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Interleukin-1β as Hallmark of Inflammation and Link to Second Disease

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Abstract

Inflammation is a refined immune mechanism essential to fight against pathogens and tumor cells, and orchestrated by a variety of cells and mediators. Among these, interleukin-1β is a key cytokine that initiates the inflammatory process. In this Review, we discuss the pathogenic role of dysregulated IL-1β in haematological malignancies and other systemic inflammatory diseases, and its potential contribution linking to complications and second disease. Fine-tuned control of IL-1β may help pave the path for development of future efficient treatments against a variety of diseases with underlying inflammation.

Keywords: Interleukin-1β; Systemic inflammatory diseases; Haematopoietic malignancies; Osteoporosis; Pain; Autoimmune disorders

The Inflammatory Context of Disease

Inflammation is a common event within the underlying mechanisms of a wide range of diseases. These include rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease, Crohn's disease, cardiovascular diseases and atherosclerosis, stroke, myocardial infarction, Type 1 and 2 diabetes, lupus nephritis, and diseases of the central nervous system like multiple sclerosis and Alzheimer's disease, among others. In addition to its pathogenic role, inflammation may indirectly accelerate other symptoms of disease. For instance, it is the starting point for atheroma plaque development [1] and leads to premature atherosclerosis in patients of diabetes mellitus [2]. Similar relations between inflammation and atherosclerosis are found in rheumatoid arthritis [3], psoriasis [4] and systemic lupus erythematosus [5]. Inflammation is linked to insulin resistance [6], which further increases the frequency of atherosclerosis in rheumatoid arthritis [7]. Considering the association between atherosclerosis and thrombosis, inflammation may predispose to thrombosis [8]. The scenario can be then translated to patients with myeloproliferative neoplasms (MPN), where morbidity and mortality are related to cardiovascular events. Chronic inflammation in MPN may promote premature atherosclerosis, and cardiovascular and thromboembolic complications. Further, a fraction of MPN patients develop chronic renal failure. Inflammation is related to hyperuricemia and thereby to renal disease [9]. Hence, inflammation seems to play key roles as hallmark of disease and/or prognosis predictor.

In the last decades, compiled data supports the hypothesis that chronic inflammation promotes cancer. This is particularly evident in haematological malignancies. In certain types of malignant lymphomas, chronic inflammation has been evidenced as potential initiating event and driver of clonal expansion [10,11]. Long systemic inflammatory activity may lead to development of non-localized lymphoma, while long-term stimulation of auto-reactive B cells may be key for abnormal lymphogenesis in organ-specific autoimmune disorder [12]. MPN patients show increased risk of second cancer [13], where increased basal inflammatory status seems to promote mutagenesis and immune deregulation [10,14]. A Swedish epidemiologic study [15] found that chronic inflammation may be the starting point for development of myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). In this study, 9,219 patients with primary AML, 1,662 patients with primary MDS, and 42,878 matched controls were included. Data showed that history of any infectious disease was associated with a 1.3-fold significantly increased risk of both AML or MDS, even when infection had occurred 3 or more years before AML or MDS.

Under normal conditions, inflammation is a fine-tuned immune mechanism essential to fight pathogens and tumor cells, and orchestrated by a variety of cell subsets and mediators. Among those, interleukin-1 (IL-1) plays a major role initiating inflammatory processes, and triggers a variety of responses in numerous target cells. When dysregulated, its pathologic role in a variety of diseases like those mentioned above has been demonstrated by efficiency of anti-IL-1 therapies to reduce symptoms and severity [16,17]. Some examples include improvement of insulin production in Type-2 diabetes patients [18], and reduction in their incidence of myocardial infarction and stroke [19]. Use of anti-IL-1 therapy improves pain and swelling in osteoarthritis [20], and restores left ventricular diastolic function in patients of rheumatoid arthritis with heart failure [3]. Taken together, IL-1 stands out as a key regulatory mechanism that should be considered aiming at understanding pathogenesis and developing efficient treatments in a wide variety of diseases that share underlying inflammation.

