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The interleukin-1 cytokine family members: Role in cancer pathogenesis and potential therapeutic applications in cancer immunotherapy

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ABSTRACT

The interleukin-1 (IL-1) family is one of the first described cytokine families and consists of eight cytokines (IL-1β, IL-1α, IL-18, IL-33, IL-36α, IL-36β, IL-36γ and IL-37) and three receptor antagonists (IL-1Ra, IL-36Ra and IL-38). The family members are known to play an essential role in inflammation. The importance of inflammation in cancer has been well established in the past decades. This review sets out to give an overview of the role of each IL-1 family member in cancer pathogenesis and show their potential as potential anticancer drug candidates. First, the molecular structure is described. Next, both the pro- and anti-tumoral properties are highlighted. Additionally, a critical interpretation of current literature is given. To conclude, the IL-1 family is a toolbox with a collection of powerful tools that can be considered as potential drugs or drug targets.

1. Introduction

Cytokines are the messengers of the immune system, allowing it to coordinate potent responses to a broad range of challenges. Cytokines can induce or inhibit inflammation and recruit or inhibit immune cells [1]. Over the past three decades, the importance of cytokines in cancer-associated inflammation has been well established. One of the oldest and best characterized families in the world of cytokines is the interleukin-1 (IL-1) family. The interleukin family is named after the location of the Second International Lymphokine Conference in 1973: Interlaken, Switzerland. Proteins belonging to the IL-1 family were first described in the pathogenesis of fever in 1943 [2]. The name IL-1 was originally given to macrophage products that caused inflammation. The nomenclature was solely based on their biological properties, because no amino acid sequence was available [2]. With the advances in molecular biology, the first cDNA sequences of two IL-1 proteins were determined and were named IL-1α and IL-1β in 1985 [3–6]. Progressively, 9 other interleukins in this family were discovered: IL-1Ra, IL-18, IL-33, IL-36α, IL-36β, IL-36γ, IL-36Ra, IL-37 and lastly IL-38 in 2001 [7].

All these interleukins show the same core structure, containing 12 β-sheets, six of which are arranged in a β-trefoil core. The trefoil is formed by three hairpins, each containing two β-sheets. The coil shows an internal 3-fold symmetry and is connected by intramolecular hydrogen bonds (Fig. 1). Every molecule has its own essential three

Abbreviations: AA, Amino acid; Balb/c, An albino, laboratory-bred mice strain; COX-2, Cyclo-oxygenase-2; DC, Dendritic cells; EC, Endothelial cells; ErbB2, Human epidermal growth factor receptor 2; GvHD, Graft-versus-host disease; IFN-γ, Interferon gamma; IL-1, Interleukin 1; IL-18R, Interleukin 18 receptor; IL-1RAcP, Interleukin-1 receptor accessory protein; IL-1RI, Interleukin 1 receptor, type I; IL-1Rrp2, Interleukin 1 receptor like 2; ILC2, Type 2 innate lymphoid cells; IRAK, Interleukin-1 receptor-associated kinase; kDa, Kilo dalton; LPS, Lipopolysaccharide; MCF-7, Michigan Cancer Foundation-7 breast cancer cells; MMP, Matrix metallopeptidase; MyD88, Myeloid differentiation primary response 88; NFkB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NKv, Natural killer cells; OSCC, Oral squamous cell carcinoma; PBMC, Peripheral blood mononuclear cells; RAW, Monocyte/macrophage-like cell line; SIGIRR, Single Ig IL-1-related receptor; SNPs, Single nucleotide polymorphism; ST2, Interleukin 1 receptor-like 1; TAB1, TGF-Beta activated kinase 1; TAK1, Mitogen-activated protein kinase kinase kinase 7; TCR, T cell receptor; TGF-β, Transforming growth factor beta; TNF-α, Tumor necrosis factor alpha; TNM stage, Classification of malignant tumors; Tph1, Tryptophan hydroxylase 1; TRAF6, TNF receptor associated factor; VCAM1, Vascular cell adhesion molecule 1; VEGF, Vascular endothelial growth factor; VLA4, Very late antigen 4.

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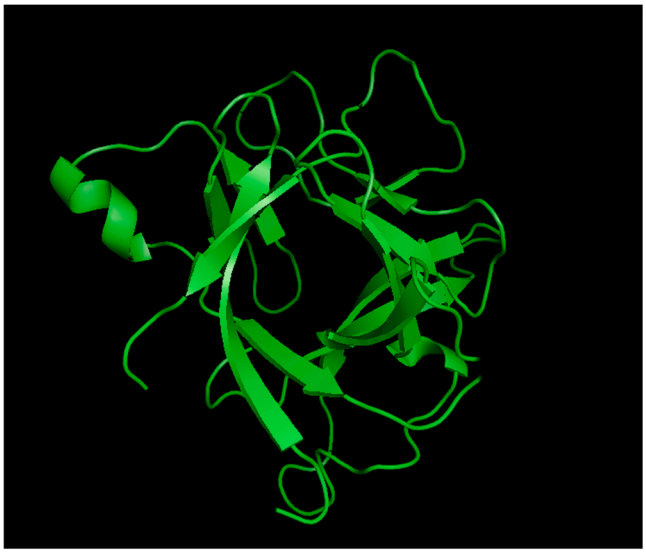

Fig. 1. Structure of IL-1β showing the characteristic IL-1 family β-trefoil structure, indicated by the flat arrows in the core. [12].

additional secondary structure elements that explain the difference in biological activity. IL-1α has three additional secondary structure elements compared to IL-β: a short β-strand near the N-terminus (amino acid (AA) 6–10), a second short β-strand (AA 97–99), and two turns of 3_{10} helix (AA 101–105) [8,9]. The only member without an elucidated structure is IL-38. A model IL-38 structure based on 4250 nonredundant Protein Data Bank structures shows the IL-1 characteristic β-trefoil core [10]. The β-trefoil allows the family members to bind to their receptor, but it is not the essential structural feature for binding. In the IL-36 family, for example, all 4 molecules show the same β-trefoil fold but do not bind the IL-1 receptor type 1 (IL-1RI) [11].

With the exception of IL-1Ra, every family member is produced as a pro-form. Most pro-forms are not able to activate their receptor and show no biological activity before they are cleaved into their mature form. However, the pro-forms of IL-1α and IL-33 are able to bind their receptor and show bioactivity [12] (Table 1). Although the 11 cytokines only bind to 4 different receptors (Table 1), the family shows a wide variety of biological activities ranging from pro- to anti-inflammatory. Some members of the family, such as IL-37 and IL-38, have only recently been discovered, while others have been extensively studied to the extent of testing recombinant forms in clinical trials, such as IL-1β and IL-18 [13,14]. Three of the family members are receptor antagonists: IL-1Ra, IL-36Ra and IL-38. They bind to their corresponding receptor without producing a signal. Because of their antagonistic function, the IL-1 family members have been described with both pro- and anti-inflammatory effects [15]. Understanding the role of these cytokines in cancer pathology is an essential step in harnessing their power and developing approaches for cancer immunotherapy.

