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Review

Interleukin-1β as emerging therapeutic target in hematological malignancies and potentially in their complications

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ABSTRACT

Interleukin-1β (IL-1β) is a pleiotropic cytokine that exerts multiple roles in both physiological and pathological conditions. It is produced by different cell subsets, and drives a wide range of inflammatory responses in numerous target cells. Enhanced IL-1β signaling is a common event in patients of hematological malignancies. Recent body of evidence obtained in preclinical models shows the pathogenic role of these alterations, and the promising therapeutic value of IL-1 targeting. In this review, we further highlight a potential contribution of IL-1β linking to complications and autoimmune disease that should be investigated in future studies. Hence, drugs that target IL-1 may be helpful to improve outcome or reduce morbidity in patients. Some of them are FDA-approved, and used efficiently against autoimmune diseases, like IL-1 receptor antagonist. In the clinic, however, this agent seems to have limited properties. Current improved drugs will allow to determine the true potential of IL-1 and IL-1β targeting as therapy in hematological malignancies and their related complications.

1. Introduction

Inflammation is a refined immune mechanism essential to fight against pathogens and tumor cells, and orchestrated by a variety of cells and mediators. When dysregulated, compiled data supports the hypothesis that chronic inflammation promotes cancer. This is particularly evident in hematological malignancies. Strikingly, a Swedish epidemiological study found that history of any infectious disease was associated with a 1.3-fold significantly increased risk of both acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), even when infection had occurred 3 or more years before AML or MDS onset. By using population-based central registries, a total of 9219 patients with primary AML (diagnosed from January 1, 1965, through December 31, 2004) and 1662 patients with primary MDS (diagnosed from January 1, 1993, through December 31, 2004), as well as 36,389 and 6489 population-based controls, respectively, were included. Further, to minimise bias, patients diagnosed with another cancer before their AML or MDS were excluded. Men represented 52.8% of the patients with AML and 54.9% of MDS patients, and the median ages at diagnoses were 68 and 76 years for AML and MDS, respectively. Interestingly, although history of any infectious disease was associated to similar increased risk of both AML and MDS, fewer individual subgroups of infections were associated to MDS. A broad range of infections were associated to AML including pneumonia, tuberculosis, intestinal infections, septicemia, hepatitis C, pyelonephritis, sinusitis, nasopharyngitis, upper respiratory tract infection, cytomegalovirus infection, and cellulitis [1]. One plausible explanation of these data is that chronic immune stimulation may act as trigger for AML and MDS development.

Chronic inflammation and autoimmune conditions have been consistently linked with increased risk of malignant lymphomas, with varying risk levels [2]. More recently, in patients of myeloproliferative neoplasms (MPN), chronic inflammation has been evidenced as potential initiating event and driver of clonal expansion that predisposes to second cancer [3–5]. Interestingly, another Swedish large population-based study found that patients with prior history of autoimmune disease had 20% increased risk of MPN development. In total, 11,039 MPN patients (diagnosed from 1958 to 2005) were included together with 43,550 matched controls. Men represented 48.4% of MPN patients, and the mean age at diagnosis was 67 years. A total of 288 (2.6%) MPN patients had a previous history of autoimmune disease. Higher risk of MPN was associated with prior thrombocytopenic purpura, Crohn's disease, polymyalgia rheumatic, giant cell arteritis, Reiter's syndrome and aplastic anemia [6]. High basal inflammatory status seems to promote mutagenesis through induction of chronic

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Table 1
IL-1 family member nomenclatures and main activity.

Family member	Alternative name	Function
IL-1α	IL-1F1	Inflammatory
IL-1β	IL-1F2	Inflammatory
IL-1Ra	IL-1F3	Anti-inflammatory (Receptor antagonist)
IL-18	IL-1F4	Inflammatory
IL-33	IL-1F11	Inflammatory
IL-36α	IL-1F6	Inflammatory
IL-36β	IL-1F7	Inflammatory
IL-36γ	IL-1F8	Inflammatory
IL-36Ra	IL-1F5	Anti-inflammatory (Receptor antagonist)
IL-37	IL-1F7	Anti-inflammatory
IL-38	IL-1F10	Anti-inflammatory (Receptor antagonist)

oxidative stress and subsequent DNA oxidative damage, and elicits epigenetic changes that further promote inflammation [3]. In addition, the MPN population has a significant inflammation-mediated comorbidity burden, ranging from second cancer to cardiovascular and thromboembolic disease, chronic kidney disease, autoimmune disease and osteopenia [7].

One of the cytokine families most related to innate immune responses and inflammation is the IL-1 family. It comprises 11 members (Table 1) with agonist activity, receptor antagonists and an anti-inflammatory cytokine, for a tight control of inflammatory responses [8]. IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra) and IL-18 have been extensively studied *in vitro*, animal models of disease and humans [9]. Among these, IL-1β stands out as initiator of inflammatory processes, and blocking its activity in humans is currently applied in clinical treatments. This review presents the pathogenic role of dysregulated IL-1β in patients of hematological malignancies, its promising therapeutic value in preclinical models, and its potential contribution linking to second disease and complications based on lessons learned from other systemic inflammatory diseases.

