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Review

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

Lorena Arranz[a,b,c,*], Maria del Mar Arriero[a], Alicia Villatoro[a]

[a] Stem Cell Aging and Cancer Research Group, Department of Medical Biology, Faculty of Health Sciences, UiT – The Arctic University of Norway, Norway
[b] Department of Hematology, University Hospital of North Norway, Norway
[c] Young Associate Investigator, Norwegian Center for Molecular Medicine (NCMM), Norway

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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

* Corresponding author at: Stem Cell Aging and Cancer Research Group, Department of Medical Biology, Faculty of Health Sciences, UiT – The Arctic University of Norway, MH building level 6, 9019 Tromsø, Norway.
E-mail address: lorena.arranz@uit.no (L. Arranz).

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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

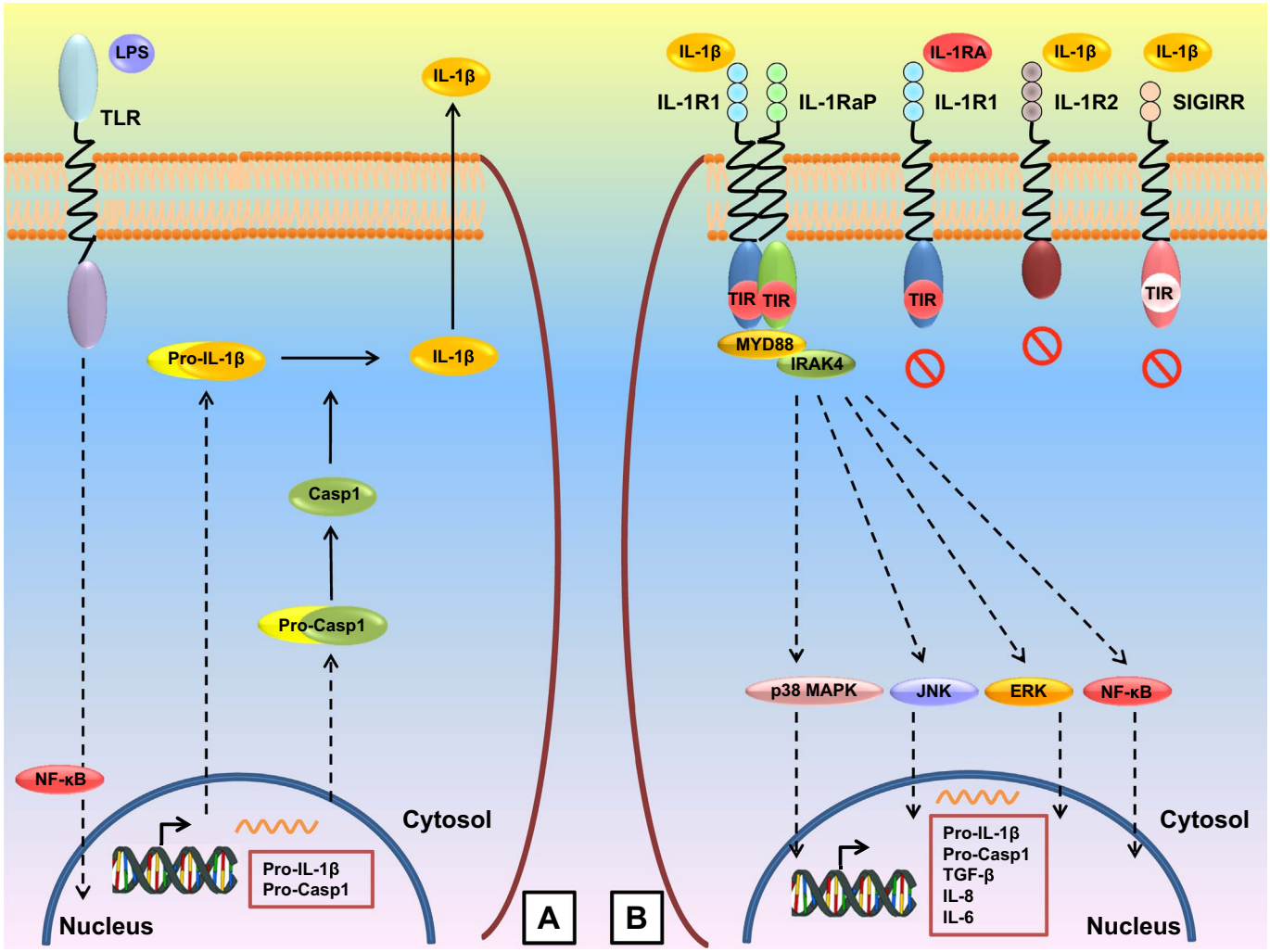

Fig. 1. Interleukin-1β initiates inflammation and controls essential cell responses. A) Several external inflammatory stimuli that signal through TLR, activate a cascade of events that culminate in activation of the transcription factor NF-κB. Following NF-κB activation, IL-1β is synthesized as its inactive form, pro-IL-1β, which is activated by cleavage through caspase 1. Pro-caspase 1 is synthesized and activated in response to similar stimuli. B) Secreted IL-1β binds to its IL-1R1 and triggers a signaling cascade, which involves p38 MAPK, JNK, ERK and NF-κB activation that control gene expression of multiple transcription factors, growth factors and interleukins involved in cell functional activation, survival responses and cell fate. Under normal conditions, IL-1β signaling is negatively regulated through IL-1Ra, IL-1R2 and SIGIRR. LPS, lipopolysaccharide; TLR, toll-like receptors; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; Casp1, caspase 1; IL-1Ra, IL-1 receptor antagonist; IL-1R, IL-1 receptor; IL-1RAP, IL-1 receptor accessory protein; TIR, toll-IL-1 receptor; SIGIRR; single immunoglobulin and TIR domain containing; MYD88, myeloid differentiation primary response 88; IRAK4, IL-1 receptor associated kinase 4; MAPK, mitogen-activated protein kinases; JNK, c-Jun N-terminal kinases; ERK, extracellular signal-regulated kinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TGF-β, transforming growth factor β.