The aim of this review is to give an overview of the role of the individual IL-1 family members in cancer pathogenesis. The role of each IL-1 family member in cancer immunology will be illustrated separately. First, the molecular structure is described, and corresponding receptors are defined. Both the tumor-promoting and tumor suppressive effects of each cytokine is detailed with recent advances in the field. Additionally, a critical interpretation and the connection between published literature is given. Finally, the main conclusions are summarized and possible applications are suggested.

2. IL-1 family members

2.1. IL-1

IL-1α and IL-1β are non-homologous proteins and were the first discovered cytokines of the IL-1 family [5,6,16–19]. Both interleukins are classified as proinflammatory cytokines and bind to the IL-1 receptor type 1 (IL-1RI) [12], which is expressed on the cell membrane [20].

Both IL-1α and IL-1β are expressed as pro-forms of 31 kDa that are enzymatically cleaved into their fully active 17 kDa state. IL-1α and IL-1β show high similarity in their biological activity, potentially due to the high sequence similarity although some structural differences exist. Despite the functional similarities, there are differences in the expression and activation of the two interleukins. First, the factors that influence the cleavage of IL-1α and IL-1β into their mature form are different. The pro-form of IL-1β is cleaved by aspartic protease caspase-1 downstream of the inflammasome. The inflammasome, but not aspartic protease caspase-1, plays a role in the cleavage of pro-IL-1α [20–22]. Secondly, the mature form of IL-1α functions while membrane-bound, whereas IL-1β is secreted as a mature form and functions in solution [23]. IL-1β is absent in cells under homeostatic conditions and is only expressed after upregulation in lymphoid and myeloid cells. In contrast, IL-1α is present in a wide variety of healthy cells, including homeostatic lymphoid and myeloid cells [24]. Discovered in parallel with the IL-1 receptor, the interleukin-1 receptor antagonist (IL-1Ra) was described. This antagonist binds to IL-1RI without causing a biological response. Although the existence of IL-1Ra has been known for a relatively long time, the role of the antagonist in cancer is relatively undefined compared to IL-1α and IL-1β.

2.1.1. IL-1α

The proform of IL-1α is cleaved by caspase-5 (human) or caspase-11 (mouse) and is excreted from the cytosol into the extracellular space [25]. Once the cytokine is cleaved into its mature form, it is able to bind to IL-1RI. The complex then recruits interleukin-1 receptor accessory protein (IL-1RAcP) to initiate signal transduction. The adaptor molecule on IL-1RI, MyD88, helps recruit IRAK and IRAK2 which, in turn, recruit TRAF6. TRAF6 activates the kinases TAB1 and TAK1, inducing the expression of several genes including the NFkB genes, which is highly active in cancer but also in inflammation (Fig. 2) [26–28].

IL-1α is expressed constitutively, in its pro-form, in many types of

Table 1
Summary of the IL-1 family cytokines and their biological characteristics.

Cytokine	Receptor	Coreceptor	Chromosomal location	Pro-domain	Functional Pro-form	Cleavage
IL-1α	IL-1RI	IL-1RAcP	2q14	Yes	Yes	Caspase-5/ caspase-11
IL-1β	IL-1RI	IL-1RAcP	2q14	Yes	No	Caspase-1
IL-1Ra	IL-1RI	NA	2q14.2	No	No	Caspase-1
IL-18	IL-18Rα	IL-18Rβ	11q22.2-q22.3	Yes	No	Caspase-1
IL-33	ST2	IL-1RAcP	9p24.1	Yes	Yes	Caspase-1
IL-36Ra	IL-1Rrp2	NA	2q14	Yes	No	Unknown
IL-36α	IL-1Rrp2	IL-1RAcP	2q12-q14.1	Yes	No	Unknown
IL-36β	IL-1Rrp2	IL-1RAcP	2q14	Yes	No	Unknown
IL-36γ	IL-1Rrp2	IL-1RAcP	2q12-q21	Yes	No	Unknown
IL-37	IL-18Rα	SIGIRR	2q12-q14.1	Yes	No	Caspase-1
IL-38	IL-1Rrp2	Unknown	2q13	Yes	No	Proteases in apoptotic cell medium

