complicated scenario. GHR is ubiquitinated (and this ubiquitination is stimulated by GHR), however, the role of ubiquitination per se in GHR endocytosis has been disputed based on receptor truncation analysis. Yet a role of several E3 ubiquitin ligases, including SOCS, Triad1, CHIP, and β -Trcp in GHR downregulation has been suggested [Strous and Gent, 2002; Landsman and Waxman, 2005; van Kerkhof et al., 2007, 2011; Hassink et al., 2012; Slotman et al., 2012]. JAK2 was proposed to negatively regulate ubiquitin-mediated endocytosis [Putters et al., 2011], however, numerous other studies using pharmacological [Saito et al., 1994; Moulin et al., 2003] or molecular approaches [Deng et al., 2007] strongly suggest that JAK2 activation within the context of growth hormone signaling promotes downregulation of this receptor. Future studies aimed to tease apart constitutive versus ligand-inducible and ubiquitination-driven versus ubiquitination-independent mechanisms should shed the light on the role of JAK2 in elimination of GHR.

PROLACTIN RECEPTOR

Several forms of prolactin receptor (long, intermediate, Δ S1, and two short forms) have been described in mammalian cells (reviewed in Clevenger and Kline [2001] and Swaminathan et al. [2008a]). The preformed homodimer of the long form of this receptor is known to mediate the entire plethora of signaling events triggered by prolactin including the activation of associated JAK2 shown by several groups to represent a key mediator of effects elicited by this hormone [Dusanter-Fourt et al., 1994; Rui et al., 1994]. This long form (known to be stabilized in breast cancer cells [Li et al., 2006]) undergoes constitutive phosphorylation-dependent ubiquitination, endocytosis,

and lysosomal degradation that is dependent on the glycogen synthase kinase 3 β and β -Trcp E3 ubiquitin ligase [Li et al., 2004; Plotnikov et al., 2008, 2009].

Importantly, within the context of prolactin signaling, activation of JAK2 (as well as Src) appears to further stimulate the degradation of prolactin receptor. Among the mechanisms underlying this phenomenon are ubiquitination-stimulated receptor internalization [Swaminathan et al., 2008b], trafficking of already internalized receptor into the lysosomes [Varghese et al., 2008], and proteolytic processing of the receptor at the membrane followed by proteasomal degradation of the fragments [Lu et al., 2005; Piazza et al., 2009]. Intriguingly, a recent possibility of JAK2-mediated cross talk between prolactin and growth hormone in the regulation of respective receptors has been recently suggested [Xu et al., 2012].

Prolactin represents a major activator of JAK2 in mammary glands. Unlike myeloproliferative diseases featuring constitutively active JAK2 mutants, these types of aberrations are not found in breast cancers. However, constitutively active variants of prolactin receptor that mediate an augmented JAK2 activation in mammary fibroadenomas have been recently identified [Bogorad et al., 2008; Courtillot et al., 2010]. Relative susceptibility of these mutant receptors to basal and ligand-inducible downregulation remains to be elucidated.

OTHER RECEPTORS

Stabilizing effects of JAK1 on cell surface levels of the oncostatin M receptor [Radtke et al., 2002, 2006] and IL-9R α , and IL-2R β [Malka et al., 2008] have been reported. Similar regulation by JAK3 was proposed for the common γ -chain of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptor complexes [Hofmann et al., 2004]. The ligand-stimulated internalization and degradation of interleukin-7 receptor- α has been demonstrated to depend on the activity of associated JAK3 in T cells [Henriques et al., 2010]. Whereas ubiquitination of the interleukin-10 receptor appears to be constitutive [Jiang et al., 2011], an acceleration of its degradation was shown to be stimulated by the ligand [Wei et al., 2006] suggesting at least some sort of involvement for the JAK-dependent stem signaling.