[41,42]. Increased IL-1β is seen in advanced blast phase as compared to chronic phase and healthy controls, and correlates with blast expansion in bone marrow and peripheral blood, poor prognosis and shorter survival in patients [41,43]. IL-1β stimulates proliferation of mutant long-term HSC *ex vivo*, at concentrations comparable to those observed in CML bone marrow [44], and helps promote colony growth of mutant hematopoietic progenitors [45]. Use of IL-1Ra or soluble IL-1 receptor suppressed this effect, suggesting that IL-1β could confer a proliferative advantage to leukemic stem cells (LSC) [45]. Interestingly, IL-1 receptor accessory protein (IL-1RAP) that is a required component of the IL-1R complex (Fig. 1B), is highly expressed in *BCR-ABL*+ CML cells [46]. In particular, IL-1RAP is up-regulated in CD34+ and CD34+ CD38- cells from CML patients compared to controls, and its expression increases with disease progression [47]. Further, anti-IL1RAP antibody targets CML CD34+ CD38- cells *via* antibody-dependent cell-mediated cytotoxicity [46]. Hence, alterations in several components of the pathway leading to strengthened IL-1 signaling may contribute to disease.

CML patients may display relapses through mechanisms dependent on *BCR-ABL* [48,49] or through additional mutations, like those in genes promoting HSC survival or multidrug resistance [50–52]. Importantly, IL-1β contributes to resistance to BCR-ABL tyrosine kinase inhibitor imatinib in CML cells, where it increases cell survival and decreases apoptosis rate through cyclooxygenase 2 [53]. Interferon (IFN) family members, alternative treatment against CML, have anti-inflammatory effects and inhibit IL-1β [54–57]. Higher levels of IL-1β were seen in IFN-α-resistant CML patients as compared to sensitive patients and healthy controls, and IL-1β stimulates colony growth in IFN-α-sensitive CML cells [45].

In mouse models of disease, IL-1Ra in combination with nilotinib, drug with greater power and selectivity for BCR-ABL than imatinib [58,59], reduces numbers of leukemic cells in blood and bone marrow, and the self-renewal potential of leukemic stem cells (LSC). This correlates with extended survival after completion of treatment compared to mice treated with nilotinib alone (Table 3) [60]. *In vitro*, this combination significantly reduced human CML progenitor cell growth, including CD34+ CD38+ and CD34+ CD38- cells [61]. Then, blockade of IL-1 signaling together with BCR-ABL tyrosine kinase inhibition may pave the way to more efficient therapies against CML in patients.