Role of IL-1β in Healthy and Malignant Haematopoiesis

IL-1β is a member of the IL-1 family cytokines and it is mainly produced by hematopoietic cells, like monocytes, macrophages and dendritic cells [21,22]. It is synthesized as an inactive form, proIL-1β that is activated intracellularly by caspase 1 [22,23]. Under normal conditions, IL-1β is secreted in low levels, and its expression and/or caspase 1-mediated activation increases under disease [24,25]. High IL-1β tissue levels usually reflect in an increase in blood levels [26-30]. 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

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in haematological function [21] (Figure 1). 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 [31-33]. 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 [26], among others.

Likewise, IL-1β modulates haematopoietic stem cell (HSC) function. IL-1 promotes HSC differentiation biased into myeloid linage, in part through activation of PU-1 signaling [34]. While acute IL-1 exposure contributes to HSC regeneration after myeloablation and transplantation [34,35], chronic exposure promotes uncontrolled HSC division and eventual exhaustion of the HSC pool [34]. Inhibition of IL-1 signaling using IL-1 receptor antagonist (IL-1ra), which competitively binds to IL-1R1 and prevents binding of IL-1α and IL-1β [36], reduces colony formation *ex vivo* [37,38]. *In vivo*, IL-1ra suppresses HSC cell cycle in the bone marrow, and reduces numbers of white blood cells and platelets [38]. In contrast, IL-1β gives raise to neutrophilia, leukocytosis and thrombocytosis [24,39]. Thus, fine-tuned IL-1 levels play a physiological role in hematopoiesis, and their dysregulation may participate in haematological diseases [21,34,40].

MPN are haematological disorders characterized by myeloproliferation and splenomegaly, and underlying chronic inflammation that has been suggested to contribute to disease initiation and/or progression. Classical Philadelphia chromosome negative (negative for BCR-ABL gene fusion) MPN includes essential thrombocytemia (ET), polycitemia vera (PV) and primary myelofibrosis (PMF). Most frequent BCR-ABL negative MPN are associated with Janus kinase 2 (JAK2), calreticulin and myeloproliferative leukemia virus oncogene (MPL) mutations. MPN patients show increased levels of inflammatory cytokines in serum [41,42], and gene expression profiling and functional annotation analysis confirms deregulation of inflammatory and immune system genes [43]. Pro-inflammatory cytokines have traditionally been related to initiation and progression of myelofibrosis at advanced stages of disease [44]. Unlike PV or ET patients [45-47], PMF patients show high levels of IL-1β together with other pro-inflammatory cytokines and growth factors in plasma [45,47]. Actually, high IL-1β levels in PV patients predispose to fibrotic transformation, poor prognosis and lower survival [47]. Aggressive phenotypes of systemic mastocytosis, that is a less common form of BCR-ABL negative MPN characterized by mast cell expansion in bone marrow and other organs [40], are also related to up-regulation of IL-1β in mast cells [48]. Our recent work has shed light on the pathogenic role of IL-1β in 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 the mutant HSC [49]. 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* [49]. Additionally, high levels of IL-1β are associated with poor prognosis in BCR-ABL positive MPN or chronic myeloid leukemia (CML) [50,51]. High IL-1β was seen in advanced blast phase as compared to chronic phase and healthy controls, and it was correlated with blast expansion in bone marrow and peripheral blood, poor prognosis and shorter survival in patients [50,52]. Besides, IL-1β at concentrations comparable to those observed in CML bone marrow stimulates proliferation of long-term HSC in CML *ex vivo* [53] and helps promote colony growth in mutant cells together with other cytokines and growth factors (54). Further, use of IL-1ra or soluble IL-1 receptor suppressed this effect, suggesting that IL-1 could confer a proliferative advantage to leukemic

