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Survey

The role of cytokines in the initiation and progression of myelofibrosis

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ABSTRACT

Myelofibrosis (MF) is a life-threatening blood cancer characterized by progressive bone marrow fibrosis, splenomegaly, cytopenias, and debilitating constitutional symptoms. Abnormal expression and activity of a number of proinflammatory cytokines are associated with MF, in which immune dysregulation is pronounced as evidenced by dysregulation of several immune and inflammation genes. The discovery of the Janus kinase 2 (*JAK2*) V617F mutation has led to the development of a number of JAK1/2 inhibitors in the treatment of MF and similar neoplasms. Here, the role of cytokines in MF initiation and progression is discussed, the impact of current therapies is reviewed, and new combination therapies are proposed, such as JAK1/2 inhibitors with interferons, statins, and epigenetic modifiers for patients with MF and related neoplasms.

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Contents

1. Introduction

Cytokines are soluble proteins that are key regulators of a variety of biological processes and are most commonly known for their immunomodulatory functions [1]. In addition to the classically defined cytokines, such as interleukins and interferons, a variety of other soluble factors, including a range of growth factors, have often been classified as cytokines. In general, cytokines are produced in response to cellular stresses including infection by pathogens, inflammation, or injury. Their release exerts effects on several somatic cell types to modulate a host response. In the case of injury or inflammation, macrophages and neutrophils locally infiltrate and secrete a number of cytokines, including a variety of angiogenic factors, growth factors, and proteases, resulting in an assortment of cellular responses including increased angiogenesis, cell proliferation, cell migration, and hematopoiesis [2–4].

Within the complex milieu of cytokines released, both proinflammatory and anti-inflammatory cytokines act to control cellular stress and minimize tissue damage. In general, following the resolution of the injury or inflammatory state, cytokines return to homeostatic levels [5–7]. However, it is becoming increasingly clear that chronic inflammation resulting in abnormal cytokine production and dysregulation of cytokine levels contributes to the pathophysiology of a number of diseases including cancer. Indeed, tumors have often been referred to as "wounds that never heal" [8–10]. The engagement of immune cells to areas of chronic inflammation activates a number of cytokine networks, including those that result in the production of cyclooxygenase 2, inducible nitric oxide synthase, tumor necrosis factor-α (TNFα), and

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interleukin 6 (IL-6), as well as a number of growth factors including fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), and thereby contributes to tumor initiation and maintenance [11–13].

Tumor cells themselves can contribute to this process via the production of growth factors that stimulate the neighboring stromal tissue. For example, macrophages recruited to sites of chronic inflammation secrete proinflammatory cytokines such as TNFα, which results in the activation of the transcription factor nuclear factor κB (NF-κB). In turn, NF-κB induces the transcription of genes involved in many of the major hallmarks of cancer, including cell survival, proliferation, and angiogenesis [14–16].

While the evidence for the relationship among chronic inflammation, cytokines, and solid tumors is robust, the evidence for the role of cytokines in hematopoietic malignancies is less well understood. This paper reviews the preclinical and clinical evidence of the role of cytokines in the initiation and progression of myelofibrosis (MF), a myeloid cancer that belongs to the so-called Philadelphia chromosome-negative chronic myeloproliferative neoplasms (MPNs) that include essential thrombocythemia (ET), polycythemia vera (PV), and MF [17]. These neoplasms constitute a biological continuum from early disease stage (ET and PV) to the advanced "burnt-out" MF phase and ultimately to leukemic transformation. Most recently, their development from early to advanced disease has been proposed to depict a "Human Inflammation Model for Cancer Development" [18], taking into account that chronic inflammation, which is also generated by the neoplastic cells themselves, may be an important driver of clonal evolution, premature atherosclerosis, and development of secondary cancer as well [19]. In this scenario, chronic inflammation may also be a promoter of mutations and accordingly contributes to the steady increase in mutations [18] that characterize MPNs [20–26]. In the context of chronic inflammation as a potential critical driver of clonal evolution in MPNs [19] and the marked dysregulation of inflammation and immune genes [27–29] with highly elevated circulating inflammatory cytokines [30,31], the effect of current therapeutic options on cytokine levels is described and novel potential combination therapies are proposed that may improve the current paradigm of MF therapy.