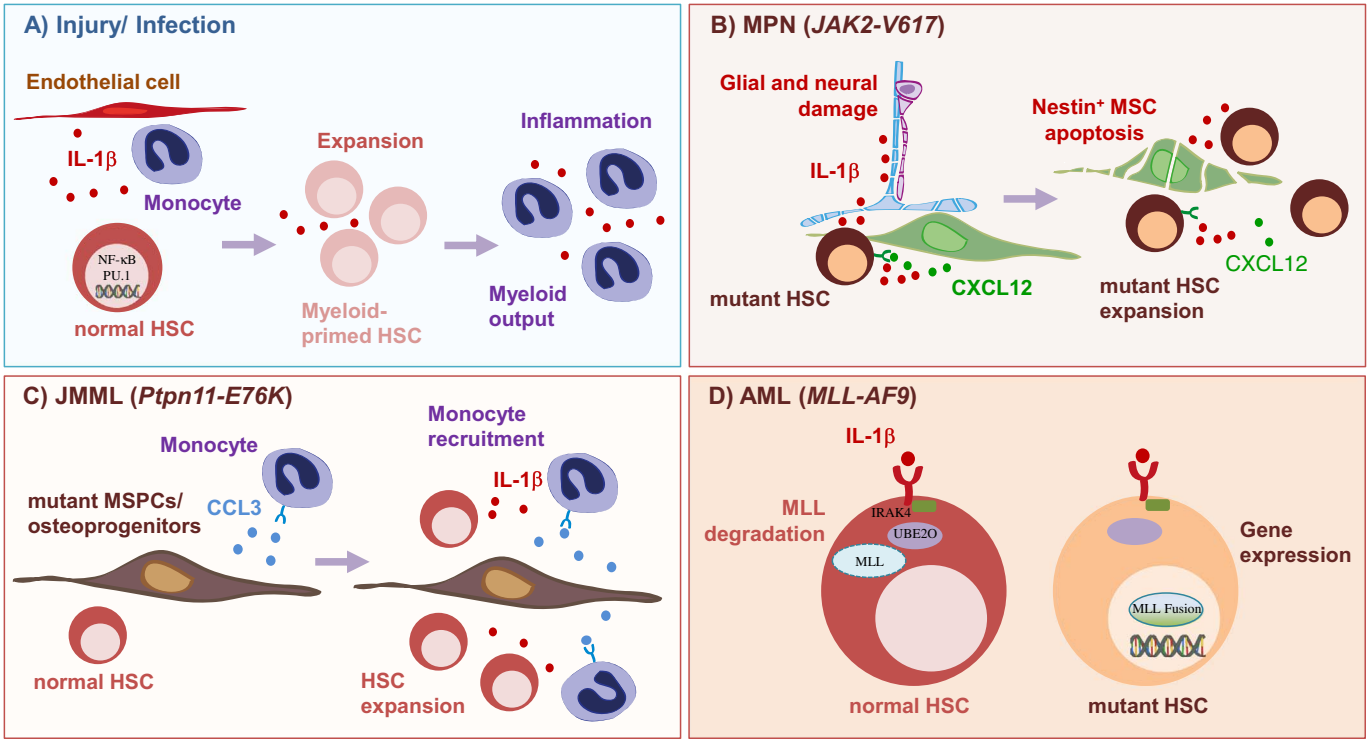

Fig. 2. Pathological mechanisms of IL-1β on hematopoietic stem cell function identified in mouse models. A) Upon injury or infection, IL-1 is produced at high levels in the bone marrow by monocytes and endothelial cells, among others. IL-1 drives myeloid differentiation through activation of the NF-κB pathway and a PU.1-dependent myeloid gene program that results in HSC expansion, biased differentiation into myeloid progenitors and ultimately myeloid cells [21]. B) In a mouse model of MPN that expresses the human mutant JAK2-V617F, IL-1β is produced at early stages of disease by mutant HSCs, and induces damage of the neuroglial components in the bone marrow. Reduced neural regulation together with enhanced IL-1β results in mesenchymal stem cell apoptosis that then allows expansion of mutant HSCs [39]. C) In a mouse model of JMML that results from *Ptpn11* activating mutation in MSCs and progenitor cells, and in osteoprogenitors, increased levels of CCL3 recruits monocytes to the bone marrow. These produce IL-1β that promotes HSC expansion [65]. D) In normal HSCs, IL-1β signaling through IL-1R1 drives UBE2O phosphorylation mediated by IRAK4. This increases UBE2O interaction with MLL and its degradation. In contrast, in a mouse model of AML that results from expression of MLL-AF9 fusion protein, MLL chimeras are resistant to degradation driven by IL-1β [86]. IL-1β, interleukin-1β; HSC, hematopoietic stem cell; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PU.1, purine-rich nucleic acid binding protein 1; MPN, myeloproliferative neoplasm; JAK2, Janus kinase 2; MSC, mesenchymal stem cell; CXCL12, C-X-C motif chemokine ligand 12; JMML, juvenile myelomonocytic leukemia; Ptpn11, tyrosine-protein phosphatase non-receptor type 11; MSPCs, mesenchymal stem and progenitor cells; CCL3, C-C motif chemokine ligand 3; AML, acute myeloid leukemia; MLL, mixed-lineage leukemia gene; IRAK4, interleukin-1 receptor associated kinase 4; UBE2O, ubiquitin conjugating enzyme E2 O.

3.3. Juvenile myelomonocytic leukemia (JMML)

JMML is a childhood MDS/MPN (Table 2 [29]) that may arise as consequence of germline activating mutations of the protein tyrosine phosphatase SHP2, encoded by the gene *PTPN11* [62,63]. Interestingly, both cell-autonomous [64] as well as *Ptpn11* activating mutations in the bone marrow microenvironment [65] promote development and progression of JMML. In mouse models of disease, *Ptpn11* activating mutations in MSCs and progenitor cells as well as in osteoprogenitors cause increased secretion of the chemokine (C-C motif) ligand 3 (CCL3) or macrophage inflammatory protein 1α (MIP-1α). CCL3 recruits monocytes to the bone marrow microenvironment where HSCs reside. Recruited monocytes produce IL-1β, and this in turn hyperactivates HSCs leading to JMML (Fig. 2C). Interestingly, treatment with CLL3 receptor antagonists reverses JMML originated by the mutated microenvironment (Table 3) [65]. However, it remains to be seen how broadly applicable this mechanism will be, given that no human cases were examined for presence of *PTPN11* activating mutations particularly in the bone marrow microenvironment. Further, from 4 patients examined positive for *PTPN11* activating mutations and with Noonan syndrome, which predisposes to JMML, MSCs and progenitor cells showed in culture varying levels of CLL3.

