IL-1 Signaling in Tumor Microenvironment

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Abstract

Interleukin 1 (IL-1) has long been known for its pleiotropic effects on inflammation that plays a complex, and sometimes contrasting, role in different stages of cancer development. As a major proinflammatory cytokine, IL-1β is mainly expressed by innate immune cells. IL-1α, however, is expressed by various cell types under physiological and pathological conditions. IL-1R1 is the main receptor for both ligands and is expressed by various cell types, including innate and adaptive immune cell types, epithelial cells, endothelial cells, adipocytes, chondrocytes, fibroblasts, etc. IL-1 and IL-1R1 receptor interaction leads to a set of common signaling pathways, mainly the NF-kB and MAP kinase pathways, as a result of complex positive and negative regulations. The variety of cell types with IL-1R1 expression dictates the role of IL-1 signaling at different stages of cancer, which under certain circumstances leads to contrasting roles in tumor development. Recent availability of IL-1R1 conditional knockout mouse model has made it possible to dissect the role of IL-1/IL-1R1 signaling transduction in different cell types within the tumor microenvironment. This chapter will focus on the role of IL-1/IL-1R1 in different cell types within the tumor microenvironment and discuss the potential of targeting this pathway in cancer therapy.

Keywords

Interleukin-1α · Interleukin-1β · IL-1R1 · IL-1RA · IL-1 signaling pathway · Tumor microenvironment · Breast cancer · Sarcoma · Melanoma · Colorectal cancer · Hepatocellular carcinoma · Mouse models · Pleiotropic effects · Cancer progression · Cancer therapy

1.1 Introduction

Starting with the identification of interleukin protein function in the early 1970s, the nomenclature of IL-1 was established in 1979 [1]. IL-1 signaling transduction is well controlled and regulated via different levels of positive and negative regulators. There are two major agonistic IL-1 ligands, IL-1α and IL-1β, and one antagonistic ligand IL-1RA (anakinra). At the receptor level, IL-1R1 is the major receptor mediating positive signaling transduction from agonistic ligands and is ubiquitously expressed across many cell types.

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The IL-1 receptor accessory protein (IL-1RaP, also referred to as IL-1R3) facilitates the positive signaling via the formation of a tertiary complex (IL-1α or IL-1β, IL-1R1, IL-1RaP) with IL-1R1 and accessory proteins, which recruits downstream signaling proteins. IL-1R2 is a decoy receptor that has no intracellular signaling domain and leads to the sequestration of agonistic ligands, thus quenching downstream signaling activation. At the downstream effector level, the tertiary complex leads to activation of two major pathways, NF-κB and MAP kinase pathways (Fig. 1.1). This intracellular level of signaling regulation is much more complicated than the level of ligand-receptor interaction due to the interaction of a number of the downstream effector proteins, including scaffolding proteins, kinases, ubiquitin/de-ubiquitin enzymes, etc. The complex protein interactions and regulations often crosstalk with other signaling pathways such as those mediated by Toll-like receptors (TLRs). The detailed signaling transduction networks have been extensively reviewed and will not be discussed here [2–6]. As a negative feedback, IL-1 signaling activation can induce the expression of the negative regulator IL-1RA by NF-κB- and AP-1-dependent transcription [7, 8].