Gp130 is a common chain for many cytokine receptors such as IL-6 (in combination with IL6R chain) or leukemia inhibitory factor (reviewed in Silver and Hunter [2010]). Ligand treatment robustly promotes downregulation of IL6R [Zohnhofer et al., 1992]. IL6-induced activation of associated JAK2 precedes post-translational modification of gp130 followed by its internalization [Wang and Fuller, 1994] that is dependent on a di-leucine endocytic motif [Dittrich et al., 1994, 1996; Dumanov et al., 2006]. A phosphorylation of a serine adjacent to this motif that stimulates its unmasking and subsequent receptor downregulation and degradation can be induced by diverse ligands that utilize gp130 as a component of their receptor [Gibson et al., 2000; Blanchard et al., 2001]. This phosphorylation is mediated by the MK2 kinase that could be activated not only by a ligand (in a manner presumably dependent on JAK activity), but also by numerous stress stimuli that could stimulate MK2 in a JAK-independent manner [Hideshima et al., 2003; Radtke et al., 2010]. Accordingly, JAK activation was shown to be not essential for overall gp130 internalization [Thiel et al., 1998a,b]. Given that other cytokines (e.g., interferon- α [Anthes et al., 1995]) are

capable of joining the plethora of stimuli that could cross-eliminate gp130, the experimental assessment of the role of JAK solely within the context of the ligand-dependent signaling appears problematic.

The common beta chain shared by the cognate receptors for interleukin-3, interleukin-5, and the granulocyte-macrophage colony-stimulating factor was shown to be ubiquitinated, internalized, and degraded in a manner dependent on activity of associated JAK2 [Martinez-Moczygemba and Huston, 2001] and, perhaps, of JAK1 that is associated with the interleukin-5-specific alpha chain [Martinez-Moczygemba et al., 2007]. Similarly to the JAK-inducible IFNAR1 ubiquitination [Kumar et al., 2007], specific ubiquitin-acceptor sites appear to be responsible for the downregulation of common chain induced by interleukin-5 [Lei et al., 2011].

MEDICAL ASPECTS OF JAK-MEDIATED ELIMINATIVE SIGNALING

Given obvious medical importance of balancing activity of JAK in cells, an intensive search for pharmacologic modulators of these kinases is warranted [Wilks, 2008]. Both approaches to activate and to inhibit JAKs are being considered. Use of hormones/cytokines to stimulate JAK activities and ensuing “forward” signaling has been obviously used within the context of the hormone/cytokine action. Such therapeutic approaches include the use of growth hormone in replacement therapy in deficient patients [Giannoulis et al., 2012], use of erythropoietin to combat anemia [San Miguel and Garcia-Sanz, 1998] as well to protect kidney, liver, and neural tissues from injury [Sargin et al., 2010; Moore et al., 2011], use of interferons to treat cancers, chronic viral infections, and multiple sclerosis [Borden et al., 2007; Fuchs, 2013], and many others. Conversely, the inhibitors of JAKs are proposed to be used as immunosuppressants, anti-inflammatory, and anti-cancer agents [Borie et al., 2004; Zhao et al., 2005; O’Neill, 2006]. Ongoing clinical trials are examining the efficacy of diverse JAK-targeting agents against psoriasis [Kwatra et al., 2012], rheumatoid arthritis [Cohen and Fleischmann, 2010; Vaddi and Luchi, 2012], and myeloproliferative neoplasias [Stein et al., 2011; Tefferi and Pardanani, 2011].

Understanding the eliminative aspect of JAK’s function adds another dimension to the development and practical use of both activators and inhibitors of these kinases within the context of diverse pathologic conditions. Potential development of potent therapeutic modalities aimed at the eliminative function of JAK might be beneficial for various patient groups. Agents that could promote dissociation of JAK from its cognate receptor may act to desensitize the cell to a given cytokine/hormone and prevent its potentially harmful effect. As both type 1 interferons and TYK2 play a key role in augmenting the lethality during the septic shock [Karaghiosoff et al., 2003], patients suffering from this condition could benefit from agents that promote dissociation of TYK2 from IFNAR1 are expected to inactivate TYK2 and promote the loss of IFNAR1 from the cell surface.

Additional efforts could be expanded toward the agents or their combination that may selectively target either “forward” or “eliminative” signaling outcomes. For example, if inhibitors of the constitutively JAK2^{V617F} are combined with another agent that maintains a high level of degradation of JAK2-associated receptors,

the cumulative efficacy of treatment in patients with myeloproliferative diseases could be increased. Future progress in this area of research may lead to development of novel and exciting therapeutic approaches.

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