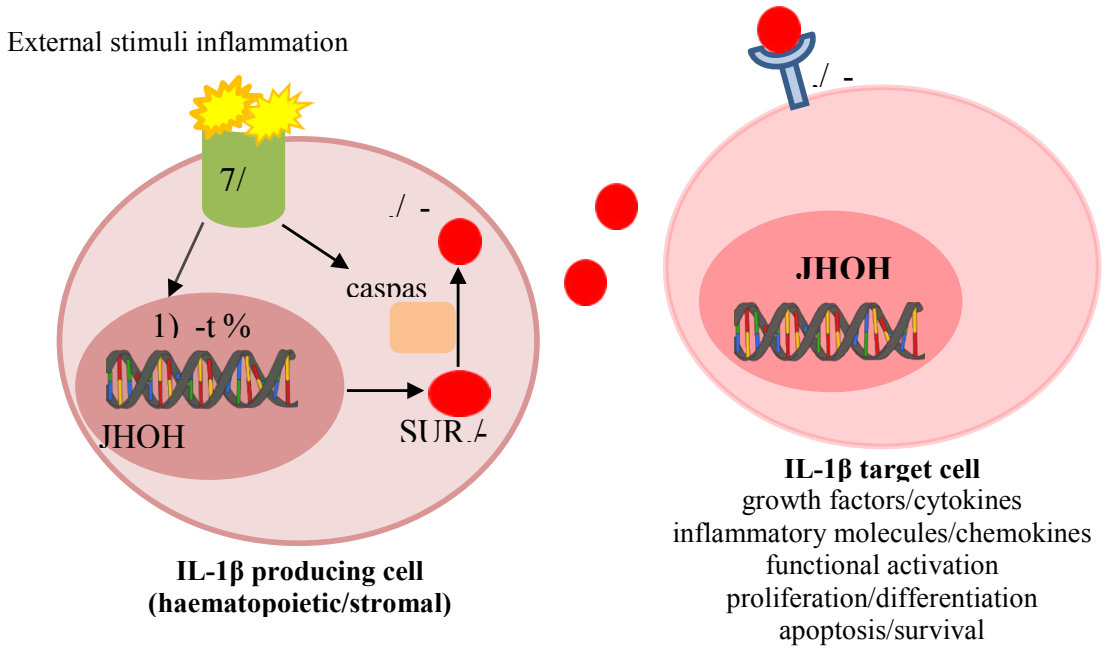

Figure 1: Interleukin-1β initiates inflammation and controls essential cell responses. Several stimuli like external inflammatory stimuli that signal through toll-like receptors (TLR), activate a cascade of events that culminate in activation of the transcription factor nuclear factor-kappaB (NF-κB), and of the catalytic activity of caspase 1. Following NF-κB activation, interleukin-1β (IL-1β) is synthesized as its inactive form, proIL-1β that is activated by cleavage through caspase 1. 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 the functional activation of numerous target cells. Further, IL-1β determines survival responses and cell fate.

stem cells (LSC) and thereby contribute to leukemia development [54]. Interestingly, IL-1 receptor accessory protein (IL-1RAP) that is a required component of the IL-1R complex which initiates IL-1 signaling events, is highly expressed in BCR-ABL+ CML cells [55]. In particular, IL-1RAP is up-regulated in CD34+ and CD34+CD38- cells from patients with CML compared to controls, and its expression increases with disease progression [56]. 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 [57,58] or through additional mutations, like those in genes promoting HSC survival or multidrug resistance [59-61]. 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 [62]. Interferon (IFN) family members, alternative treatment against CML, have anti-inflammatory effects and inhibit IL-1 [63-66]. 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. Further, in mouse models of disease, IL-1ra in combination with nilotinib, drug with greater potency and selectivity for BCR-ABL than imatinib, reduces numbers of leukaemic cells in blood and bone marrow, and the self-renewal potential of leukemic stem cells (LSC). This correlated with extended survival after completion of treatment compared to mice treated with nilotinib alone. *In vitro*, this combination significantly reduced human CML progenitor cell growth, including CD34+CD38+ and CD34+CD38- cells [67]. Then, blockade of IL-1 signaling together with BCR-ABL tyrosine kinase inhibition may pave the way to more efficient therapies against CML.