2. Janus kinase/signal transducer and activator of transcription pathway

2.1. Janus kinase/signal transducer and activator of transcription signaling

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway is a major mediator of cytokine signaling, and the dysregulation of this pathway is a hallmark of MF [32,33]. Gene-targeting studies have established the critical role of the entire JAK family, including JAK1, JAK2, JAK3, and TYK2, in the biological response to cytokines [34–36]. Most notably, JAK1 plays a major role in signaling of inflammatory cytokines, often in association with other JAK family members as heterodimers [37–39]. In general, JAKs are critical for the signaling of many surface cytokine and growth factor receptors that lack intrinsic kinase activity [32]. In the absence of cytokines, receptors and their JAK partners are maintained in inactive complexes; in response to specific cytokine binding, JAKs undergo transautophosphorylation and subsequently phosphorylate several tyrosine residues on their respective receptors. This phosphorylation provides an SH2 docking site for the STAT transcription factors [35,40–42]. Many receptors for a variety of cytokines signal through a small number of JAKs, and both type I and type II cytokine receptors use specific cooperating JAK combinations or single JAK enzymes (Table 1) [32,39].

JAKs in turn activate the STAT proteins, and following dimerization, STAT heterodimers transmit the cytokine activation signals from the cytoplasm into the nucleus and induce the transcription of a number of downstream targets. Specific STAT proteins are activated by a defined set of cytokines; about 50 cytokine receptors signal through combinations of the JAK and STAT family members, suggesting commonality across the JAK/STAT signaling system [32]. STAT-mediated transcriptional activation of known target genes mediates diverse cellular events that affect cell growth, differentiation, and apoptosis (Table 2) [33,43,44].

Transcriptional targets of STATs are involved in a number of potential cancer pathways, including the regulation of cell survival, proliferation, differentiation, and the angiogenic cascade [45–47]. In particular, STAT3 has been implicated in inducing cancer-promoting inflammation [48]. By triggering the NF-κB and JAK pathways, STAT3 activates the production of enzymes such as matrix metalloproteinases, classic immunomodulatory cytokines including IL-6, IL-10, IL-17, and IL-23, and growth factors (e.g., VEGF and FGF) [19]. It is clear that target genes of STATs include cytokines and other growth factors and thereby create a potential autocrine positive feedback loop of JAK-mediated cytokine production and JAK/STAT signaling activation. Therefore, the JAK/STAT pathway not only plays a role in the intrinsic cancer cascade but also the extrinsic cancer-associated inflammatory microenvironment through its cytokine production (Fig. 1).

2.2. JAK/STAT dysregulation in MPNs

There is an increasing wealth of evidence demonstrating that persistently activated JAK/STAT signaling is associated with tumorigenesis and cancer progression, including patients with MPNs [45,49,50]. In 2005, the discovery of the *JAK2* V617F activating mutation generated a remarkable amount of research into the role of JAK/STAT dysregulation in MPNs [38]. The frequency of the V617F mutation is estimated at approximately 98% in patients with PV and 50–60% in patients with primary MF (PMF) or ET [51–54]. In addition to the V617F mutation, a number of other JAK-activating mutations have been observed in patients with MPNs (e.g., several different mutations in exon 12 of *JAK2* and gain-of-function mutations in exon 12 of the thrombopoietin receptor, *MPL*) [50,55–58]. Patients with MPNs have an

Table 1
JAK family combinations and single enzyme receptor specificities.

JAK family enzyme	JAK family combination partner	
	JAK1	JAK2
JAK1	IL-10R, IL-6R, IL-11R, OSMR, LIFR, CNTFR, IL-22R	IFNγ, G-CSFR
JAK2	IFNγ, G-CSFR	EPOR, TPOR, IL-3R, IL-5R, leptin receptor, GMCSFR, prolactin receptor, GHR
JAK3	IL-2R, IL-4R, IL-7R, IL-9R, IL-15R, IL-21R	
TYK2	IFNα/β	IL-12R, IL-23R

CNTFR, ciliary neurotrophic factor receptor; EPOR, erythropoietin receptor; G-CSFR, granulocyte colony-stimulating factor receptor; GHR, growth hormone receptor; GMCSFR, granulocyte–macrophage colony-stimulating factor receptor; IFN, interferon; IL, interleukin; JAK, Janus kinase; LIFR, leukemia inhibitory factor receptor; OSMR, oncostatin M receptor; TPOR, thrombopoietin receptor; TYK2, tyrosine kinase 2.

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