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REVIEW ARTICLE

Interleukin-1 beta signaling in cancer: A double-edged sword in inflammation and tumorigenesis

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Abstract

Interleukin-1 beta (IL-1β) is a central pro-inflammatory cytokine with critical roles in immune regulation, inflammation, and tumor biology. Synthesized as an inactive precursor and activated through inflammasome-mediated cleavage, IL-1β signals via the IL-1 receptor to orchestrate immune responses. While essential for host defense, sustained IL-1β activity in the tumor microenvironment promotes angiogenesis, metastasis, epithelial–mesenchymal transition, and immune suppression, thereby facilitating the progression of cancers such as breast, lung, pancreatic, and colorectal. Conversely, IL-1β can enhance anti-tumor immunity by driving dendritic cell maturation, T-cell priming, and pyroptosis, thereby contributing to beneficial immune surveillance in certain hematologic malignancies. This dual role presents both challenges and opportunities for therapeutic intervention. Clinical blockade of IL-1β with agents such as anakinra, canakinumab, and rilonacept has shown promise, notably in the CANTOS trial, where IL-1β inhibition was associated with a reduction in lung cancer incidence. However, outcomes in colorectal and pancreatic cancer remain variable. The potential for immune suppression, combined with the absence of predictive biomarkers, underscores the need for precision-based strategies. Emerging approaches, including serum and tissue IL-1β profiling, analysis of inflammasome components, liquid biopsy, spatial transcriptomics, and single-cell technologies, may enable context-specific modulation. This review synthesizes current understanding of IL-1β's paradoxical functions in cancer, evaluates therapeutic strategies targeting its signaling axis, and highlights future directions for integrating IL-1β modulation into precision oncology.

Keywords: Interleukin-1 beta; Cancer; Inflammation; Tumor microenvironment; Cytokines; Immunotherapy; Pyroptosis

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1. Introduction

Interleukin-1 beta (IL-1β) is a potent pro-inflammatory cytokine that plays a critical role in orchestrating innate immune responses, host defense, and the regulation of inflammation. It is primarily produced by activated monocytes, macrophages, dendritic cells, and other innate immune cells in response to exposure to microbial products, tissue damage signals, or tumor-derived cues. Unlike many cytokines, IL-1β is synthesized as an inactive precursor protein (pro-IL-1β) that requires proteolytic cleavage by caspase-1

within the inflammasome complex, most notably NLR family pyrin domain-containing 3 (NLRP3), for activation and secretion.[1] Upon release, IL-1β exerts its biological effects through binding to the interleukin-1 receptor type I (IL-1R1), triggering a signaling cascade that involves recruitment of the adaptor protein myeloid differentiation primary response protein 88 (MyD88) and activation of downstream pathways such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK).[2] These pathways induce the transcription of a wide variety of pro-inflammatory genes, including cytokines, chemokines, adhesion molecules, and matrix-degrading enzymes.

The persistent activation of IL-1β signaling is a defining feature of chronic inflammation, a condition that has long been linked to increased cancer risk and progression. Chronic inflammation contributes to tumorigenesis by facilitating genomic instability, promoting cell proliferation, inhibiting apoptosis, supporting angiogenesis, and enabling invasion and metastasis.[3] IL-1β has been shown to shape the tumor microenvironment (TME) by recruiting immunosuppressive myeloid cells, enhancing the production of matrix metalloproteinases (MMPs), and stimulating the secretion of vascular endothelial growth factor (VEGF), thereby supporting both tumor growth and neovascularization.[4-6] Its expression is elevated in a wide range of malignancies, including, but not limited to, breast, colorectal, pancreatic, melanoma, and lung cancers.[7-9]

However, the role of IL-1β in cancer is far from unidimensional. Emerging evidence reveals a paradoxical duality: While IL-1β frequently facilitates tumor progression, it can also initiate or support anti-tumor immune responses under specific circumstances. IL-1β has been implicated in promoting the activation and maturation of dendritic cells, enhancing antigen presentation, and potentiating $CD4^+$ and $CD8^+$ T cell responses.[10] Furthermore, IL-1β can contribute to pyroptotic cell death, a highly inflammatory form of programmed cell death, which can make tumor cells more visible to the immune system and stimulate immunogenicity.[11,12] These tumor-suppressive effects are often context-dependent, varying with tumor type, immune cell composition, cytokine milieu, and disease stage. Moreover, emerging evidence highlights epigenetic regulation (DNA methylation, histone acetylation, and microRNAs, such as miR-223) as well as metabolic regulation (glycolysis and hypoxia-inducible factor 1-alpha stabilization) as essential determinants of IL-1β transcription and secretion in cancer. These layers of regulation, together with cytokine cross-talk (e.g., IL-6, IL-18, and tumor necrosis factor alpha), critically shape IL-1β activity in the TME. Recent studies further strengthen this dual role, demonstrating that $IL\text{-}1\beta^+$ tumor-associated macrophages (TAMs) are the primary source of pathogenic IL-1β in pancreatic cancer, fueling stromal inflammation and therapy resistance.[86] It was also demonstrated that IL-1β promotes the growth and metastasis of esophageal squamous cell carcinoma by activating the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)-forkhead box protein O3a (FOXO3A) signaling pathway, thereby linking IL-1β to epithelial–mesenchymal transition (EMT) and autophagy.[87] Recently, IL-1β has been comprehensively reviewed as both a friend and a foe in gastrointestinal cancers, underscoring its context-dependent functions.[88]

This dichotomy renders IL-1β both an attractive and a challenging target in cancer therapy. Several IL-1β inhibitors, such as anakinra (a recombinant IL-1 receptor antagonist), canakinumab (a monoclonal anti-IL-1β antibody), and rilonacept (a soluble decoy receptor fusion protein), have been developed and tested in inflammatory and oncologic contexts.[13] Notably, findings from the CANTOS trial demonstrated a reduced incidence and mortality of lung cancer in patients receiving IL-1β blockade, sparking renewed interest in its role in cancer control.[14] However, therapeutic inhibition of IL-1β also raises concerns about increased infection risk and potential dampening of anti-tumor immunity.