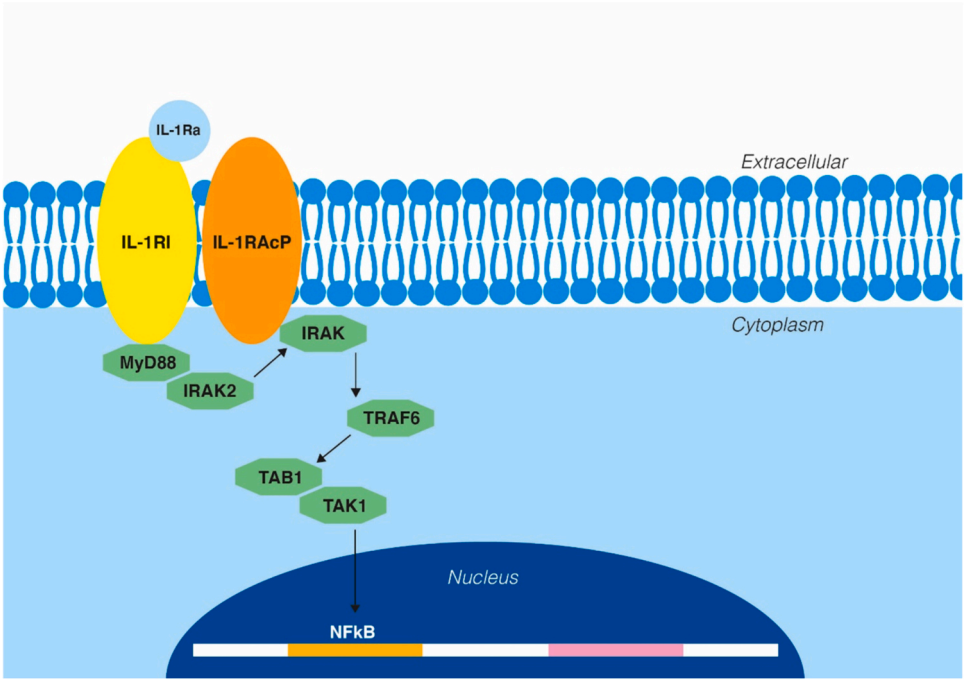

Fig. 2. Graphical representation of the IL-1α-induced IL-1RI signal. Shown are IL-1a (cyan), the IL-1RI receptor (yellow), the IL-1RAcP co-receptor (orange) and the mechanistic cascade (green). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cells in healthy tissue. An example of these are endothelial and epithelial cells [16,24,29]. When the cells are damaged, IL-1α expression is upregulated. Surrounding cells respond to the soluble and membrane-bound IL-1α by also upregulating their production. This creates a loop of sustained inflammation [30,31]. This can result in considerable tissue and DNA damage until IL-1RI is depleted. This is a critical mechanism in containing a viral infection but could also lead to tumorigenesis. Studies show a correlation between this sustained inflammation loop, IL-1α and tumor formation, malignant transformation and metastasis [30–37]. Both the pro-form and the mature form show bioactivity and both show tumor-promoting effects. It was reported that the pro-form of the cytokine is able to activate NFkB, thereby inducing acute T-lymphocytic leukemia [38]. The mature form of IL-1α is able to enhance crosstalk between pancreatic ductal adenocarcinoma cells and cancer-associated fibroblasts, which creates a chronic inflammatory tumor milieu [39]. IL-1α stimulates tumor-infiltrating myeloid cells in breast cancer, and fibroblasts in pancreatic cancer. This stimulation leads to the secretion of proliferation-, invasion- and angiogenesis-stimulating proteins [40–42]. IL-1α was reported to be upregulated in patients suffering from head and neck squamous carcinomas and gastric carcinomas with metastasis compared to patients without metastasis [43,44]. The expression of IL-1α proved to be a marker for poor prognostic for both types of cancer [45]. IL-1α also proved to be prognostic for patients with liver metastasis in gastric carcinoma [39]. Single nucleotide polymorphisms (SNPs) in the IL-1α gene have been associated with an increased risk of cancer [46]. This shows the essential role of IL-1α in cancer inflammation [47].

IL-1α also shows a number of tumor-suppressive effects. When IL-1α was overexpressed in either T lymphoma and fibrosarcoma cells, the cells would not transform into malignant cells [48,49]. When the cells overexpressing IL-1α were then injected into an existing tumor, the tumor would subsequently regress, mediated by CD8+ T cells, NK cells and macrophages [48,49]. When IL-1α was administered to MCF-7 human breast cancer cells, prostate progenitor/stem cells or mammary epithelial cells, an arrest in growth in the Go/G1 phase of the cell cycle was detected [50–53]. These studies demonstrated the potential of IL-1α as a therapeutic target, and clinical trials with antibodies targeting IL-1α have shown promising results with low adverse effects [54,55]. One clinical trial published in 2014 assessed the benefits of a systemic anti-IL-1α treatment in 52 patients suffering from metastatic cancer. A strong and significant decrease in IL-1α plasma levels was found. Approximately one fifth of the patients showed a stabilization of the disease following the treatment and no dose-limiting toxicity or severe side effects were registered [55]. Two randomized controlled phase II clinical studies were initiated to determine if the treatment results in real patient benefit compared to existing treatments and are still ongoing. In conclusion, IL-1α shows the effects of inflammation on tumor formation and progression. Prolonged inflammation increases the risk of tumor formation. While short acute inflammation, like therapeutic administration results in tumor growth inhibition.

2.1.2. IL-1β

Activation of IL-1β requires two distinct signals: priming and inflammasome activation. The first signal is caused by tissue damage, inflammasome components and microbial components, and initiates the expression of full-length IL-1β. The second signal, also caused by tissue damage, inflammasome components and microbial components, activates the inflammasome, allowing caspase-1 activation to cleave full-length IL-1β into its mature form. The mature secreted form is then able to bind to the IL-1RI receptor [56].

The majority of research on the role of IL-1β in cancer describes a pro-tumorigenic effect of the cytokine. This is due to the ability of IL-1β to induce Th17 cells from CD4+ T cells. IL-1β expression was increased significantly in murine tumor models of breast, colon, lung, head and neck cancer and melanomas. In these models, the cytokine caused an increase in inflammation that promoted invasiveness [57]. When tumors were induced, using carcinogenic chemicals, in IL-1β-deficient mice, tumors developed more slowly and invasiveness was decreased [58]. When 3-MCA fibrosarcoma, a cancer cell line with increased IL-1β secretion, was injected into mice, an increase in development and invasiveness of these cells was witnessed compared to fibrosarcoma cells with normal IL-1β expression levels [58]. IL-1β also induces macrophage-mediated neovascularization and aids tumor growth [59]. This effect could be observed in multiple murine cancer models where

IL-1β also caused increased metastatic rates. Tumor progression was associated with an increase in IL-1β levels at both the primary and metastatic sites [60].

However, simply injecting IL-1β into L5178Y lymphoma led to T-cell-mediated regression in established tumors [61]. In addition, in myeloma and B-cell lymphoma in mice, an inflammatory response induced by IL-1β was able to inhibit cancer growth. This effect was mediated by tumor-specific CD4+ T cells. When different proinflammatory cytokines were knocked out in the same tumor model, it was determined that IL-1β was essential for the anti-tumor response. The response was mainly carried out by tumor-specific Th1 cells and tumor-infiltrating macrophages [62,63]. IL-1β levels also correlated with a decrease in NLRP3 inflammasome formation. This decrease led to a reduction in tumor burden in mice with colorectal cancer [64]. The mechanism was recently explained by a decrease in IL-17 and IL-22 secretion by endothelial cells, causing a decrease in activation of NFkB, which resulted in reduced tumor proliferation [65].

Despite the pleiotropic nature of IL-1β it has been evaluated in a range of clinical trials. The recombinant cytokine was assessed for its hematopoietic, anti-tumoral effects and toxicity in melanoma, renal cell carcinomas and other malignancies. The hematopoietic effect of IL-1β proved to be too modest in relation to its side effects, such as fever, flu-like symptoms and dose-limiting hypotension [66,67]. A recent phase III clinical trial assessed the effects of canakinumab, an IL-1β-targeting monoclonal antibody, on the prevention of cardiac events. A subset analysis showed a decrease in occurrence of lung cancer in 10,500 patients that were treated with canakinumab [68]. IL-1β is implicated as a target in other diseases than cancer. Canakinumab is currently on the market for systemic juvenile idiopathic arthritis (SJIA) and active Still's disease, an auto inflammatory disease. Overall, this shows that sustained inflammation favors tumor progression while acute inflammation favor tumor inhibition. However, taken together, these studies show the potential of IL-1β as a potential therapeutic target.

2.1.3. IL-1Ra

The interleukin-1 receptor antagonist (IL-1Ra) is a stranger within the IL-1 family. Although IL-1Ra was discovered at about the same time as IL-1α and IL-1β, it did not receive as much attention as the other cytokines in the family. It is one of three receptor antagonists in the family. It binds to IL-1RI but does not induce a biologic response. The 12 anti-parallel β-strands that form the IL-1 family β-trefoil fold give IL-1Ra the ability to bind IL-1RI [69]. It blocks the receptor by binding to it and preventing IL-1RAcP co-receptor recruitment, thus preventing the signaling cascade (Fig. 3).

This mechanism represents one of the regulatory means of IL-1RI. Since it blocks the receptor for the pro-inflammatory effects of IL-1α and IL-1β, IL-1Ra can be classified as an anti-inflammatory molecule. Therefore, IL-1Ra could potentially inhibit the tumor-promoting effects of the cytokines.