AML is a clonal expansion disease driven by both uncontrolled proliferation of abnormal myeloid progenitors and blockade of normal myeloid differentiation. IL-1β is produced by human AML blasts, where its expression relates to poor patient prognosis [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]. Poor patient prognosis and lower survival is observed in those patients with higher proliferative response to exogenous IL-1β [75]. Further, direct inhibition of IL-1β, 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. A more recent work [80] showed lower levels of IL-1β in the plasma of AML patients compared to healthy controls. Further, CD34+CD38- progenitors are enriched within the LSC cell subset and down-regulate IL-1β expression through epigenetic mechanisms, compared with more mature CD34+CD38+ AML progenitors and normal CD34+ cells [81]. High doses of IL-1β stimulate cell cycle and apoptosis in CD34+CD38- AML progenitors, by down-regulating cyclin-depend 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 in immunodeficient mice. Interestingly, in the same study, the authors showed that low dose IL-1β exposure stimulated colony formation in AML cells, while high doses promoted 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 and its potential therapeutic value.

A role for IL-1β has been suggested in lymphoid malignancies. In chronic lymphocytic leukemia (CLL), the specific single nucleotide polymorphism IL1B-511T, when presented in homozygosis, correlates with low risk of CLL. Interestingly, a different single nucleotide polymorphism in IL-1β gene (IL1B-511C) together with IL6-174C, both in homozygosis, increase to 11-fold the risk of CLL, compared to 4.5 fold increase with IL6-174C alone [83]. This points to an association between IL-1β and IL-6 in CLL development. In both CLL and its variant B cell-specific B-CLL, low levels of IL-1β and high levels of IL-6 are found in the plasma of patients [83,84]. However, previous work showed that IL-1β induces differentiation and activation of leukemic cells in B-CLL patients [85]. Thus, future work should elucidate the potential participation of IL-1β in CLL.

Finally, it is important to note that IL-1β is additionally produced by certain subsets of non-haematopoietic cells, like some stromal components of the haematopoietic 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 haematopoietic progenitor cells [86]. Bone marrow stromal cells from healthy controls co-cultured with different leukemia cell lines, up-regulate IL-1β [87]. 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. Conversely, MSC from ALL patients show increased IL-1β expression at diagnosis [88]. Future studies are required to determine the role of stromal derived-IL-1β in leukemia development.

In summary, numerous evidence suggests a role for IL-1β in the pathogenesis of haematological diseases, and particularly in myeloid leukemia's. Studies will be needed aiming at gaining further insights on its specific contribution and exploring its value as potential therapeutic target.

IL-1β as the Link to Second Disease

Bone complications in haematopoietic malignancies

A fine-tuned balance between bone resorption and formation maintains homeostasis in bone. Circulating cytokines and their producing haematopoietic cells have easy access to bone via bone marrow. It is therefore not surprising that several systemic inflammatory diseases are associated to bone alterations, particularly increased bone resorption, and thereby to higher fracture rate in patients [89,90]. In addition to their major role in inflammatory processes, inflammatory cytokines may activate bone degradation given that the degree of inflammation correlates with the amount of bone loss [89]. In this context, 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 bone resorption via TNF ligand superfamily member 11 (RANKL) [93]. As part of its potent inflammatory effects, IL-1 induces vasodilatation and promotes attraction of granulocytes into the tissue, and induces expression of prostaglandins, events that further help bone resorption [94].

The typical manifestation that results from accelerated bone remodeling is osteoporosis. Osteoporosis characterizes by thinning

of the bones, damage in their architecture and reduced mechanical strength due to diminished bone mineral density. This is accompanied by high fracture risk [95]. It is most frequent in older adults, and particularly in postmenopausal women. Thus, loss of bone mineral density during menopause has been traditionally attributed to estrogen loss [96]. More recently, estrogens have been suggested to have only minor effects [95], and inflammatory cytokines like IL-1 have been pointed out [96]. In ovariectomized rats, levels of pro-inflammatory cytokines correlate inversely with bone mineral density. Following ovariectomy, administration of IL-1ra improves bone mineral density, uncovering the pathogenic role of IL-1 [97]. In women who had undergone surgical menopause, increase in IL-1 secretion by peripheral blood mononuclear cells associate with significant loss in bone mineral density [98], suggesting that IL-1 may play an important pathogenic role in humans as well.