In this review, the multifaceted role of IL-1β in cancer biology was comprehensively examined. The cellular and molecular mechanisms by which IL-1β promotes or suppresses tumor development were explored, emphasizing both its pro-tumorigenic contributions to chronic inflammation and immune evasion, as well as its anti-tumor capabilities through immune activation and immunogenic cell death. In addition, current therapeutic strategies targeting IL-1β were critically assessed, and ongoing clinical trials and future directions for optimizing its modulation were reviewed. By illuminating the dual nature of IL-1β signaling in the TME, this review provides guidance for its rational integration into cancer immunotherapy.

This review differs from previous syntheses by incorporating the most recent evidence, including studies that identify TAMs as dominant IL-1β producers, link IL-1β to PI3K/AKT-FOXO3A signaling in esophageal cancer, and review its context-dependent roles in gastrointestinal tumors. In addition, a comprehensive evaluation of both tumor-promoting and tumor-suppressive functions is presented, with a focus on translational aspects, including biomarkers, trial outcomes, and emerging precision strategies. This updated synthesis aims to bridge molecular mechanisms with clinical and therapeutic perspectives.

2. Methodology

A structured literature review was conducted using PubMed, Scopus, and Web of Science (2000–2024). Keywords included "IL-1β," "cancer," "inflammasome," "pyroptosis," "immunotherapy," and "tumor microenvironment." The inclusion criteria were peer-reviewed studies, studies in English, and those relevant to cancer biology, immunology, or therapy. The exclusion criteria included non-oncology IL-1β studies, preprints, and non-peer-reviewed sources. Reference lists of included articles were also screened to identify additional studies.

3. IL-1β biology and signaling pathways

The biological activity of IL-1β is tightly regulated at both transcriptional and post-translational levels, reflecting its potent pro-inflammatory nature and its capacity to influence pathological outcomes such as tumorigenesis. Unlike many secreted cytokines, IL-1β lacks a signal peptide for conventional secretion and is synthesized as an inactive precursor, pro-IL-1β, which requires proteolytic cleavage for activation and release.[15]

The synthesis of pro-IL-1β is primarily induced through pattern recognition receptor signaling, such as toll-like receptors (TLRs) or NOD-like receptors (NLRs), which activate NF-κB and drive *IL1B* gene transcription.[16] However, the mere presence of pro-IL-1β is insufficient for its biological function. The activation requires a second signal: The assembly of inflammasomes, multiprotein complexes that serve as platforms for caspase-1 activation. Among them, the NLRP3 inflammasome is the most extensively studied in the context of cancer and sterile inflammation.[17] Upon activation, caspase-1 cleaves pro-IL-1β into its mature, biologically active 17-kDa form, which is then secreted through unconventional pathways involving gasdermin-D pore formation or secretory lysosomes.[18-20]

Once secreted, IL-1β binds to IL-1R1, which requires co-receptor IL-1 receptor accessory protein (IL-1RAcP) for signal transduction. This leads to the recruitment of the adaptor molecule MyD88, a universal adapter for the IL-1 and TLR families.[21] MyD88 subsequently recruits IL-1 receptor-associated kinases (IRAKs), primarily IRAK4 and IRAK1, and the E3 ubiquitin ligase tumor necrosis factor receptor-associated factor 6. These molecules initiate downstream signaling that culminates in the activation of NF-κB and MAPKs, including extracellular signal-regulated kinase, c-Jun N-terminal kinase, and p38[22] (Figure 1). These transcriptional programs induce the expression of inflammatory mediators, adhesion molecules, and other cytokines, thereby amplifying the inflammatory response within the TME.[23]

To prevent unchecked inflammation, IL-1β signaling is modulated by several endogenous feedback mechanisms. One major negative regulator is the IL-1 receptor antagonist (IL-1Ra), which binds IL-1R1 without eliciting a signal, competitively inhibiting IL-1β activity.[24] Soluble IL-1 receptors (sIL-1R1 and sIL-1R2) can also bind IL-1β extracellularly, reducing ligand availability. Intracellularly, ubiquitination and degradation of signaling intermediates (e.g., IRAKs and tumor necrosis factor receptor-associated factor 6) contribute to signal termination.[25] In addition, the transcriptional induction of A20 (TNFα-induced protein 3), a zinc finger protein with deubiquitinase activity, serves as a critical negative regulator of NF-κB signaling.[26] Emerging evidence also points to the role of non-coding RNAs, such as microRNAs (e.g., miR-146a and miR-223), in dampening IL-1β-mediated signaling by targeting key components of the IL-1 pathway.[27]

Together, this tightly coordinated sequence, from pro-IL-1β induction and inflammasome activation to receptor-mediated signaling and regulatory checkpoints, ensures that IL-1β acts as a dynamic modulator of inflammation, with substantial implications for cancer progression and immune control.