3.4. AML

AML is a heterogeneous disease characterized by aberrant myeloid lineage proliferation and differentiation, and at least one clonal somatic abnormality on mutational profiling in the majority of the patients (> 97%) [66] (Table 2 [29]). IL-1β is produced by human AML blasts, where its expression relates to poor patient prognosis [67,68]. Both endogenous and exogenous IL-1β promote blast proliferation, by induction of growth factors and other cytokines like granulocyte-macrophage colony stimulating factor [69–74]. Poorer patient prognosis and lower survival is observed in those patients with higher proliferative response to exogenous IL-1β [75]. Further, IL-1β direct inhibition or indirect inhibition targeting IL-1RAP, blocks colony formation and proliferation of AML cells [76,77]. Endogenous IL-1 has also been related to apoptosis resistance in human AML, and addition of recombinant human IL-1 in culture enhances cell survival through pathways like phosphoinositide-3 kinase and ceramidase [78]. In addition, IL-1β secreted by human AML blasts, stimulates expression of adhesion molecules that promote their recruitment by epithelial cells [79], effect that may be relevant for tissue infiltration and metastasis.

In spite of these studies, the role of IL-1β in human AML remains controversial. According to Su et al. [80], lower levels of IL-1β are present in the plasma of AML patients compared to healthy controls. Further, CD34+ CD38- progenitors, enriched within the LSC subset, down-regulate IL-1β expression through epigenetic mechanisms, compared with more mature CD34+ CD38+ AML progenitors and normal CD34+ cells [81]. Forced expression of IL-1β stimulates cell cycle and apoptosis in CD34+ CD38- AML progenitors, by down-regulation of cyclin-dependent kinase inhibitor 1 ($p21^{waf1}$) and antiapoptotic proteins respectively. Similarly, over-expression of IL-1β in CD34+ CD38- cells, reduces engraftment and reconstitution after transplantation into

Table 2
2016 World Health Organization classification of myeloid neoplasms and acute leukemia.

WHO classification of myeloid neoplasm and acute leukemia classification
Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood
Myeloid neoplasms with germ line predisposition
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv.(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv.(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2);*GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

immunodeficient mice [82]. Interestingly, in the same study, the authors showed that low dose IL-1β exposure stimulates colony formation in AML cells, while high doses promote the opposite effect [82]. This highlights the importance of balanced levels of IL-1β in AML, where future studies are required aiming at understanding the specific role played by IL-1β.

It is important to note that IL-1β may be produced by certain subsets of non-hematopoietic cells, like some stromal components of the hematopoietic stem cell niche that supports HSC function. In normal conditions, IL-1β at levels similar to those found in human serum, stimulates MSC proliferation *in vitro* and their capacity to maintain hematopoietic progenitor cells [83]. Bone marrow stromal cells from healthy controls co-cultured with different leukemia cell lines, show an up-regulation of IL-1β [84]. However, MSC from AML patients show lower expression of IL-1β at the time of diagnosis, previous to bone marrow transplantation and at least 6 months after the transplant, compared to healthy controls [85].

Recently, preclinical models of AML have pinpointed IL-1 as a potential therapeutic strategy. Using mixed-lineage leukemia (*MLL*)-rearranged leukemia models, Liang et al. showed that IL-1 negatively regulates the stability of wild-type but not chimeric MLL protein, resulting in improved stability of the latter (Fig. 2D) [86]. Strikingly, pharmacological inhibition of this signaling pathway using IL-1 receptor-associated kinase (IRAK) inhibitors (Fig. 1B), remarkably delays disease progression and improves survival in *MLL-AF9+* murine leukemia (Table 3) [86]. Future studies are required to extend these promising mouse studies to primary human samples.

3.5. Lymphoid malignancies

A role for IL-1β has been suggested in lymphoid malignancies. Chronic lymphocytic leukemia (CLL) is a malignancy of mature clonal B lymphocytes that accumulate in the blood, bone marrow and other lymphoid tissues [87]. The specific single nucleotide polymorphism *IL1B-511*T, when presented in homozygosis, correlates with low risk of CLL. Interestingly, a different single nucleotide polymorphism in *IL1B* gene (*IL1B-511*C) together with *IL6-174*C, both in homozygosis, increase to 11-fold the risk of CLL, compared to 4.5 fold increase with *IL6-174*C alone [88]. This points to an association between IL-1β and IL-6 in CLL development. Low levels of IL-1β and high levels of IL-6 are found in the plasma of patients [88,89]. However, previous work showed that IL-1β induces differentiation and activation of leukemic cells in CLL patients [90]. Besides, MSCs from acute lymphocytic leukemia (ALL) patients show increased IL-1β expression at diagnosis [85]. Thus, future work should elucidate the potential participation of IL-1β in lymphoid malignancies.

Table 3
Summary of treatments targeting IL-1 pathway efficient in mouse models of hematological malignancies.