Several studies suggest that IL-1Ra is able to decrease metastatic rates by downregulation of ICAM-1, an intercellular adhesion molecule [70,71]. When C57BL/6 mice were co-injected with IL-1Ra, B16 tumor cells and IL-1Ra every second day, tumor growth was significantly inhibited in the later stages of the cancer. However, the survival of the IL-1Ra mice did not significantly improve [25].

A study from 1993 showed that when IL-1 (the study does not specify the submember) was administered simultaneously with A375M lung tumor cells, the number of lung metastases was significantly increased. When IL-1Ra was administered simultaneously, this effect could not be detected. The authors hypothesized that IL-1Ra prevented IL-1-mediated endothelial cell (EC) activation, causing a decrease in tumor cell adhesion. [26] However, the underlying mechanism of IL-1 stimulated metastasis is complex and EC activation is only part of the story. A more recent study explained the mechanism by which IL-1 mediates metastasis. The study states that increased VCAM1 expression on ECs, induced by IL-1, is recognized by VLA4 expressed on melanoma cells or E-selectin ligand on colon cancer cells [72]. Administration of IL-1Ra, in murine solid tumor models, reduced tumor invasiveness and tumor-mediated immune infiltrate suppression. This shows the feasibility of IL-1Ra as a potential cancer therapeutic [57].

IL-1Ra is a potentially interesting therapeutic candidate, for more than only cancer [73]. Anakinra is a recombinant slightly modified (one methionine is connected to the N-terminus) therapeutic version of the IL-1Ra molecule. It is used to treat rheumatoid arthritis, but is also being

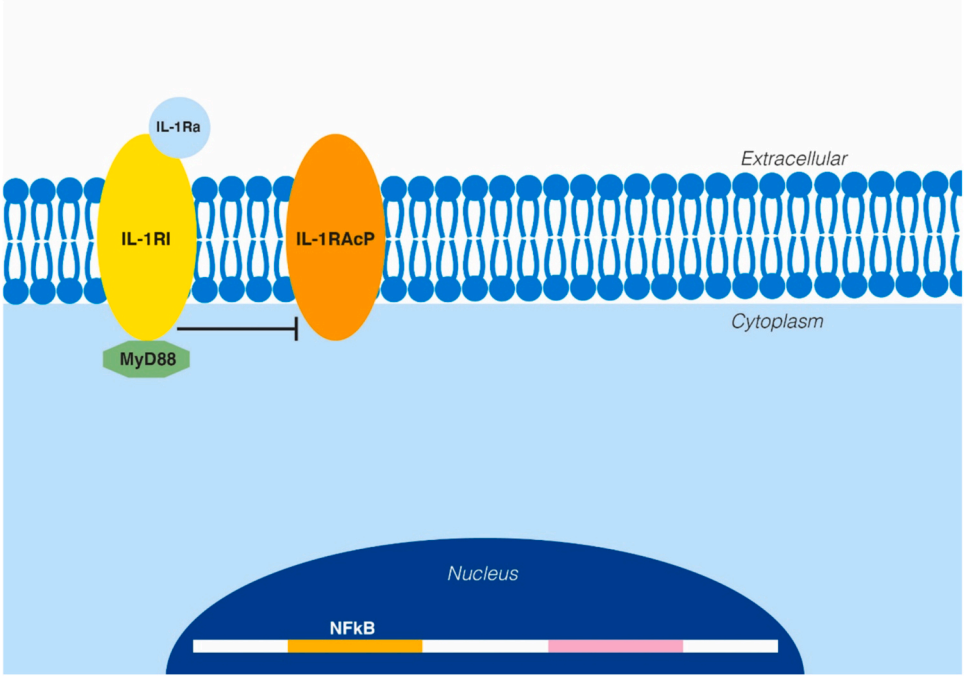

Fig. 3. Graphical representation of IL-1RI (yellow), IL-1Ra (orange) and IL-1RAcP (cyan). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

studied as a chemotherapeutic agent. A clinical trial in patients with indolent myeloma showed that the molecule is able to inhibit IL-6 production and increase progression free survival [74]. A clinical study in patients with primary breast cancer showed that anakinra, in combination with standard chemotherapeutics, fluorouracil and bevacizumab, is able to prevent cancer progression [75–78].

2.2. IL-18

Together with IL-1α and IL-1β, IL-18 is one of the most studied cytokines in the family. IL-18, like most IL-1 family cytokines, is produced in its 24 kDa pro-form and is then cleaved by caspase-1 intracellularly into an 18 kDa mature form [79]. IL-18 is originally described as an endotoxin induced serum factor [80]. IL-18 binds IL-18Ra, which is mainly located in the mitochondria [81]. The structure of IL-18 consists of 12 strands that form 3 twisted four stranded β-sheets (the IL-1-like fold), one α-helix and one 3_{10}-helix [82]. Despite the low sequence homology, the structure of IL-18 is similar to that of IL-1β. The biological function of both proteins is also similar in that they both induce IFN-γ production in mainly NK and T cells. Almost all healthy human cells produce IL-18, although macrophages and dendritic cells (DC) and healthy barrier cells are the main producers [83,84].

The IFN-γ-inducing capabilities of IL-18 led to it being considered a proinflammatory cytokine and thus with potential anti-tumoral effects, however, the function of IL-18 in cancer is two-sided [85].

A correlation has been shown between gene polymorphisms in the IL-18 gene, 11q22.2-q22.3, and cancer [86]. A meta-analysis proposed that a nucleotide 607 C to A polymorphism was strongly correlated with an elevated risk of gastric cancer occurrence [87,88]. Additionally, IL-18 is known to help cancerous cells escape immune surveillance by downregulating CD70, a highly expressed protein by lymphocytes [89,90]. An immunosuppressed mouse model, Balb/C (nu/nu), was injected with NCI-N87 human stomach cancer cells. The NCI-N87 cells were treated with siRNA to silence the IL-18 expression. This resulted in a regression of the tumor mass compared to non-IL-18-silenced NCI-N87cells [89].

Furthermore, IL-18 increases vascular endothelial growth factor (VEGF) and CD44 levels [89]. VEGF leads to neovascularization in tumors and CD44 is involved in cell-cell interactions, cell adhesion and cell migration. After silencing IL-18 in mice, a decrease in the expression of CD70 and CD44 proteins was seen (Fig. 4) [89].

An anti-tumoral role of IL-18 has also been described. Healthy epithelial cells produce IL-18. When the colon undergoes neoplastic transformation, these cells are no longer able to produce IL-18, leading to a decrease in IFN-γ levels. It is hypothesized that the lack of IFN-γ helps the cancer escape the immune system [91]. Lowered IL-18 expression is associated with an increase in different colorectal cancers like colitis, polyp formation and ovarian cancer in humans [92–94].