4. Tumor-promoting functions of IL-1β

While IL-1β is central to the orchestration of host defense and immune activation, it also plays a significant pro-tumorigenic role across a range of malignancies. By shaping the TME, influencing stromal cell behavior, and modulating angiogenesis and metastasis, IL-1β promotes cancer progression through multiple, interconnected mechanisms (Figure 2).

4.1. Angiogenesis and metastasis

IL-1β is a potent driver of angiogenesis, acting directly and indirectly to stimulate endothelial cell proliferation and vascular remodeling. It induces the expression of VEGF, basic fibroblast growth factor, and IL-8, all of which support the process of neovascularization.[28] In addition, IL-1β promotes the expression of MMPs, particularly MMP-9, facilitating extracellular matrix degradation, tumor invasion, and dissemination.[29] Experimental models have demonstrated that IL-1β enhances metastatic spread in breast and melanoma models, often through a VEGF- and MMP-dependent axis.[30] In colorectal cancer, elevated IL-1β levels correlate with increased vascular density and hepatic metastases.[31] In pancreatic ductal adenocarcinoma, IL-1β$^+$ TAMs have been pinpointed as drivers of pathological angiogenesis and metastatic inflammation.[86]

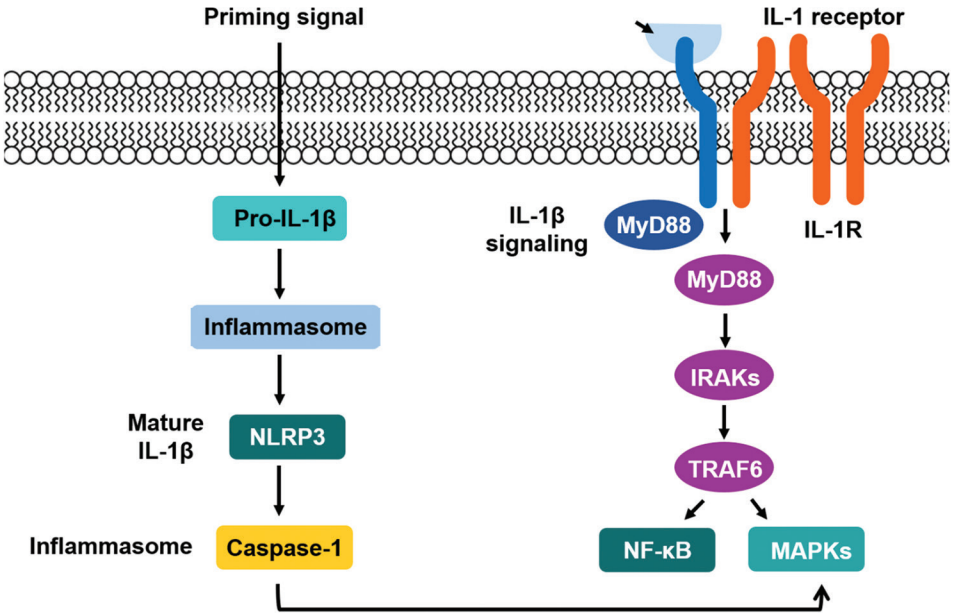

Figure 1. Schematic overview of interleukin-1 beta (IL-1β) maturation and signaling cascade. This diagram illustrates the two-step process of IL-1β activation and downstream signaling. The priming signal, typically mediated by toll-like receptors (TLRs), activates nuclear factor kappa B (NF-κB) and promotes pro-IL-1β transcription. A secondary activation signal induces NLRP3 inflammasome assembly and caspase-1-mediated cleavage of pro-IL-1β into its active form. Mature IL-1β binds to interleukin-1 receptor type I (IL-1R1) and, with IL-1 receptor accessory protein (IL-1RAcP), initiates myeloid differentiation primary response protein 88 (MyD88)-dependent signaling leading to IL-1 receptor-associated kinase (IRAK) and tumor necrosis factor receptor-associated factor 6 (TRAF6) activation, culminating in downstream NF-κB and mitogen-activated protein kinase (MAPK) pathway activation. Image created by the author using Adobe Illustrator 2024.