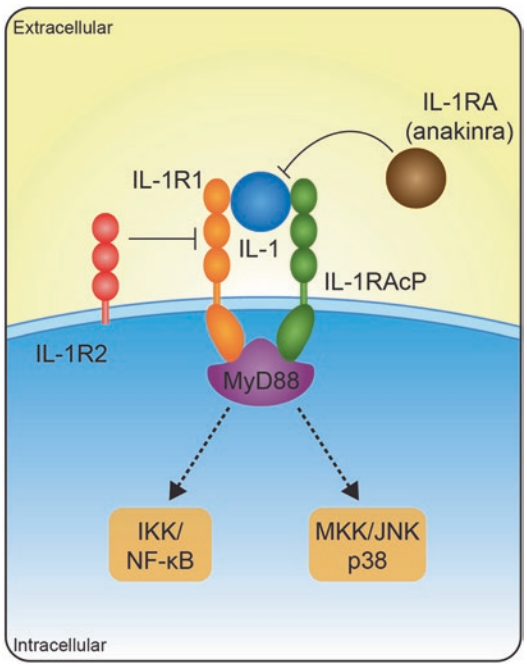

Fig. 1.1 Essential components of IL-1 signaling transduction

As the major agonistic ligands, IL-1α and IL-1β are encoded by two distinct genes with moderate shared homology. Both genes and proteins are tightly regulated at transcriptional and posttranslational levels. The transcription is generally activated by NF-κB family transcription factors. NF-κB signaling can be activated by various factors, such as pathogen infection (pathogen-associated molecular patterns, PAMP) or sterile inflammation/tissue damage (danger-associated molecular patterns, DAMP) via TLRs, NOD-like receptors (NLRs), or other cytokines/growth factors/chemokines. IL-1 signaling can propagate IL-1 production via a positive feedback loop mediated by IκB kinase (IKK)/NF-kB activation. IL-1α and IL-1β are not secreted via classic endoplasmic reticulum/Golgi pathways. IL-1α and IL-1β proteins are translated as pro-forms and secreted via distinct mechanisms.

IL-1α Biogenesis: Pro-IL-1α can be posttranslationally modified by phosphorylation, myristoylation, and acetylation, although the functional significance of these modifications is yet to be determined. Pro-IL-1α is active and binds to IL-1R1 equally compared to the cleaved IL-1α. Several proteases including calpain, granzyme B, elastase, or chymase can cleave pro-IL-1α into the mature forms at different cleavage sites. The biological function of pro-IL-1α/IL-1α comes from different locations, including the induction of IL-1R1 canonical signaling transduction via released or membrane-bound pro-IL-1α/IL-1α or nuclear pro-IL-1α/IL-1α. Current theory involves the release of pro-IL-1α through necrosis-mediated passive release as an "alarmin." The alarmin function of IL-1α notifies adjacent immune cells of potential damage to tissues and stimulates regeneration. The release of mature or cleaved IL-1α is less understood, likely via a similar mechanism as mature IL-1β release.

IL-1β Biogenesis: Even though pro-IL-1β is similarly translated, it has no bioactivity to induce IL-1R1-mediated signaling pathways in the pro-form. Protease-mediated cleavage, primarily

via caspase-1 (Casp-1), leads to the release of mature IL-1β from the cytosol to extracellular space, via either pyroptosis (inflammatory cell death) or some other not-well-defined mechanism. The key enzyme Casp-1 is activated via a controlled mechanism during infection or sterile inflammation during injury, stress, and metabolic alterations. Innate immune cells, such as macrophages, can sense different molecular signatures, PAMPs or DAMPs, through sensing molecules in the NLR family, including NLRP1, NLRP3, and NLRC4, or pyrin family protein AIM-2. Via the adaptor protein apoptosis-associated speck-like containing CARD (ASC), the sensors, ASC, and pro-Casp-1 form an activating complex referred to as an inflammasome. Upon sensing various molecular signatures, the inflammasome complex forms, leading to the auto-cleavage of Casp-1 from pro-Casp-1 into p20/p10 tetramers with protease activity. The protease activity of the tetramers results in the cleavage of pro-IL-1β and pro-IL-18 into their mature forms. It is critical to understand how these different inflammasomes are activated in a tumor microenvironment in order to understand the cellular sources of IL-1β production and the downstream events. Most inflammasome-relevant studies have focused on macrophages in tumor microenvironment. Others and we have extensively reviewed the role of different inflammasomes in different cancers that will not be discussed in detail in this chapter [9–13]. There are other mechanisms that can lead to IL-1β processing and activation in neutrophils via neutrophil-specific proteases upon certain bacterial infections [14]. Neutrophil-based IL-1ββ activation may be dependent on cathepsin G in lung cancer, which is critical to mediate cancer resistance to IKK/NF-κB inhibition [15]. There are emerging reports of the pathogenic role of neutrophils in cancer [16–18], and neutrophil-produced IL-1β likely plays an important role for cancer inflammation, progression, and metastasis.