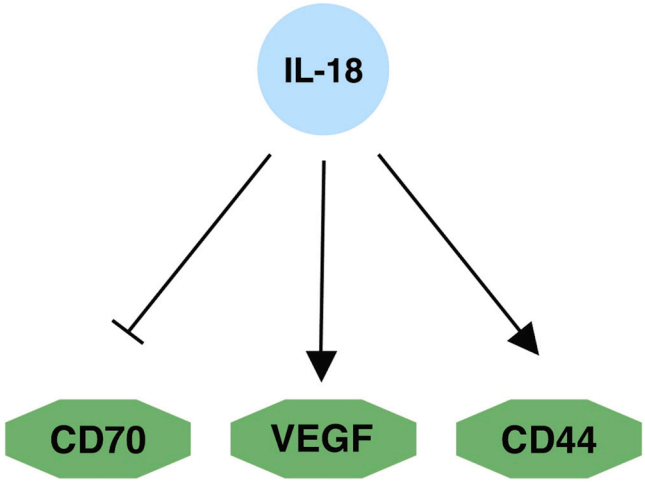

Fig. 4. Graphical representation showing the escape mechanism of cancer cells with the involvement of IL-18 showing IL-18 (cyan), CD70 (green), VEGF (green) and CD44 (green). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

This evidence led to the clinical assessment of IL-18 as a potential drug for the treatment of ovarian carcinoma. During a phase I study recombinant human IL-18 was administered intravenously, leading to an increased level of most pro-inflammatory cytokines and increased Fas ligand density on NK and T cells in the serum of two patients [95]. A different phase I study showed no dose-limiting toxicities. The dosing regimen led to a heightened serum concentration of IFN-γ, granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-18-binding protein, resulting in an average regression of lesions of 69% in 3 months [96]. A phase II study was started with 64 patients suffering from stage IV melanoma. The study was stopped because of limited clinical efficacy [97].

The most recent discoveries on IL-18 include IL-18-secreting T cells with a modified T cell receptor (TCR). The study showed that tumor-directed TCR-modified T cells, secreting IL-18, provide a superior pro-inflammatory tumor environment. This resulted in an increased overall survival of mice with the pmel-1 syngeneic tumor model [98,99]. Another recent development involving IL-18 is the development of an IL-18 immunoadjuvant xenogeneic canine matrix metallopeptidase (MMP)-7 DNA vaccine against murine mammary tumors. MMP-7 aids the development of angiogenesis through proteolytic cleavage of the extracellular matrix. IL-18 was used as an immunoadjuvant with MMP-7 to immunize Balb/c mice. This significantly reduced tumor growth, increased survival time by increasing tumoral CD4+ and CD8+ T cell populations. In addition, IFN-γ and IL-2 were significantly upregulated [78], demonstrating the ability of IL-18 to act as an immunoadjuvant and induce a type 1 immune response [98,99].

2.3. IL-33

IL-33 is a relatively newly discovered member of the IL-1 family [100–102]. Like IL-1α, the pro-form of IL-33 is biologically active. However, IL-33 has a low sequence similarity with IL-1β (16%) but does show similar structural features to IL-18 and IL-1β [103,104]. IL-33 is mainly known for its ability to induce a type 2 immune response [105,106].

IL-33 is constitutively expressed by a variety of stromal cells of organs including the abdomen, the central nervous system and the lungs [105,107]. The main receptor for IL-33 is the ST2 receptor, also called the interleukin-1 receptor like 1 [108–110]. The ST2 receptor is mainly located on the cell membrane and in the cytosol [111]. The ST2 receptor is primarily expressed on fibroblasts, hematopoietic cells, and mast cells [112]. After active release of IL-33 from damaged cells or passive release from dead cells, IL-33 binds directly to ST2 (Fig. 5) and recruits the IL-1RAcP co-receptor [113–115]. This allows for the activation of the NFκB pathway [116]. This mechanism plays a critical role in wound healing processes, such as angiogenesis, production of matrix components and modulation of immune cell involvement [114].

This is also where the link to cancer pathology can be made. The involvement of ST2 IL-33 signaling in wound healing suggests a potential tumor-promoting effect of IL-33 [117]. Studies have found an elevated expression of both the receptor and the cytokine in breast cancer, non-small-cell lung carcinoma and epithelial ovarian cancer. The expression correlated with other biomarkers associated with a poor prognosis [118–120]. *In vivo,* IL-33 also showed tumor-promoting effects. Systemic administration of IL-33 in tumor-bearing mice was enough to induce metastasis and tumor growth, but failed to do so in ST2−/− mice. This shows that the ST2 receptor is essential for the tumor-promoting role of IL-33 [121]. The recent findings delineate IL-33 as a tumor-inducing factor and determine that IL-33 induces the inflammatory enzyme Tph1. The constant induction resulted in a

Fig. 5. Graphical representation of IL-33 (red) and ST2 (green) complex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

depletion of Tph1, leading to a selective impairment of pro-inflammatory group 2 innate lymphoid cells (ILC2) [122]. A very recent study showed that IL-33-dependent ILC2s activation is centrally involved in promoting tumor burden by suppressing NK cells [117].

In contrast with the tumor-promoting effects already described, studies also have shown a tumor-inhibiting role for IL-33 and the ST2 signaling pathway. IL-33 and ST2 expression decreases with increasing tumor stage. The reason for decreased IL-33/ST2 levels being a cause or effect of advanced tumor stages is currently unknown. However, mRNA levels of IL-33/ST2 decreased significantly in patients with severe cervical intraepithelial neoplasia (CIN) compared to those with CIN in the initial stages [123]. The same reverse correlation can be seen in patients with myeloma and lung cancer patients [124,125]. The expression of IL-33 was witnessed to be decreased in many carcinomas as soon as their transition to a metastatic form was made [126]. A recent finding demonstrated that IL-33 is able to induce a cytotoxic immune response in CD8+ T cells and NK cells. IL-33 increased the number, the IFN-γ production and the CD8+ tumor specificity, resulting in a decrease of the tumor size in B16 mouse models [127,128]. Loss of the ST2 receptor leads to an increase in the expression levels of IL-17 and an increase in cytotoxic activity of NK cells and CD8+ T cells. The increased cytotoxic activity of these cells and protein levels lead, in turn, to an inhibition in the growth of breast cancer cells and decreased metastasis. It has been hypothesized that the loss of the ST2 signaling promotes the Th1/Th17 polarization, leading to a stronger immune response [129,130]. The same inhibition of ST2 signaling decreased ErbB2-induced cell migration of breast cancer cells [131].

Although there are some indications of an anti-tumoral effect of IL-33, there is a stronger case for its tumor-promoting effects. Much caution should be exercised with developing an IL-33 drug product that can be directly administered and all off-target effects should be fully understood. An IL-33, or ST2, inhibiting factor would be a more logical potential therapeutic. ST2 blockers have been tested in vivo in a graft-versus-host disease (GvHD) mouse model and has shown real potential. However, a structure-activity optimization process is needed before therapy should be considered [132,133].