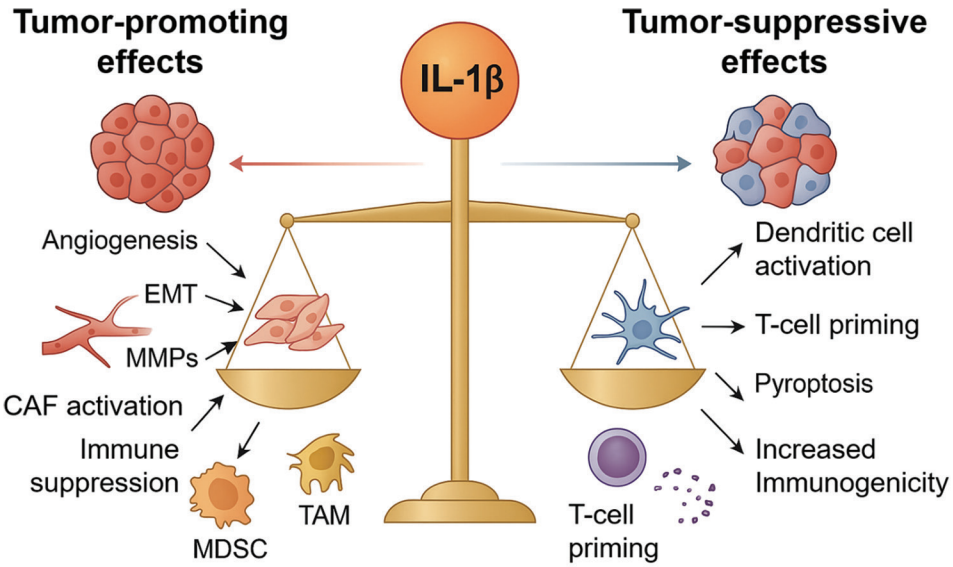

Figure 2. Dual role of interleukin-1 beta (IL-1β) in cancer. The diagram illustrates the paradoxical functions of IL-1β in tumor biology. On the left, IL-1β promotes tumor progression through angiogenesis, immune suppression (via myeloid-derived suppressor cells [MDSCs] and tumor-associated macrophages [TAM]), epithelial–mesenchymal transition (EMT), and activation of cancer-associated fibroblasts (CAFs). On the right, IL-1β enhances anti-tumor immunity by promoting dendritic cell maturation, T-cell priming, and pyroptotic cell death, contributing to increased tumor immunogenicity. Image created by the author using Adobe Illustrator 2024.
Abbreviation: MMP: Matrix metalloproteinase.

4.2. Immune suppression in the TME

IL-1β contributes to immune evasion by fostering an immunosuppressive TME. It supports the expansion and recruitment of myeloid-derived suppressor cells and TAMs, both of which inhibit cytotoxic T lymphocyte activity.[32] It also induces expression of programmed death-ligand 1 on both tumor and stromal cells, indirectly promoting immune checkpoint resistance.[33] Furthermore, IL-1β enhances the production of prostaglandin E2, a key mediator of immune suppression that impairs natural killer cell cytotoxicity and antigen presentation by dendritic cells.[34] This immunosuppressive network is particularly evident in pancreatic, lung, and glioblastoma tumors with high IL-1β expression.[35]

4.3. EMT

IL-1β plays a central role in initiating and sustaining EMT, a process by which epithelial tumor cells acquire mesenchymal features, enhancing their motility and invasiveness. IL-1β activates the NF-κB and MAPK pathways, which induce the transcription of EMT transcription factors such as Snail family zinc finger 1, Snail family transcriptional repressor 2, and zinc finger E-box binding homeobox 1.[36] Moreover, IL-1β induces expression of mesenchymal markers (e.g., vimentin and N-cadherin) while suppressing epithelial markers such as E-cadherin.[37] In non-small cell lung cancer (NSCLC), IL-1β-induced EMT is associated with increased metastatic potential and poor response to therapy.[38] Recently, it was demonstrated that IL-1β activates PI3K/AKT-FOXO3A signaling in esophageal squamous cell carcinoma, directly linking IL-1β to EMT progression, autophagy suppression, and metastasis.[87]

4.4. Cancer-associated fibroblast activation

IL-1β is a critical mediator in the reprogramming of resident fibroblasts into cancer-associated fibroblasts (CAFs), which constitute a major stromal component of the TME. It indirectly upregulates CAF markers such as α-smooth muscle actin and fibroblast activation protein, primarily through IL-6 and transforming growth factor beta paracrine signaling, enhancing extracellular matrix remodeling and tumor support.[39] IL-1β-activated CAFs secrete pro-tumorigenic cytokines, including IL-6 and chemokine (C-X-C motif) ligand 12, facilitating tumor growth and immune evasion.[40] In breast cancer, IL-1β-driven CAF activation correlates with increased tumor stiffness and invasiveness.[41] Recent single-cell and spatial analyses suggest that IL-1β drives specific CAF subsets with distinct stromal remodeling signatures, suggesting potential biomarkers for stratification.[82]

4.5. Clinical correlations in solid tumors

Clinically, elevated IL-1β levels in serum or tumor biopsies are associated with poor prognosis in multiple solid tumors. In breast cancer, *IL1B* expression is linked to the triple-negative subtype and increased metastasis.[42] In colorectal cancer, high IL-1β levels correlate with tumor stage, lymph node involvement, and systemic inflammation markers such as C-reactive protein.[43] In NSCLC, IL-1β overexpression is associated with shorter overall survival and resistance to immune checkpoint inhibitors.[44] Importantly, pharmacological inhibition of IL-1β has demonstrated survival benefit in clinical trials, as exemplified by the CANTOS study's exploratory findings in lung cancer patients.[45] Notably, serum IL-1β levels do not always correlate with tumor tissue expression. Tissue IL-1β and inflammasome activity markers (NLRP3 and caspase-1) provide stronger prognostic signals.[77] Liquid biopsy approaches that measure IL-1β-related signatures are emerging as non-invasive tools for monitoring.[78] These clinical observations underscore the relevance of IL-1β as both a biomarker and therapeutic target in oncology.

5. Tumor-suppressive and immunostimulatory roles of IL-1β

Although IL-1β is widely associated with tumor promotion, growing evidence suggests that it can also exert potent tumor-suppressive effects, particularly in immunologically active TMEs. Under specific cellular and molecular contexts, IL-1β facilitates anti-tumor immunity by enhancing dendritic cell maturation, promoting T-cell priming, and supporting immunogenic cell death pathways. Moreover, in select hematologic malignancies, IL-1β exhibits complex and occasionally protective roles that are highly dependent on disease subtype and immune status (Figure 2).