Hematological malignancy	Preclinical model	Drug	Mechanism	Reference
MPN	*JAK2-V617F*	IL-1Ra	IL-1Ra is a competitive inhibitor of α and IL-1β signaling that binds to IL-1R1	[39]
CML	*BCR-ABL*	IL-1Ra and Imatinib	impeding its interaction with the cytokines	[60]
JMML	*Ptpn11-E76K* in MSPCs	CCR1a or CCR5a	Antagonists that block CCL3 binding to CCR1 or CCR5, respectively	[65]
AML	*MLL-AF*9	IRAK1/4 or IRAK4 inhibitors	Inhibition of IL-1R-associated kinases that impedes signaling downstream IL-1R1	[86]

4. Additional roles for IL-1β in pathophysiology: lessons from systemic inflammatory diseases

4.1. Bone

IL-1 is a pleiotropic cytokine that exerts numerous roles in other systems like bone, where it contributes to the fine-tuned balance between bone resorption and formation that maintains its homeostasis. In particular, IL-1 enhances the expression of extracellular matrix enzymes, like collagenases that facilitate destruction of articular cartilage [91,92]. Further, IL-1 induces differentiation of bone-resorbing osteoclasts from mononuclear precursors, and has stimulating effects on osteoclasts and resorption *via* TNF ligand superfamily member 11 (RANKL) [93]. It also induces vasodilatation, promotes attraction of granulocytes, and enhances expression of prostaglandins, events that further help bone resorption [94].

The typical manifestation of accelerated bone remodeling is osteoporosis. Osteoporosis characterizes by bone thinning, damage in its architecture and reduced mechanical strength due to diminished mineral density. This is accompanied by high fracture risk [95]. It is most frequent in postmenopausal women, so loss of bone mineral density was traditionally attributed to estrogen loss [96]. More recently, estrogens were suggested to have only minor effects [95], and inflammatory cytokines like IL-1 were pointed out [96]. In women who had undergone surgical menopause, increase in IL-1 secretion by peripheral blood mononuclear cells associates with significant loss in bone mineral density [97]. Administration of IL-1Ra improves bone mineral density in ovariectomized rats, uncovering the therapeutic value of targeting IL-1 against bone loss [98].

Osteoporosis and fractures are frequent in patients of systemic inflammatory diseases, like rheumatoid arthritis [96], disease that primarily affects synovial joints. In rheumatoid arthritis, high levels of pro-inflammatory cytokines promote osteoclast differentiation and bone degradation, resulting in osteoporosis [99]. High levels of IL-1 were found in the synovial membrane and fluid of patients [100,101], while experimental models showed a major role for IL-1 in cartilage and bone degradation [92,102,103]. This disease was the first where IL-1 antagonism was tested and proved for clinical use. Use of IL-1 inhibitors was supported by severe arthritis development in IL-1Ra deficient mice [104].

In osteoarthritis, IL-1 promotes cartilage degradation [105]. While IL-1Ra prevents cartilage degeneration in animal models and improves clinical outcomes in patients [106,107], intra-articular gene transfer of IL-1Ra showed improved results in experimental models [108]. Recently, a method was developed to produce an autologous conditioned serum rich in IL-1Ra that seems to be an option as supplementary therapy in patients [108,109].

4.2. Pain

IL-1 induces hyperalgesia that is increased sensitivity to pain, through damage to nociceptors or peripheral nerves. Hyperalgesia may affect primary afferent fibers for mechanical stimuli, resulting in a highly disabling symptom [110]. IL-1 activates nociceptors directly causing activation of intracellular signaling cascades, and indirectly *via* production of kinins and prostanoids [111].

In certain chronic inflammatory diseases, like osteoarthritis, pain is one of the most prominent symptoms. Studies have related IL-1 levels with pain perception and radiographic knee lesions in patients [112]. Inflammatory stimuli, and in particular IL-1, start the cascade of events that cause disease and drive pain in parallel [113,114]. Treatments that reduce cartilage degeneration, reduce pain as well [106,107].

5. Clinical complications derived from hematological malignancies

5.1. Bone morbidity

Increased inflammatory cytokines in MPN patients relate to myelofibrosis at advanced stages of disease [34]. Fibrosis typically derives in osteosclerotic lesions, particularly in PMF. PMF is a severe form of MPN characterized by hematopoietic failure and osteosclerosis, which originates as result of growth and thickening of bone trabeculae, and new bone formation in abnormal budding plaques [115]. PMF patients show high levels of IL-1β in plasma [35,37], and high IL-1β levels in PV patients predispose to fibrotic transformation [37]. Histomorphometric measurements in 75 PMF patients showed elevated bone mineral density compared to other forms of MPN, and correlation between amount of bone and degree of fibrosis [116]. Surprisingly, a more recent study using non-invasive methods in 18 patients with MF and healthy controls matched for age, sex, and height, showed that bone mineral density, geometry and microarchitecture in MF patients were not significantly different [117]. Several reasons may underlie differences in results, including sample size or disease stage. Hence, future work will be required for a better understanding of the bone disease and a potential link to IL-1β in PMF patients.

In MPN and CML patients, epidemiological studies have concluded increased risk of osteoporosis. For instance, a Danish study reported increased risk of fractures among MPN patients [118]. This study compared fracture risk among 7595 MPN patients and a cohort of 338,974 members of the general population. The fracture rates were consistently higher at several anatomic locations including femur, humerus, and distal forearm. The 10-year hip fracture risk was 7% in ET patients and 9% in PV patients, with a risk of 5% among matched controls. Interestingly, the same study showed risk of hip fracture 2.7-fold higher in CML patients than in the general population [118]. CML patients were stratified according to presence or absence of tyrosine kinase inhibitor treatment. Treatment turns CML into a more chronic condition with longer life expectancy, and reduces the need for allogeneic bone marrow transplantation [119]. However, it does not influence the fracture risk in CML patients [118]. In another study performed on 36 CML patients, skeletal lesions were examined by x-ray. Lesions were positive in 16% of the cases, and included osteoporosis, osteolytic and osteoblastic lesions, and chloromas, *i.e.* myeloid sarcomas outside of the bone marrow [120]. Further, osteoporosis and vertebral fracture are frequent in patients with systemic mastocytosis with respectively 31 and 17% in a cohort of 75 patients [121]. Nevertheless, the direct contribution of chronic inflammation and IL-1 to bone loss specifically in myeloid leukemias remains unknown, and should be subject of future investigation (Table 4).