2.4. IL-36

The IL-36 subset consist of 3 cytokines, IL-36α, IL-36β and IL-36γ, and one receptor antagonist, IL-36Ra. All 4 proteins bind to the IL-36 receptor complex, which consists of 4 subunits: IL-36R, IL-I1RRP2, IL-1RL1 and the IL-1 receptor accessory protein. The IL-36 receptor complex is mainly expressed on immune cells, such as monocytes, macrophages, DCs and T cells. The receptor is also expressed on epithelial cells in healthy tissue like lung, and emerging data also suggest expression on the skin and intestinal tissue [134,135]. Like most IL-1 family members, the IL-36 subset is cleaved from its pro-form to its mature form. Elastase, proteinase-3, and cathepsin G, mostly neutrophil-derived, cleave all 3 cytokines near the N-terminal of the pro-form [136].

2.4.1. IL-36α

The role of IL-36α in cancer has not been well established in comparison to its pro-inflammatory role in the pathogenesis of inflammatory diseases. However, the few studies that have been done suggest a tumor-inhibiting role. IL-36α expression was decreased in poorly differentiated hepatocellular carcinoma (HCC) cells. When expression levels were analyzed in patients low IL-36α expression levels correlated with larger tumor size, poor histological differentiation, advanced tumor stage, and increased vascular invasion. Additionally, low IL-36α expression levels in patients correlated with a decrease in life expectancy. When IL-36α expression was elevated, an increase in intratumoral CD3+ and CD8+ tumor-infiltrating lymphocytes was observed [137]. When IL-36α expression levels were analyzed in colorectal cancer tissue samples, a decrease in expression was correlated with larger tumor size and advanced Classification of Malignant Tumors (TNM) stage. The decrease in expression also correlated with a poor prognosis for patients [138]. A knockdown of IL-36α led to an increase in the growth and metastasis in epithelial ovarian cancer cells [139]. Inversely, when IL-36α was overexpressed, this mechanism could be rescued and a decrease was seen in the growth and metastasis of the ovarian cells [139].

There are no studies showing a pro-tumoral role for IL-36α. The data mentioned above show that IL-36α could be of therapeutic interest. A first step could be determining the in vivo effects of IL-36α in a murine tumor model.

2.4.2. IL-36β

The role of IL-36β in cancer pathology, like IL-36α, has not received considerable attention. There is evidence showing a pro-inflammatory involvement of IL-36β in inflammatory diseases, such as psoriasis, rheumatoid arthritis and Crohn's disease [140]. IL-36β does show an antiviral role and is able to provide protection in the skin against the herpes simplex virus (HSV) by inducing CD8+ cells and IFN-γ-producing CD4+ cells [141]. However, no studies were found that investigated the role of IL-36β in cancer pathology. IL-36β does warrant attention in the cancer field as a recent study has shown that the cytokine inhibits differentiation of keratinocytes [142]. A first interesting step to define the role of IL-36β in cancer would be to identify expression levels in different types of cancer, followed by in vivo murine studies on the specific effects of IL-*36β*.

2.4.3. IL-36γ

Studies on the role of IL-36 in cancer research have mainly been focused on IL-36γ. Endogenous IL-36γ in cancer was witnessed to be predominantly expressed in M1 macrophages, tumor cells and vascular cells in human colon cancer. This pattern of IL-36γ expression is associated with a CD4+ central memory T-cell infiltrate [143]. This shows the involvement of IL-36γ in the immune response in the tumor.

One of the first studies determined that recombinant IL-36γ

stimulates CD8+ T cells, NK cells, and gamma delta T cells. This promoted a type 1 anti-tumor response and created a microenvironment favoring tumor elimination. [144] A different study showed a potential therapeutic role for IL-36γ. When IL-36γ was co-administered with an irradiated B16 melanoma cell vaccine, the efficacy of the vaccination was strongly increased in mice [143,144]. This showed the strong stimulating effect of IL-36γ on CD8+ T cells. CD4+ T cells did not respond as strongly to IL-36γ. Furthermore, when a plasmid expressing IL-36γ was co-administered with doxorubicin, a chemotherapy drug, the metastatic spread of breast cancer was significantly decreased. This was explained by the increase in IFN-γ positive CD4+ and CD8+ T cells and a decrease in immunosuppressive myeloid-derived suppressor cells was registered [145]. In another study using a murine tumor model, IL-36γ was injected intratumorally, resulting in the formation of tertiary lymphoid organs (TLOs). TLOs contain anti-tumoral B cells, DC, NK cells, and T cells. The treatment resulted in a decreased in vivo tumor progression [146]. Considering the majority of research has been done on IL-36γ in inflammatory disease, a potential translational step can be made from its role in inflammatory disease to its role in cancer. However, interspecies variation will need consideration, as human T cells are not activated by IL-36γ, in contrast to murine T cells [147].

2.4.4. IL-36Ra

Although the recognized antagonist of the IL-1RI is called IL-36Ra, its previous name IL-1F5, is still commonly used. It is one of the three antagonists in the IL-1 family. Its role in both cancer and inflammatory diseases has been partly defined. A metastasis gene expression profile study showed that increased expression of IL36Ra correlated with a poor prognosis in patients suffering from colorectal cancer [148]. On top of this, different polymorphisms in the IL-36Ra gene are correlated with a significant increased risk for gastric cancer incidence [149]. Furthermore, the expression of IL-36Ra was associated with intra-tumoral expression of PD-1, PD-L1, and CTLA4. These immune checkpoint molecules can suppress the immune system and are associated with a decrease in anti-tumoral immune responses [143]. One of the reasons IL-36Ra has lost interest as a therapeutic is its low binding affinity. The antagonist has a 100- to 1000-fold lower binding affinity to IL-36R than IL-36γ [150]. This makes it difficult to accomplish therapeutic effects with an IL-36Ra therapeutic or IL-36Ra inhibitor. A possible solution to this would be to modulate the affinity by engineering a therapeutic IL-36Ra analog.

2.5. IL-37

IL-37 is one of the most recently discovered members of the IL-1 family and one of the few members that show anti-inflammatory properties. A possible explanation of the relatively late discovery of the cytokine is the absence of the gene in mice. Like most IL-1 family members, the non-active preform of IL-37 is cleaved by caspase-1 into the active mature form [151,152]. IL-37 has 5 isoforms but only three of them form the characteristic IL-1 family β-trefoil structure. These structural differences are thought to result in only 3 isoforms with biological activity [153–158].

A broad spectrum of cells express IL-37, including natural killer (NK) cells, stimulated B cells, monocytes, skin keratinocytes and epithelial cells. Expression of IL-37 is observed mainly in lymph nodes, thymus, lung, colon, uterus and bone marrow [153–158]. The expression of IL-37 is dependent on an inflammatory environment. Upregulation is dependent on pro-inflammatory cytokines, including IL-18, IFN-γ, IL-1β, TGF-β and TNF-α and other pro-inflammatory stimuli [159–161]. IL-37 was found to be released upon LPS administration in the macrophage RAW model, a common cellular response model, in a dose-dependent fashion [159]. Activated IL-37 interacts with IL-18Rα [151,152,158,162,163].