5.1. IL-1β and anti-tumor immunity

IL-1β plays a pivotal role in priming and amplifying adaptive immune responses against tumors. It promotes the activation and maturation of dendritic cells, enhancing their capacity to present tumor antigens and migrate to lymph nodes for T-cell stimulation.[46] IL-1β increases the expression of co-stimulatory molecules such as CD80, CD86, and major histocompatibility complex Class II on dendritic cells, thereby facilitating the priming of naïve $CD4^+$ and $CD8^+$ T cells.[47] Furthermore, IL-1β boosts the survival and expansion of antigen-specific T cells by increasing IL-2 production and upregulating the expression of IL-2 receptor components (CD25).[48] In pre-clinical models, intratumoral delivery of IL-1β has been shown to enhance $CD8^+$ T-cell infiltration and effector

function, leading to tumor regression in melanoma and sarcoma models.[49] These findings highlight the importance of spatiotemporal control in IL-1β signaling to unleash its immunostimulatory potential.

5.2. Role in pyroptosis and immunogenic cell death

Another tumor-suppressive function of IL-1β involves its role in pyroptosis, a form of caspase-1-dependent programmed cell death characterized by cellular swelling, membrane rupture, and the robust release of inflammatory mediators. Pyroptosis not only limits tumor cell viability but also enhances anti-tumor immunity by releasing damage-associated molecular patterns (DAMPs) and cytokines, including IL-1β itself.[50] Gasdermin D, the executor of pyroptosis, forms pores in the plasma membrane, allowing IL-1β to exit the cell and amplify local inflammation.[51] In tumor models, the induction of pyroptosis in cancer cells, either genetically or via inflammasome activation, leads to increased antigen presentation and effector T-cell responses.[52] Furthermore, pyroptosis-associated IL-1β release has been shown to boost the efficacy of immune checkpoint inhibitors by enhancing the immunogenicity of the TME.[53] Thus, IL-1β serves as both a product and a driver of immunogenic cell death that can synergize with immunotherapy.

In colorectal cancer models, IL-1β has also been implicated in enhancing anti-tumor immunity when coupled with STING activation. Pre-clinical studies show that STING agonists induce IL-1β production in dendritic cells and TAMs, which synergize to promote T-cell priming and effector function. This highlights how IL-1β, often viewed as a tumor-promoting factor, can instead act as a co-stimulatory mediator in immunogenic tumor settings.[89,90]

5.3. Context-dependent effects in hematologic malignancies

In hematologic cancers, the role of IL-1β is highly nuanced and context-dependent. In some myeloid malignancies, such as acute myeloid leukemia, IL-1β can promote leukemogenesis by sustaining an inflammatory niche that supports leukemic stem cells.[54] However, in lymphoid malignancies, including specific subtypes of non-Hodgkin lymphoma and chronic lymphocytic leukemia, IL-1β may exert anti-tumor effects by enhancing T helper 1-type immune responses and promoting cytotoxic lymphocyte activation.[55] In addition, IL-1β has been implicated in promoting graft-versus-leukemia effects in the context of allogeneic hematopoietic stem cell transplantation, where it facilitates donor T cell-mediated clearance of residual leukemia cells without exacerbating graft-versus-host disease.[56] These divergent roles underscore the importance of disease-specific context, immune composition, and treatment setting in shaping IL-1β's functional outcome in hematologic malignancies.

In summary, IL-1β is not solely a pro-tumorigenic agent. When appropriately activated or localized, it can act as a potent immunostimulatory cytokine that promotes tumor clearance through T-cell activation, induction of pyroptosis, and modulation of both innate and adaptive immune responses. These findings highlight the therapeutic potential of strategies that harness IL-1β's tumor-suppressive functions while mitigating its pathological inflammation.

6. Therapeutic targeting of IL-1β

Given the prominent role of IL-1β in cancer-related inflammation and immune modulation, pharmacological strategies targeting its inhibition have gained momentum in oncology. Several IL-1 targeted therapies, initially developed for autoinflammatory diseases, are now being repurposed or clinically evaluated for their potential anti-tumor effects. Among them, anakinra, canakinumab, and rilonacept are the most advanced agents with established safety profiles (Table 1).

6.1. IL-1β blockers: Anakinra, canakinumab, and rilonacept

Anakinra is a recombinant, non-glycosylated form of the human IL-1Ra that competitively inhibits the binding of IL-1β (and IL-1α) to IL-1R1.[57] It is a Food and Drug Administration-approved drug for rheumatoid arthritis and cryopyrin-associated periodic syndromes. It is now being investigated for its capacity to mitigate tumor-promoting inflammation, especially in pancreatic and breast cancers.[58]

Canakinumab, a human monoclonal antibody that neutralizes IL-1β with high affinity, prevents receptor engagement and signaling. Its long half-life and specificity have supported evaluation in cardiovascular and oncology settings.[59]

Rilonacept is a soluble decoy receptor (IL-1R1/IL-1RAcP–Fc) that sequesters IL-1β and IL-1α, preventing receptor binding. Although less explored in cancer, it may benefit malignancies with systemic inflammation.[60]