Table 4
Summary of clinical data in hematological malignancies where both increased IL-1β and bone morbidity are present in patients.

Hematological malignancy	Increased IL-1β	Bone morbidity
PMF	[35,37]	[37,115,116]
PV	[37]	[118]
Mastocytosis	[38]	[121]
CML	[41–43,46,47]	[118,120]
ALL	[85]	[122–124]

Bone morbidity seems to be present in other types of hematological malignancies like ALL (Table 4). ALL is the most common leukemia in childhood, and induces significant effects on the skeleton of children and adolescents that show, at the moment of diagnosis, lower bone density than their healthy counterparts [122]. Low bone turnover status explains through reduced bone formation but normal resorption markers [123]. Further, ALL patients have increased fracture rate compared to healthy controls [124], and fracture risk is higher in ALL survivors after the end of the treatment [125,126]. However, little is known about the molecular mechanisms driving bone complications in ALL patients.

5.2. Hematopoietic malignancies and pain

Interestingly, the most important hematopoietic disease-related pain affects bone, and it was traditionally related to osteolytic lesions and infiltration of bone marrow with malignant cells. In the context of hematopoietic disorders, pain may be correlated to disease and its complications, or to diagnostic procedures and treatments [127]. When pain is present at disease onset, treatment with chemotherapeutic agents or other therapies usually drive pain relief. This is frequent in ALL patients [128].

Our recent work may provide hints linking pathogenesis and pain in hematopoietic malignancies. Particularly in experimental models of MPN, we showed that mutant cells produce IL-1β that damages the neuroglial components in the bone marrow at early stages of the disorder. Schwann cells, that cover and protect the integrity of the peripheral neural fiber, are rapidly reduced in the disease bone marrow. Sympathetic fibers are subsequently injured, in both disease mice and humans, which may contribute to bone pain reported in MPN patients [129]. Reduction in sympathetic regulation together with IL-1β stimulation results eventually in expansion of mutant cells, that is ameliorated by treatment with IL-1Ra *in vivo* [39]. Hence, IL-1 may be pathogenic factor and pain driver in MPN, and represents a good candidate for clinical interventions.

Additionally, both ALL and AML survivors may experience chronic pain due to complications associated to hematopoietic cell transplantation [130]. Pain origin after transplantation seems to relate to injury to mucosal tissues induced by the conditioning regimen, like chemotherapy [131]. In mouse models and clinical settings, cisplatin, that is a common chemotherapy, induces sensory neuropathy [132,133]. Further, experimental models demonstrated cisplatin-induced bone marrow nerve injury that impairs hematopoietic regeneration and could thereby compromise success of the transplant [132]. To date, the molecular mechanisms driving neural damage after chemotherapy have not been thoroughly defined.

6. Hematopoietic malignancies and autoimmune diseases

The connection between autoimmune diseases and hematopoietic malignancies goes beyond common bone affectation and pain. Actually, a number of epidemiological studies show higher risk of hematopoietic malignancies in patients with autoimmune diseases compared to the general population, with further increase after cytotoxic treatment [134]. Interestingly, autoimmune disease patients with secondary acute leukemia usually develop AML rather than ALL [135]. History of any autoimmune disease has been associated with increased risk of AML and MDS [1,136]. In particular, AML risk is significantly associated with rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, autoimmune hemolytic anemia, systemic vasculitis, pernicious anemia, and inflammatory bowel disease like ulcerative colitis and Crohn's disease [134,136,137]. Additionally, systemic mastocytosis is related to higher prevalence of inflammatory joint diseases like spondyloarthritis and rheumatoid arthritis [138,139]. Interestingly, the clinical appearance of non-Hodgkin's lymphoma and systemic lupus erythematosus is similar, making them difficult to distinguish at early stages. This raises the possibility that systemic lupus erythematosus may be a paraneoplastic syndrome and appears on the grounds of the hematopoietic malignancy [140]. Conversely, a hematopoietic disorder may precede the autoimmune disease, and for instance early manifestation of an occult malignancy may be fast development of rheumatoid arthritis-like syndromes [141].

Additionally, increased risk of AML is associated to an autoimmune disease of the central nervous system: multiple sclerosis. Multiple sclerosis develops as consequence of autoimmune demyelination of the central nervous system leading to progressive disability. Immunomodulatory drugs like IFN-β are used as first-line therapy, and non-responsive patients are treated with strong immunosuppressive and cytotoxic drugs like mitoxantrone [142]. Multiple sclerosis patients treated with mitoxantrone are at particularly high risk of developing AML. However, not all patients exposed to this drug develop AML, whereas others do without mitoxantrone treatment [143,144].