As previously discussed, chronic inflammation contributes to pathogenesis in myeloid malignancies, and it is related to second disease and complications. MPN patients show increased levels and expression of inflammatory cytokines [41,42] that relate to myelofibrosis at advanced stages [44]. Fibrosis typically derives in osteosclerotic lesions, particularly in PMF. PMF is a severe form of MPN characterized by haematopoietic failure and osteosclerosis, which originates as result of growth and thickening of bone trabeculae, and new bone formation in abnormal budding plaques [18]. PMF patients show high levels of IL-1β in plasma [45,47], and high IL-1β levels in PV patients predispose to fibrotic transformation [47]. 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 [99]. 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 [100]. 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 its potential link to IL-1β in PMF patients.

The scenario seems more certain in MPN and CML patients, where epidemiological studies have concluded increased risk of osteoporosis. For instance, a Danish study reported increased risk of fractures among MPN patients [101]. This study compared fracture risk among 7,595 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 [101]. 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 [102]. However, it does not influence the fracture risk in CML patients [101]. 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 [103]. Further, osteoporosis and vertebral fracture are frequent in patients with systemic mastocytosis with respectively 31 and 17% in a cohort of 75 patients [104]. Nevertheless, the direct contribution of chronic inflammation and IL-1 to bone loss specifically in myeloid leukaemias remains unknown, and should be subject of future investigation.

Bone morbidity seems to be present in other types of haematological malignancies like acute lymphoblastic leukaemia (ALL). ALL is the most common leukaemia 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 [105]. Low bone turnover status explains through reduced bone formation but normal resorption markers [106]. Further, ALL patients have increased fracture rate compared to healthy controls [107], and fracture risk is higher in ALL survivors after the end of the treatment [108,109]. However, little is known about the molecular mechanisms driving bone complications in ALL patients.

Osteoporosis and fractures are more frequent in patients of other systemic inflammatory diseases as well, like rheumatoid arthritis [96]. Rheumatoid arthritis is a systemic autoimmune and inflammatory disorder that primarily affects synovial joints. In rheumatoid arthritis, high levels of pro-inflammatory cytokines promote osteoclast differentiation and bone degradation, resulting in osteoporosis [110]. Experimental models of arthritis showed a major role for IL-1 in cartilage and bone degradation [92,111,112], while high levels of IL-1 were found in the synovial membrane and fluid of patients with rheumatoid arthritis [113,114]. Actually, this disease was the first in which IL-1 inhibition was tested and proved for clinical use. Use of IL-1 inhibitors was supported by severe arthritis development in IL-1ra deficient mice [115].

In view of the above, IL-1β stands out as the link to bone complications in different types of systemic inflammatory diseases, including haematopoietic malignancies.

Haematopoietic malignancies and pain

In certain chronic inflammatory diseases, like osteoarthritis, pain is one of the most prominent symptoms. Inflammatory stimuli start a cascade of events that originate osteoarthritis, and produce pain in parallel [116,117]. Pro-inflammatory cytokines like IL-1 induce 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 pain symptom [118]. In osteoarthritis, IL-1 inhibits the synthesis of extracellular matrix in chondrocytes and cartilage, and promotes degradation of the latter [119,120]. Additionally, IL-1 activates nociceptors directly causing activation of intracellular signaling cascades, and indirectly via production of kinins and prostanoids [119]. Studies have related IL-1 levels with pain perception and radiographic knee lesions in patients [121]. Further, IL-1ra prevents cartilage degeneration in animal models, and improves clinical outcomes in patients [122,123]. Thus, IL-1 is cause of disease and pain driver in osteoarthritis.

Interestingly, the most important haematopoietic 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 haematopoietic disorders, pain may be correlated to disease and its complications, or to diagnostic procedures and treatments [124]. When pain is present at disease onset, treatment with chemotherapeutic agents or other therapies usually drive pain relief. This is frequent in ALL patients [125]. Our recent work may provide hints linking pathogenesis and pain in haematopoietic 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 underlie bone pain reported in MPN patients [126]. 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* [48]. Hence, IL-1 may be pathogenic factor and pain driver in MPN as well.