6.2. Clinical trials in cancer: Insights from the CANTOS trial

The most significant clinical evidence linking IL-1β blockade to cancer prevention and control stems from the CANTOS trial, a large-scale randomized trial originally designed to assess cardiovascular outcomes in patients with atherosclerosis.[61] Unexpectedly, secondary analyses

revealed that patients receiving canakinumab (especially at the 300 mg dose) had significantly lower incidence and mortality of lung cancer compared to placebo.[62] This finding suggested that chronic IL-1β inhibition may reduce cancer risk and progression, particularly in inflammation-driven malignancies. However, IL-1β inhibition has not been universally effective. In colorectal cancer and pancreatic ductal adenocarcinoma, clinical trials have failed to replicate the lung cancer survival benefits.[72] These negative trials emphasize the tumor-type specificity of IL-1β modulation and the need for predictive biomarkers. Furthermore, long-term follow-up of CANTOS patients has shown persistent survival benefits in lung cancer but limited evidence in other tumor contexts.[61]

Following these results, multiple clinical trials were initiated to test canakinumab and anakinra in various cancers, including NSCLC, triple-negative breast cancer, and pancreatic ductal adenocarcinoma.[63-65] Preliminary findings show that IL-1β blockade may improve progression-free survival and enhance responsiveness to immune checkpoint inhibitors in certain tumor types (Table 2).

6.3. Risks of long-term IL-1β inhibition

Despite its therapeutic promise, chronic inhibition of IL-1β carries risks, primarily due to its essential role in host defense and immunity. IL-1β is crucial for effective responses to bacterial and fungal infections; thus, its blockade may predispose patients to opportunistic infections, including sepsis and pneumonia.[66] In addition, IL-1β may support certain aspects of anti-tumor immunity, such that broad suppression could dampen beneficial immune responses, particularly in tumors with pre-existing immune infiltration.[67] The risk-benefit ratio may vary depending on cancer type, stage, and immune status, underscoring the need for patient stratification.

6.4. Combination therapies with checkpoint inhibitors or chemotherapy

To enhance therapeutic efficacy while mitigating risks, combination strategies involving IL-1β inhibitors and other anticancer agents are under active investigation. IL-1β blockade has been shown to remodel the immunosuppressive TME, thereby sensitizing tumors to immune checkpoint blockade (e.g., anti-programmed cell death protein 1/programmed death-ligand 1).[68] In pre-clinical models, anakinra or canakinumab, when combined with anti-programmed cell death protein 1 therapy, enhanced $CD8^+$ T-cell responses and tumor rejection.[69] Similarly, IL-1β inhibition may reduce systemic inflammation and cachexia, improving patient

Table 1. Clinical landscape of interleukin-1 beta blockade in cancer therapy

Drug	Mechanism of action	Approved indications	Cancer trials	Dosing/Half-life	Patient selection	Cost considerations	Benefits/Limitations
Anakinra	Interleukin-1 receptor type I (IL-1R) antagonist	Rheumatoid arthritis, cryopyrin-associated periodic syndrome (CAPS)	Non-small cell lung cancer (NSCLC), breast, pancreatic (ongoing)	Daily subcutaneous injection; short half-life (~4–6 h *in vivo*)	Patients with inflammation-driven tumors	Relatively low	Broad anti-inflammatory effect, but infection risk
Canakinumab	Anti-interleukin-1 beta (IL-1β) monoclonal antibody	CAPS	CANTOS, NSCLC, breast, colorectal	Monthly subcutaneous injection; long half-life (~21–28 days *in vivo*)	High C-reactive protein/ IL-1β-high patients	Very high cost	Strongest clinical data (lung), but mixed results in colorectal cancer/ pancreatic ductal adenocarcinoma
Rilonacept	IL-1 trap (IL-1R1+IL-1 receptor accessory protein–Fc)	CAPS	Limited (pancreatic pilot trials)	Weekly injection; intermediate half-life (~6–8 days *in vivo*)	Patients with systemic inflammation	Moderate	Safe but limited oncology data

Table 2. Selected ongoing clinical trials targeting interleukin-1 beta in cancer (as of 2024)

Agent	Trial phase	Cancer type	Primary endpoint	National clinical trial number
Canakinumab	Phase III	Non-small cell lung cancer	Overall survival	NCT03447769
Anakinra	Phase II	Pancreatic cancer	Progression-free survival	NCT04940286
Canakinumab+spartalizumab	Phase I/II	Solid tumors (basket)	Safety, objective response rate	NCT02900664
Rilonacept	Phase I	Pancreatic pilot	Safety/tolerability	NCT03798626

tolerance to cytotoxic chemotherapy.[70] These synergistic effects have motivated ongoing trials evaluating IL-1β inhibitors in combination with checkpoint inhibitors or chemotherapeutic regimens in NSCLC, colorectal, and ovarian cancers.

In summary, therapeutic targeting of IL-1β offers a promising avenue in cancer management. While monotherapy may benefit subsets of patients, the future of IL-1β blockade likely lies in rational combination approaches that exploit its immunomodulatory potential without compromising host defense.

A summary of key IL-1β-targeting agents currently explored in oncology is presented in Table 1. The table includes drug mechanisms, approved indications, cancer-related clinical trials, and a brief overview of each agent's therapeutic advantages and limitations.

7. Challenges and controversies

Despite the growing interest in targeting IL-1β for cancer therapy, several challenges and unresolved controversies remain. These include the context-dependent nature of IL-1β function, contradictory clinical data, and the lack of robust predictive biomarkers to guide patient selection. Epigenetic regulation (histone acetylation, miRNAs) and metabolic control (glycolysis, succinate) shape IL-1β activity but remain underexplored. Cross-talk with cytokines such as IL-6 and IL-10 further complicates interpretation. As our understanding of the TME evolves, it has become increasingly clear that IL-1β's impact is highly nuanced and influenced by tumor type, stage, immune landscape, and treatment modality (Figure 3).