The factors predisposing to AML in autoimmune diseases are currently subject of extensive research. Defective immune system and, as previously mentioned, immunosuppressive therapies seem to be risk factors that allow tumor progression [145,146]. Mutations in certain genes are shared by both autoimmune diseases and cancer, including the tumor suppressor *p53*, the death receptor *Fas*, and the signaling pathway phosphatidylinositol 3-kinase/protein kinase B/mammalian Target Of Rapamycin, among others [147–151]. Further, inflammation is a common event within both pathogenic processes. Inflammation enhances tumor progression through complex inflammatory signaling cascades that involve NF-κB activation, related to both leukemia and autoimmune diseases like rheumatoid arthritis [152–154]. Importantly, it is well-described that activated NF-κB induces transcription of proIL-1β.

As discussed in the previous sections, IL-1 and specifically IL-1β plays a pathogenic role in a variety of hematopoietic malignancies, particularly those involving the myeloid lineage. This statement holds true for a wide range of systemic inflammatory and autoimmune diseases [155]. In both hematopoietic malignancies and autoimmune diseases, there is a link to bone and pain complications. Hence, it is reasonable to hypothesize that IL-1 may underlie morbidity and may as well provide a link between hematopoietic malignancies and autoimmune diseases. Future work is required to validate this hypothesis. If IL-1 participates in pathogenesis, complications and second disease in both hematopoietic malignancies and autoimmune diseases, fine-tuned management of IL-1 levels would have utility in numerous disorders and substantially improve quality of life in patients.

7. FDA-approved therapeutic strategies for IL-1 blockade

Extensive clinical research is being performed with a variety of agents that reduce IL-1 activity. Currently, these drugs include IL-1Ra, soluble receptors, antibodies, and IL-1 traps among others. Some of these drugs are being actively pursued at Phases I to III in clinical trials to treat a broad spectrum of diseases [155–158]. In spite of their therapeutic potential, so far few studies have evaluated their effects against different types of cancer and hematological malignancies. One example of the latter is MABp1, naturally occurring monoclonal antibody that neutralizes IL-1α. In 2012, a Phase I clinical study was

completed with patients of advanced hematological malignancies (NCT01260545), but its results are not published yet. One prevailing presumption for this little interest is that IL-1 blockade may be contraindicated for patients as it may further promote cancer-related immunosuppression [158]. However, this theory may be misinterpreted [159], given that IL-1 neutralization reduces the inflammation that contributes to cancer-related immunosuppression [160]. Future studies are required to further clarify this perspective. As of today, the following therapeutic opportunities targeting IL-1 are FDA-approved: anakinra, rilanocept and canakinumab.

7.1. Anakinra (Kineret)

Anakinra is the recombinant form of the naturally occurring IL-1Ra, it exerts its function blocking the IL-1 receptor and thus reduces the activity of both IL-1α and IL-1β. Anakinra was FDA-approved in 2001 to treat rheumatoid arthritis, and since then it has been proved as an efficient and safe therapy in a variety of diseases [156]. It is currently being tested in numerous clinical trials. A Phase II study in patients with smoldering or indolent multiple myeloma (NCT00635154), who were at risk of progression to active myeloma, tested the ability of anakinra to delay or prevent active myeloma. Between November 19, 2002, and May 24, 2007, 47 patients were enrolled in the study and treated with anakinra [161]. In 25 (53%) of the patients, low-dose dexamethasone was administered in addition. Treatment with anakinra alone lead to a minor response in 3 patients, a partial response in 5 patients and a minor response after addition of dexamethasone in 4 patients. In those who responded, anakinra decreased high-sensitivity C-reactive protein (hs-CRP) levels and myeloma proliferative rate, which correlated with prolonged chronic disease state and improved progression-free survival [161]. A Phase I/II clinical study (NCT02492750) is currently recruiting participants for treatment of early stage multiple myeloma patients with lenalidomide and dexamethasone with or without anakinra.

Intravenous administration is preferred considering its safety even at blood levels 100-fold higher than those achieved following subcutaneous injection [156]. In addition, one important limitation of anakinra is its relatively short half-life of 4 to 6 h [155], leading to drop in blood levels within hours after injection [156]. Evidence from preclinical models of disease indicates that the therapeutic effectiveness of IL-1Ra is crucially dependent on optimal level of dosing for continuous saturation of IL-1 receptors [162]. Hence, anakinra may not allow adequate evaluation of the efficiency of anti-IL-1 treatments, given that partial reactivation of inflammation may occur during 24-hour dosage.

7.2. Rilanocept (Arcalyst)

Rilonacept, also known as IL-1 trap, is a soluble decoy receptor comprising the human IL-1 receptor 1 (extracellular domain and accessory protein) and the Fc portion of human IgG1 [163]. This recombinant fusion protein neutralizes both free IL-α and IL-β with high affinity [155]. Rilonacept was approved by FDA in 2008 for the treatment of cryopyrin-associated periodic syndromes, a group of diseases caused by inherited mutations on the genes *CIAS*1 or *NLRP*3, encoding cryopyrin or NALP3, respectively, which result in spontaneous assembly of the inflammasome with caspase 1 over-activation and IL-1β secretion [164]. A number of clinical trials are currently being developed to use rilanocept against a variety of diseases, including type 1 diabetes (NCT00962026), atherosclerosis (NCT00417417), hepatitis (NCT01903798) and chronic kidney disease (NCT01663103). However, none of these studies involve patients of hematological malignancies.