Considering the anti-inflammatory properties of IL-37, it is unsurprising that the majority of studies have explored the inhibitory effects on the immune environment in the tumor. It was found that low levels of the cytokine correlate with a poor prognosis [164–167]. Additionally, the literature shows that overexpression of IL-37 results, surprisingly, in a decrease in tumor progression and metastasis in cancers including fibrosarcoma, hepatocellular carcinoma, cervical, lung and colon cancer [168–172]. When IL-37 was administered systemically, tumor growth was also inhibited [164,166,168]. There are multiple studies that propose several mechanisms for this anti-tumoral effect (Fig. 6). Firstly, IL-37 transduces its anti-inflammatory properties by binding to the IL-18Ra SIGIRR complex on the surface of peripheral blood mononuclear cells (PBMC), macrophages, and DCs [173–175]. Secondly, activated IL-37 is able to bind cytosolic SMAD-3 [164,176]. This complex is then able to translocate to the nucleus where it inhibits the expression pro-inflammatory genes, such as IL-6 and TNF-α [172,177,178].

The activation of these two pathways results in the activation of PTEN/FOXO/AMPK, STAT-3, MER/DOK(P62) pathways and inhibition of theTAK-1/NF-κB, mTOR/FYN and MAPK pathways in both immune and tumor cells (Fig. 6) [170,179–183].

Some suggest that IL-37 does this by inhibiting STAT3 signaling [164,170,172]. STAT3 is known to increase cell proliferation, invasion and inflammation in the tumor environment. [184] Other studies suggest that the inflammatory suppressive mechanism of IL-37 functions through the inhibition of RAC1 [166]. RAC1 is a protein that is involved in cell growth and movement and is often connected to cancer.

The function of IL-37 in tumor immunity is not solely anti-tumoral, as adverse roles of IL-37 in tumor progression have also been described. High systemic levels of IL-37 in ovarian cancer patients were associated with a poor survival rate [185]. Similarly, IL-37 expression was also elevated with the increase of malignancy in oral squamous cell carcinoma (OSCC). Expression was higher in OSCC with metastasis in the lymph nodes than OSCC without metastasis. This suggests that IL-37 also is able to play a role in the transformation of cells [186].

Overall, the majority of the evidence points towards a more tumor-inhibiting effect for IL-37. Recent studies in murine tumor models do show potential therapeutic effects of IL-37. When transgenic mice, expressing human IL-37, were treated with celecoxib to induce colon carcinogenesis, no tumors were found. This was explained by the decrease observed in IL-6, IL-17, IFN-γ and TNF-α levels [187]. The study showed that IL-37 is able to decrease the inflammatory response in the colon and thereby inhibit the process of carcinogenesis.

2.6. IL-38

IL-38 is the most recently described member of the IL-1 family. The cytokine was discovered in 2001 [7,188]. Its structure shows similar features with both IL-1Rα and IL-36Rα. This led researchers to hypothesize that it might act as an IL-1 receptor antagonist. IL-38 is mainly released by apoptotic and necrotic cells [52]. IL-38 is, like many others in its family, processed into its mature form. It is hypothesized that the cytokine is cleaved by proteases present in the apoptotic cell medium [189]. However, the process behind its maturation is still poorly understood, but it is hypothesized to function through apoptotic mechanisms [190]. Research determined that IL-38 was able to inhibit the production of the pro-inflammatory cytokines IL-22 and IL-17 from stimulated memory T-lymphocytes in a dose-dependent manner. This response was similar to that of IL-36Ra. The immobilized extracellular domains of IL-36R were screened and the test showed that IL-38 bound to IL-36R together with IL-36Ra [191].

Since IL-38 is a relatively new member to the family, only a small number of studies have investigated its potential tumor-promoting role. One of the first studies into this field identified a correlation between IL-38 expression and high tumor grades, size and extent of the main tumor, number of metastasis, advanced stage, and the severity vessel invasion in primary lung adenocarcinomas. Patients with a high IL-38 expression also showed a decrease in disease-free survival and overall survival after

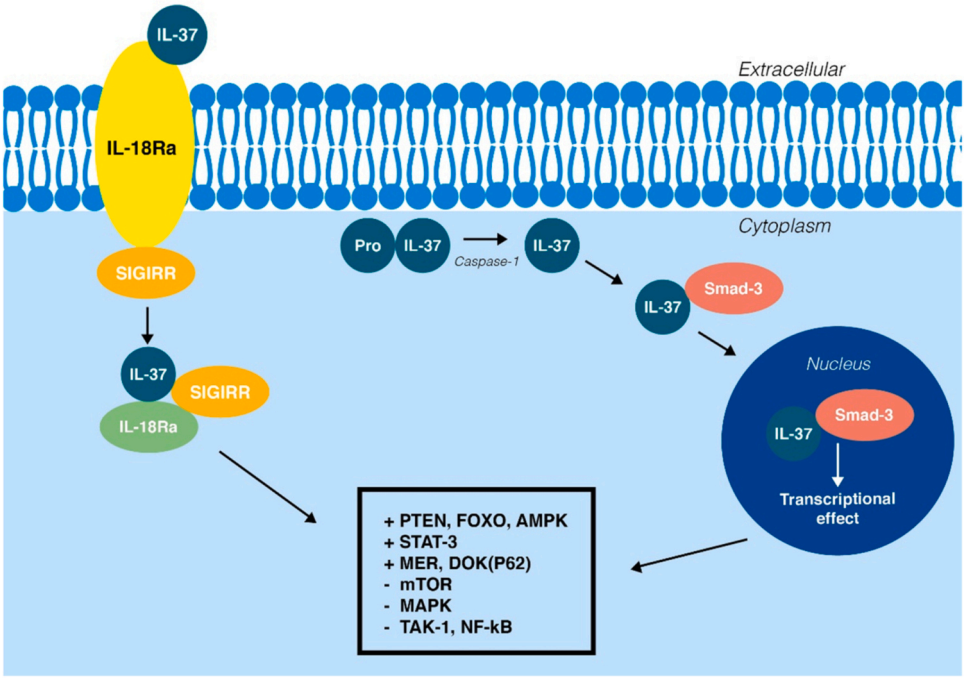

Fig. 6. Graphical representation showing the involvement of IL-37 (light green) in cancer. IL-37 is able to activate the PTEN/FOXO/AMPK, STAT-3, MER/DOK(P62) pathways and inhibit theTAK-1/NF-κB, mTOR/FYN and MAPK pathways in both immune and tumor cells through the IL-18Ra (dark green)/SIGIRR (orange) and Smad3 (pink) pathway. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

surgery [192].