7.1. Context and tumor-type specificity

One of the most significant challenges is the contextual plasticity of IL-1β. In some tumors, IL-1β acts as a pro-tumorigenic mediator, driving immunosuppression, angiogenesis, and metastasis. In others, particularly those with strong innate immune activation, IL-1β may bolster anti-tumor immunity via dendritic cell activation and pyroptosis.[71] For example, while IL-1β inhibition showed promise in lung cancer via the CANTOS trial, it failed to demonstrate similar efficacy in trials for colorectal or pancreatic cancers.[72] These discrepancies reflect the complex, dualistic biology of IL-1β and underscore the necessity of tailoring therapeutic strategies to specific tumor contexts.

7.2. Potential risks of broad IL-1β suppression

While IL-1β blockade may reduce inflammation-driven tumor progression, its long-term suppression can interfere with beneficial immune functions. IL-1β is essential for pathogen clearance, tissue repair, and vaccine responses.[73] Prolonged IL-1β inhibition has been associated with increased susceptibility to opportunistic infections, especially in immunocompromised patients.[74] Furthermore, there is concern that dampening IL-1β signaling may impair immunogenic cell death and reduce the efficacy of immunotherapy in tumors where IL-1β contributes to antigen presentation and T-cell priming.[75] Thus, any IL-1β-targeted therapy must carefully balance anti-tumor effects against potential immune compromise.

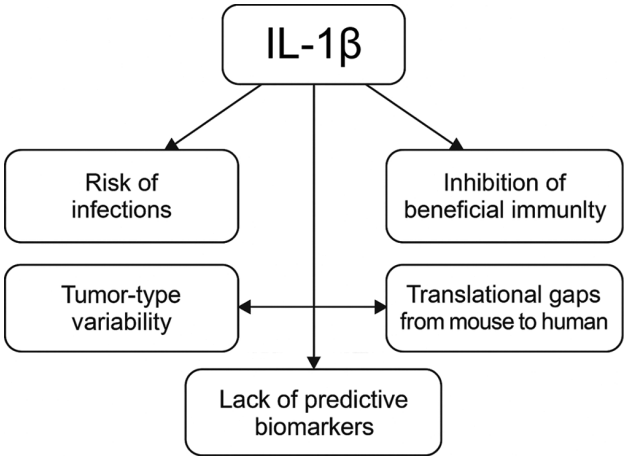

Figure 3. Risks and challenges of targeting interleukin-1 beta (IL-1β). This flowchart summarizes key concerns in the therapeutic inhibition of IL-1β in cancer. Risks include increased susceptibility to infections, potential suppression of beneficial immune responses, tumor-type-specific variability in IL-1β function, and limited translatability of pre-clinical findings to clinical efficacy. Image created by the author using Adobe Illustrator 2024.

7.3. Contradictions in pre-clinical and clinical evidence

A significant controversy lies in the inconsistency between pre-clinical and clinical data. Many murine models have demonstrated potent anti-tumor effects of IL-1β inhibition or, conversely, enhanced immunity following IL-1β activation.[76] However, translating these findings into clinical benefit has been variable. Differences in model systems, tumor genetics, and immune cell repertoire between mice and humans contribute to this translational gap. Moreover, systemic cytokine levels in patients may not accurately reflect intratumoral IL-1β activity, complicating therapeutic targeting.

7.4. Lack of predictive biomarkers

Currently, no validated biomarkers exist to predict which patients will benefit from IL-1β inhibition. Serum IL-1β levels do not consistently correlate with treatment response or disease progression, and tumor biopsy-based measurements are not routinely performed.[77] Advances in spatial transcriptomics, single-cell RNA sequencing,

and cytokine multiplex profiling may help identify IL-1β-driven tumor subtypes in the future.[78] In the absence of such markers, clinical trial design remains empiric, often leading to heterogeneous outcomes and limited reproducibility. However, emerging evidence suggests inflammasome markers (NLRP3, caspase-1) and liquid biopsy may provide predictive biomarkers.[77]

7.5. Need for precision strategies

The controversies surrounding IL-1β reflect a broader theme in immuno-oncology: the need for precision immunomodulation. Broad cytokine suppression is unlikely to be universally effective and may come at the cost of impairing immune surveillance. Future efforts should focus on context-specific targeting strategies, such as tumor-localized delivery, transient inhibition, or selective pathway modulation, that maximize therapeutic benefit while minimizing systemic toxicity.

8. Future perspectives

As our understanding of the immunobiology of IL-1β continues to evolve, new opportunities are emerging to harness its dual roles in cancer therapy. Rather than indiscriminate cytokine blockade, future strategies will likely rely on context-specific immunomodulation, guided by advances in spatial profiling, biomarker discovery, and rational drug design (Figure 4).

8.1. Precision immunomodulation

A central challenge in targeting IL-1β is achieving the right balance, suppressing its pro-tumorigenic effects without impairing its contribution to anti-tumor immunity. This has prompted growing interest in precision immunomodulation, a therapeutic paradigm that aims to manipulate immune pathways selectively within the TME.[79] For IL-1β, such strategies may include localized delivery of antagonists via nanoparticles, antibody-drug conjugates, or tumor-infiltrating cell carriers, thereby reducing systemic toxicity while enhancing tumor selectivity.[80] In addition, gene editing and clustered regularly interspaced short palindromic repeats-based approaches could enable transient and tumor-restricted IL-1β blockade.