Additionally, both ALL and AML survivors may experience chronic pain due to complications associated to haematopoietic cell transplantation [127]. Pain origin after transplantation seems to relate to injury to mucosal tissues induced by the conditioning regimen, like chemotherapy [128]. In mouse models and clinical settings, cisplatin, that is a common chemotherapy, induces sensory neuropathy [129,130]. Further, experimental models demonstrated cisplatin-induced bone marrow nerve injury that impairs haematopoietic regeneration [129]. To date, the molecular mechanisms driving neural damage after chemotherapy have not been thoroughly defined.

Autoimmune diseases and haematopoietic malignancies

The connection between autoimmune diseases and haematopoietic malignancies goes beyond common bone affectation and pain. Actually, a number of epidemiological studies show higher risk of haematopoietic malignancies in patients with autoimmune diseases compared to the general population, with further increase after cytotoxic treatment [131]. Interestingly, autoimmune disease patients with secondary acute leukaemia usually develop AML rather than ALL [132]. History of any autoimmune disease has been associated with increased risk of AML and MDS [15,133]. 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 [131,133,134]. Additionally, systemic mastocytosis is related to higher prevalence of inflammatory joint diseases like spondyloarthritis and rheumatoid arthritis [135,136]. 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 haematopoietic malignancy [137]. Conversely, a haematopoietic disorder may precede the autoimmune disease, and for instance early manifestation of an occult malignancy may be fast development of rheumatoid arthritis-like syndromes [138]. 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 [139]. 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 [140,141]. 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 [142,143]. 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 [144-148]. 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 leukaemia and autoimmune diseases like rheumatoid arthritis [149-151]. Importantly, it is well-described that activated NF-κB induces transcription of proIL-1β (Figure 1). As discussed in the previous section, IL-1 and specifically IL-1β may play a pathogenic role in a variety of haematopoietic malignancies, particularly those involving the myeloid lineage. This statement holds true for a wide range of systemic inflammatory and autoimmune diseases [17]. In both haematopoietic malignancies and autoimmune diseases, IL-1 seems to link with bone and pain complications. Hence, it is reasonable to hypothesize that IL-1 may as well provide a link between haematopoietic malignancies and autoimmune diseases. Future work is required to validate this hypothesis. If IL-1 participates in pathogenesis, complications and second disease in both haematopoietic malignancies and autoimmune diseases, fine-tuned management of IL-1 levels will have utility in numerous disorders and will substantially improve quality of life in patients.

Future Perspectives

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 haematopoietic malignancies and autoimmune diseases, their complications, and may be their connection. Hence, drugs that target IL-1 may be helpful in numerous inflammatory conditions. Currently, these drugs include IL-1ra (anakinra), 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. However, in the clinical setting, anakinra seems to be limited by its biological and pharmacokinetic properties [17]. 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* [152]. 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 [153]. These next generation of drugs with improved chemical, pharmacological and biological properties, should allow us to determine accurately the essential role of IL-1 in multiple inflammatory diseases as well as its promising therapeutic value. Finally, cumulative evidence is actually shaping our view on the key role played by inflammation in cancer. For instance, in carcinogenesis induced by 3-methylcholantrene, tumor development has been traditionally related to failure of immune surveillance mechanisms that eliminate the arising malignant cells [152]. However, recent data demonstrates that inflammation and particularly IL-1β is essential for this type of carcinogenesis that is hampered in IL-1β deficient mice and intensified in IL-1ra deficient mice [153]. IL-1 is up regulated in a variety of solid tumors like breast, colon, lung, head and neck cancers, and melanomas. Patients with IL-1 producing tumors have generally poor prognoses, and overexpression or treatment with IL-1ra have anti-tumor properties in experimental models. Thus, fine-tuned IL-1 control may pave the path to more efficient treatments against a wide variety of diseases with underlying inflammation.

Conflict of Interest

The authors declare no competing financial interests.

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