In addition to its high affinity binding IL-α and IL-β, rilonacept has been proved as a safe and well-tolerated therapy [155,165,166]. When compared to anakinra, rilonacept shows an extended circulation half-life *in vivo* of 8.6 days, and thus it is administered in patients as a weekly subcutaneous injection [166]. Further, both *in vitro* and *in vivo* studies showed that IL-1 trap is more efficient than IL-1Ra [165,167]. In mice, IL-1 trap injected subcutaneously 24 h prior to IL-1β injection was able to fully block IL-1-induced inflammation. This single dose of IL-1 trap also blocked the effect of a second IL-1β injection, 24 h later. In contrast, IL-1Ra did not inhibit IL-1-induced inflammatory response at a dose 15-fold higher than that of IL-1 trap [167]. Thus, on-going and future clinical trials with IL-1 trap should help us determine accurately the promising therapeutic value of IL-1 blockade in multiple diseases including hematological malignancies.

7.3. Canakinumab (Ilaris)

The most recent approach is canakinumab, a monoclonal antibody that specifically neutralizes human IL-1β and was produced in a transgenic mouse strain. It binds to human IL-1β with high affinity and specificity, and the complex formed with the cytokine is unable to attach to the receptor, thereby blocking IL-1β dependent signaling [168,169]. Canakinumab was FDA-approved in 2009 for the treatment of cryopyrin-associated periodic syndromes [170]. Currently, numerous clinical trials are being performed, to treat a broad spectrum of diseases like osteoarthritis (NCT01160822), chronic obstructive pulmonary disease (NCT00581945), type 2 diabetes (NCT00605475), atherosclerosis (NCT00995930) and rheumatoid arthritis (NCT00504595, NCT00424346). So far, however, no clinical trial has been registered that considers patients of hematological malignancies.

Its high affinity and specificity have been proven both *in vitro* and *in vivo*. While it does not interfere with IL-1α signaling [170], canakinumab fully blocks IL-β-induced inflammation and cartilage destruction in mouse models of arthritis [168,171]. In patients, it can be administered intravenously or subcutaneously. The maximum blood concentration is found after 7 days of a single subcutaneous dose, and its half-life is 26 days [168,170,172]. This is a substantial advantage over anakinra and rilonacept, given that canakinumab is administered bimonthly, as opposed to the weekly or daily injections with rilonacept or anakinra, respectively [173]. It is well tolerated in patients, and no severe adverse effects have been reported. Its use is approved in children [170]. IL-1β neutralization will allow to see if IL-1β is indeed a crucial mediator of numerous diseases, and its targeting may serve as therapy or coadjuvant treatment in hematological malignancies and their related complications.

8. Summary and future directions

IL-1 is a pleiotropic cytokine that exerts numerous roles in both physiological and pathological conditions. It is produced by a variety of cells, and elicits a wide range of inflammatory responses in a number of cell subsets. Dysregulated IL-1 seems to be essential in many human diseases, including hematopoietic malignancies and autoimmune diseases, their complications, and may be their connection. Hence, drugs that target IL-1 may be helpful in numerous inflammatory conditions and have shown promising therapeutic value in experimental models of hematological malignancies. Currently, these drugs include IL-1Ra, soluble receptors, antibodies, and IL-1 traps among others. Some of these agents are FDA-approved, and used safely and efficiently as therapy against autoimmune diseases like rheumatoid arthritis.

In the clinical setting, however, IL-1Ra seems to be limited by its biological and pharmacokinetic properties [155]. Likely, this has prevented the full potential of IL-1 targeting to be tested in patients. IL-1 trap is more efficient and has extended half-life *in vivo* [165,166]. The drug rilonacept is a fusion protein comprising the human IL-1 receptor 1 (extracellular domain and accessory protein) and the Fc portion of human IgG1 [163]. Further, the monoclonal antibody canakinumab neutralizes IL-1β specifically, and has even more prolonged half-life [168,170,172]. These next generation of drugs with improved chemical, pharmacological and biological properties, should

allow us to determine accurately the promising therapeutic value of IL-1 and in particular IL-1β in multiple hematological malignancies and their related complications.

Practice points

- High IL-1β signaling is present in patients of hematological malignancies, in particular those with myeloid component.
- Recent preclinical studies demonstrate the pathogenic role of IL-1β in hematological malignancies.
- Targeting of IL-1β pathway shows great therapeutic potential in mouse models.
- IL-1β is responsible for bone degeneration and pain in systemic inflammatory diseases.
- IL-1β is a good candidate promoting morbidity in patients, by linking to bone complications, pain and second disease.

Research agenda

- Clinical trials with patients of hematological diseases, combining specific treatments with targeting of IL-1 pathway.
- Test rilanocept and canakinumab in mouse models of hematological malignancies.
- Further development of drugs with improved properties and test in preclinical mouse models.
- Use of mouse models of hematological malignancies to investigate the causative role of IL-1β in complications and autoimmune disease.

Conflict of interest

The authors declare no competing financial interests.

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