2. Physiological characteristics of IL-1β and role in the hematopoietic system

IL-1β is mainly produced by myeloid cells [10,11]. It is synthesized as an inactive form (Fig. 1A), pro-IL-1β that is activated intracellularly by caspase 1 [8,11]. Under normal conditions, IL-1β is secreted in low levels, and its expression and/or caspase 1-mediated activation increases under disease [12,13]. In autoinflammatory diseases, high IL-1β tissue levels are usually accompanied by an increase in blood levels given that monocytes release more processed IL-1β [9,14–17]. Secreted IL-1β binds to its IL-1 receptor 1 (IL-1R1) and triggers a signaling cascade that controls gene expression of multiple transcription factors, growth factors and other interleukins involved in hematological function (Fig. 1B) [10]. Thereby, IL-1β plays an important role in innate and adaptive immune cellular responses. It stimulates maturation of T cells and enhances proliferation of B cells [18–20]. Further, IL-1β promotes expression of inflammatory molecules such as cyclooxygenase type 2, type 2 phospholipase A, prostaglandin E2, platelet activating factor and nitric oxide [9], among others.

Importantly, IL-1β modulates hematopoietic stem cell (HSC) function. In preclinical models, it promotes HSC differentiation biased into the myeloid linage, in part through activation of PU-1 signaling (Fig. 2A) [21]. While acute IL-1β exposure contributes to HSC regeneration after myeloablation and transplantation [21,22], chronic exposure promotes uncontrolled HSC division and eventual exhaustion of the HSC pool [21]. Several studies have shown neutrophilia, leukocytosis and thrombocytosis following IL-1β treatment [12,23]. In contrast, inhibition of IL-1β signaling using IL-1Ra, which competitively binds to IL-1R1 and prevents binding of the cytokine (Fig. 1B) [24], reduces colony formation *ex vivo* [25,26]. *In vivo*, IL-1Ra suppresses cell cycle in bone marrow HSC, and reduces numbers of leukocytes and platelets [26]. Thus, preclinical models show that fine-tuned IL-1β levels play a physiological role in hematopoiesis, and suggest that their dysregulation may participate in hematological diseases [10,21,27].

3. IL-1β in clinical and preclinical models of hematological malignancies: emerging therapeutic implications

3.1. MPN

MPN are a group of clonal HSC disorders characterized by increased proliferation of at least one of the following lineages; eythroid, megakaryocytic and myeloid, and retaining full differentiation [28]. Underlying chronic inflammation has been suggested to contribute to disease initiation and/or progression [3]. Classical Philadelphia chromosome negative (negative for *BCR-ABL* gene fusion) MPN includes mainly essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF) (Table 2 [29]). Most frequent *BCR-ABL* negative MPN are associated with Janus kinase 2 (*JAK2*), calreticulin and myeloproliferative leukemia virus oncogene (*MPL*) mutations, among others [28,30].

MPN patients show increased levels of inflammatory cytokines in serum [31,32], and gene expression profiling and functional annotation analysis confirms deregulation of inflammatory and immune system genes [33]. Pro-inflammatory cytokines have traditionally been related to initiation and progression of bone marrow myelofibrosis at advanced stages of disease [34]. Unlike PV or ET patients [35–37], PMF patients show high levels of IL-1β together with other pro-inflammatory cytokines and growth factors in plasma [35,37]. If high IL-1β levels are present in PV patients, those are correlated to fibrotic transformation, poor prognosis and lower survival [37].

Mastocytosis is a less common form of myeloid neoplasm characterized by mast cell expansion in bone marrow and other organs [27]. It has been separated from other MPNs in the 2016 revision to the WHO classification of myeloid neoplasms and acute leukemia due to its unique clinical and pathological characteristics, ranging from indolent cutaneous disease to aggressive systemic disease (Table 2 [29]). Aggressive phenotypes of mastocytosis are related to up-regulation of IL-1β in mast cells [38].

Our recent work has shed light on the pathogenic role of IL-1β in preclinical models of MPN. Using a transgenic mouse model that expresses the human mutant JAK2-V617F under the endogenous promoter of *Jak2* in an inducible way, we showed that IL-1β produced at early stages of disease, at least in part by mutant HSCs, induces damage of the neuroglial components in the bone marrow. Reduced sympathetic regulation together with IL-1β stimulation results in mesenchymal stem cell (MSC) apoptosis that then allows expansion of mutant HSCs (Fig. 2B) [39]. The pathogenic role of IL-1β was uncovered by administration of IL-1Ra, which ameliorates hallmarks of disease, recovers MSC numbers *in vivo* and prevents apoptosis of glial cells *ex vivo* (Table 3) [39]. These data suggest that targeting IL-1β may have clinical implications to improve treatment of MPN patients.

3.2. Chronic myeloid leukemia (CML)

BCR-ABL or Philadelphia positive CML is classified as an MPN disorder, but it is usually considered as a separate entity because of its unique features and responses to treatment (Table 2 [29]) [28]. CML is a biphasic disease characterized by excessive expansion of the granulocytic lineage during the initial chronic phase. Acquisition of additional genetic and/or epigenetic abnormalities causes the progression to blast phase, which characterizes by a block of cell differentiation that results in presence of 30% or more myeloid or lymphoid blast cells in peripheral blood or bone marrow, or presence of extramedullary infiltrates of blast cells [40].

High levels of IL-1β are associated with poor prognosis in CML