8.2. Spatial and single-cell technologies

Technological advances in spatial transcriptomics and single-cell RNA sequencing are beginning to clarify the cellular sources and compartmentalization of IL-1β signaling in tumors.[81] These approaches enable the mapping of cytokine expression in relation to immune cell subsets, stromal components, and tumor cell niches, revealing IL-1β-driven microenvironments with greater resolution than bulk assays.[82] Such data can inform the design of therapies tailored to the cellular and spatial context of individual tumors.

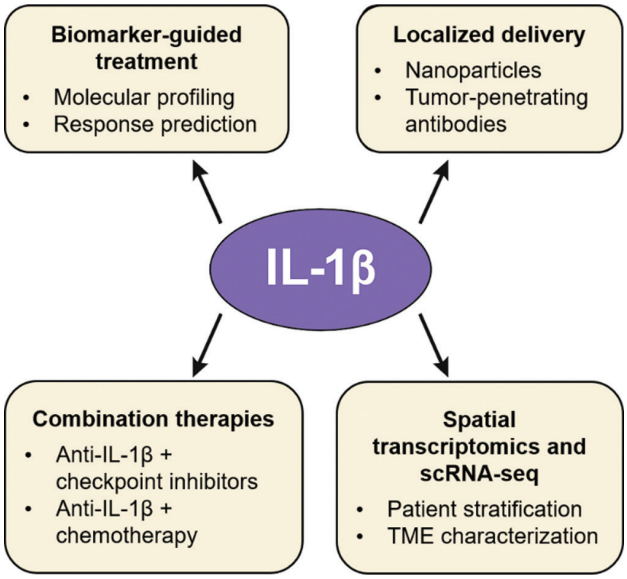

Figure 4. Future strategies for precision interleukin-1 beta (IL-1β) modulation. This conceptual diagram illustrates emerging strategies for context-specific modulation of IL-1β in cancer. These include biomarker-guided patient selection, tumor-localized delivery systems, rational combination therapies with checkpoint inhibitors, and integration of spatial transcriptomics and single-cell profiling to identify IL-1β–driven tumor subtypes. Image created by the author using Adobe Illustrator 2024 (Adobe Inc., San Jose, CA, USA).
Abbreviations: scRNA-seq: Single-cell RNA sequencing; TME: Tumor microenvironment.

8.3. Biomarkers for patient stratification

Another key priority is the development of predictive biomarkers to identify patients most likely to benefit from IL-1β blockade. Candidate biomarkers may include intratumoral *IL1B* gene expression, inflammasome activation signatures (e.g., NLRP3 and caspase-1), or soluble mediators such as IL-6 and C-reactive protein.[83] Integration of multi-omic data, including transcriptomic, proteomic, and microbiome profiles, may further refine patient stratification and trial enrollment. Companion diagnostics will be crucial in avoiding under- or overtreatment and in improving the efficiency of future clinical trials.

8.4. Innovative drug designs and combinations

Next-generation IL-1β-targeting agents are being developed to overcome the limitations of current biologics. These include bispecific antibodies targeting IL-1β and immune checkpoint receptors, allosteric inhibitors of IL-1R signaling, and selective inflammasome inhibitors that block the upstream production of IL-1β.[84,85] In addition, synergistic regimens combining IL-1β blockade with immune checkpoint inhibitors, stimulator of interferon

genes agonists, or metabolic reprogramming agents are under investigation.[86,90] As pre-clinical and early-phase clinical data accumulate, rational combinations may unlock the full therapeutic potential of IL-1β modulation.

In summary, IL-1β occupies a pivotal position at the intersection of inflammation, immunity, and malignancy. Its functional duality demands nuanced therapeutic approaches that go beyond simple inhibition. Future research should prioritize understanding IL-1β's spatiotemporal dynamics in different cancers, developing context-aware delivery systems, and embedding IL-1β modulation within broader immunotherapeutic frameworks. By aligning technological innovation with mechanistic insight, IL-1β-targeted therapy may yet find its place in precision oncology.

9. Conclusion

IL-1β represents a paradigmatic example of the dualistic nature of inflammation in cancer. As a master regulator of immune activation, IL-1β can initiate robust anti-tumor responses by enhancing dendritic cell maturation, promoting T-cell priming, and fueling immunogenic cell death. Conversely, chronic IL-1β signaling can subvert immunity, remodel the TME into a pro-tumor niche, and drive metastasis through angiogenesis, EMT, and fibroblast activation.

Therapeutic targeting of IL-1β has emerged as a promising yet complex strategy in oncology. Clinical data, most notably from the CANTOS trial, have provided encouraging signals for IL-1β inhibition in inflammation-associated cancers, particularly lung cancer. However, the efficacy of IL-1β blockade is clearly context-dependent, influenced by tumor type, disease stage, immune landscape, and host factors. Moreover, long-term cytokine inhibition carries risks, including immune suppression and increased susceptibility to infection.

Future progress will depend on precision immunomodulation guided by spatial profiling, biomarkers, and single-cell analyses. Combination regimens with checkpoint blockade, chemotherapy, or targeted therapies may enhance efficacy while preserving immune integrity.

In conclusion, IL-1β occupies a pivotal position at the intersection of inflammation and tumorigenesis. Defining the molecular switches that dictate its pro- versus anti-tumor roles will be crucial for integrating it into next-generation cancer immunotherapies.

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