In contrast, other studies have determined tumor-inhibiting effects of the cytokine. One study showed that IL-38 was highly expressed in the tissue surrounding non-small cell lung tumors, but barely in the tumor itself. The decrease in expression in tumor tissue correlated with the stage and degree of differentiation of the cancer. IL-38 expression levels showed to be an independent prognostic indicator of disease-free survival and overall survival of patients suffering from non-small cell lung cancer. IL-38 suppressed β-catenin, thereby inhibiting cell migration, invasion, proliferation and colony formation. In the same study, mouse models showed a decrease in non-small cell lung tumors and an increased sensitivity to chemotherapy when treated with IL-38 [193]. A possible explanation for these conflicting results might be the type of IL-38 released by cells. Apoptotic cells release IL-38 to limit the inflammatory macrophage response. This version of IL-38 is, primary to release, N-terminally processed. The processed IL-38 is able to induce IL-6 production in macrophages and the pre-processed molecule decreased the production by inhibiting the JNK/AP1 pathway downstream of IL-1RAPL1 [194].

As IL-38's main described function is Th17 inhibition, more attention has been paid to diseases where Th17 play an important role, such as psoriasis, psoriatic arthritis and ankylosing spondylitis [189,195,196]. Other studies have been performed on the role of IL-38 in a wide variety of inflammatory disease models, ranging from asthma to coronary artery disease [140,197–204]. The potential application of IL-38 as a medicinal product against cancer warrants more attention, as Th17 also plays an important role in cancer [205].

Further studies into the role of posttranslational modifications of IL-38 are clearly required to obtain a more complete understanding of the IL-38N-terminally processed variant that is released by apoptotic cells. Such studies should not only determine if this is the only post-translational modification of IL-38, but also to show how different forms of IL-38 may influence immune populations.

3. Discussion

The IL-1 family is an interesting and varied group of cytokines and receptor antagonists. The functions of the cytokines range from pro- to anti-tumorogenic and pro- to anti-inflammatory (Table 2). The family

Table 2
Summary of the IL-1 family cytokines, their main suggested function, their role in cancer and potential therapeutic application in cancer.

Cytokine	Main suggested function	Anti-/pro-tumoral[a]	Potential therapeutic application[b]
IL-1β	Pro-inflammatory	pro-tumoral (chronic release), anti-tumoral (short treatment)	Administer or Neutralize
IL-1Ra	Anti-inflammatory	anti-tumoral	Administer
IL-18	Pro-inflammatory	Anti-tumoral by inducing a type 1 immune response	Administer
IL-36γ	Pro-inflammatory	Anti-tumoral	Administer
IL-37	Anti-inflammatory	pro-tumoral (chronic release), anti-tumoral (short treatment)	Administer
IL-1α	Pro-inflammatory	pro-tumoral (chronic release)	Neutralize
IL-33	Pro-inflammatory	pro-tumoral (chronic release)	Neutralize
IL-36Ra	Anti-inflammatory	pro-tumoral (chronic release)	Low receptor affinity
IL-36α	Pro-inflammatory	Anti-tumoral	Further research required
IL-36β	Pro-inflammatory	Unknown	Further research required
IL-38	Anti-inflammatory	pro-tumoral (chronic release)	Further research required

[a] Sustained inflammation favors tumor progression while acute inflammation favor tumor inhibition.

[b] The administration vs. neutralization of the cytokine would lead to therapeutic effects.

has three receptor antagonists (IL-1Ra, IL-36Ra and IL-38). Despite their low sequence similarity, a feature that all members of the IL-1 family have in common is their distinct β-trefoil fold core composed of anti-parallel β-strands. This is also the main structural feature that allows for binding with the IL-1RI and IL-1Rrp2 receptor.

Care should be taken when an upregulation of these cytokines in cancer is observed. This leads, more than often, to the protein to be qualified as tumor-promoting. This type of conclusion may be premature. The upregulation of a cytokine may indeed be tumor-promoting, but equally it may represent a response from the immune system to the tumor, should it be successful or not in addressing tumor progression.

The terms pro-inflammatory and tumor-inhibiting are frequently used in the literature when describing cytokine function and in particular the IL-1 family. Regularly, the conclusion is made that if a molecule is pro-inflammatory that it can be appointed as tumor-inhibiting. Indeed an increase in immune response and inflammation can lead to the regression of a tumor. However, this is not always the case. An example of this is IL-33. As described earlier, IL-33 is a pro-inflammatory cytokine, but this does not mean the molecule is anti-tumoral. Although there is evidence suggesting an anti-tumoral role of IL-33, there is much stronger case for the tumor-promoting effects of IL-33, the time and the place playing a pivotal role in the functional outcome of the cytokines presence. This shows that sustained inflammation favors tumor progression while acute inflammation favor tumor inhibition.

The IL-1 family members possess a real therapeutic potential. As in the case of IL-1β, there are ongoing clinical trial to assess the effects an anti-IL-1β treatment in cancer [206–209]. Recombinant IL-1β was also assessed in a clinical trial [66]. The idea that IL-1β could serve as a therapeutic was abandoned because of severe side effects associated with therapeutically active doses. High therapeutic doses are often necessary due to the relatively short systemic half-life of cytokines. However, the biologic activity of the IL-1 family described in this paper renders them of therapeutic interest and there are multiple bioengineering solutions to address these problems.

Another potential solution to the short half-life of cytokines may be the use of nanoparticles. Nanoparticles offer a solution to the short half-life problem, but also may offer controlled release of encapsulated drugs [210–213]. An obstacle to this approach is that cytokines are large and fragile molecules to encapsulate [214]. Nanoparticles can be designed to target the tumor but also draining lymph nodes. This directs the immunostimulatory effects of the cytokine and avoids a generalized inflammatory response [215]. Furthermore, microparticles could also offer benefit for the sustained delivery of cytokines. Previously they have been used to form a subcutaneous depot at the site of injection from which the cytokine can be slowly released [216–218].

Another potential solution, that combines local delivery and on-site activation, first arose in the 90 s [219,220]. A tumor-targeting antibody was fused to a constitutively active TNF-α molecule, a pro-inflammatory cytokine from the TNF superfamily. This way TNF-α accumulates at the tumor site while systemic adverse effects can be decreased [220]. Adverse effects can potentially be further decreased by a tumor-mediated activation of the cytokine. The fusion of the cytokine to the vectoring antibody can be performed to attenuate the cytokine. Once the construct reaches the tumor site, enzymes, which are secreted by the tumor, can then be used to cleave the fusion protein and release fully active cytokine [221]. This cleavage should be done by enzymes that have a low systemic concentration or activity to prevent release the cytokine systemically, such as matrix metallopeptidases (MMPs). The inactive nature of precursor IL-1 family members renders them ideal candidates for application in a cytokine attenuated delivery system. However, caution should be used when using endogenous MMPs as activators to release the cytokine from the antibody. For instance, IL-38 and IL-1β possess cleavage sites for the MMP enzymes [222,223]. This could potentially affect the functionality of the released cytokine.

Overall, the role of cytokines in cancer pathology is more than often a two-faced story. *Both tumor-promoting and -inhibiting effects can be found, depending on the duration of exposure (acute* vs. *chronic), time and place the molecule is studied and its context.* In conclusion, this exciting family of proteins shows a wide array of effects and thereby offers potential therapeutic options.

Conflict of Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. All co-authors have read the manuscript and agree with its content. We certify the submission is an original work and is not under review elsewhere. The authors declare no conflict of interest.

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