The ubiquitous expression of IL-1R1 complicates clear elucidation of the role of IL-1 signaling due to the various, and sometimes opposing, roles in different effector cells. For example, reports have shown opposing effects of IL-1R1-mediated signaling transduction in myeloid cells versus T-cells in mouse model of colon cancer [18]. In addition to cancer cells, the tumor microenvironment contains most immune cell types, fibroblasts, endothelial cells, adipocytes, and tissue-specific cell types, many of which express IL-1R1. Therefore, the overall effect of the IL-1 signaling pathway in certain cancer types needs to be carefully dissected. The chapter will focus on the role of IL-1 signaling transduction in various cell types under physiological and pathological conditions, including several types of cancer (Table 1.1).

1.2 IL-1 Signaling Pathway in Different Cancers

The IL-1/IL-1R1 signaling axis primarily induces pro-survival and pro-proliferative MAP kinase signaling, which generally promotes cancer progression. The pro-tumorigenic function of IL-1 has been an accepted concept, especially in regard to IL-1β, based on in vitro data and in vivo tumorigenic models. However, there are contradictory results, indicating more complex signaling transduction/crosstalk between IL-1 and other signaling pathways. Here we will focus on the cancer types with strong support from genetically modified mouse models (GEM) related to core IL-1 signaling, including IL-1α, IL-1β, IL-1R1, and IL-1Ra. The inflammasome mouse models have been extensively discussed in outstanding reviews [9–13]. The downstream effectors are always shared with other pathways that may complicate experimental interpretation due to the signaling crosstalk. An important point of clarification before continuing is that most studies rely on whole-body knockout or cancer-cell-line injection models in wild-type or immunocompromised mice. The cancer phenotypes are a result of combinatory impacts of the IL-1 signaling on different cell types within tumor microenvironment.

Table 1.1 Cancer phenotypes related to IL-1 core signaling components

Molecules	Major functions	References
Breast cancer		
IL-1β	Inhibits ER-positive breast cancer cell growth but promotes an aggressive invasive mesenchymal phenotype	[19, 20, 22, 23]
	Promotes migration and EMT in triple-negative breast cancer cells	[26, 27]
	Cancer cell intrinsic expression is correlated with relapse	[30]
	Promotes metastasis in lobular carcinoma mouse model	[17]
	Macrophage-produced IL-1β promotes angiogenesis and progression under obese conditions	[50, 51]
	Promotes an imbalance between tumor-infiltrating macrophages and dendritic cells leading to decreased CD8 T-cell activation	[49]
	IL-1 deficiency reduces tumorigenesis in a PyMT spontaneous breast cancer mouse model	[56]
IL-1α	Suppresses ER-positive breast cancer cell growth in vitro	[34]
	Promotes ER-positive breast cancer tumor growth in vivo	[35]
	Expression in ER cells is correlated with a more malignant phenotype and cancer progression	[36–40]
	4T1 cancer cell-derived IL-1α promotes cell survival and metastasis via inductions of TSLP from neutrophils	[16]
Sarcoma		
IL-1β	Polymorphisms are associated with risk of osteosarcoma	[71]
	Expression in fibrosarcoma cells induces a more aggressive phenotype and increased angiogenesis	[72]
	Promotes tumorigenesis and invasiveness in 3-MCA-induced fibrosarcoma model	[75]
IL-1α	Induces genes associated with survival, cell cycle, inflammation, and ECM remodeling in sarcoma cell lines	[60–62]
	Expression in fibrosarcoma cells induces antitumor immunity	[72]
	Involved in escape form immunosurveillance	[76]
Liver cancer		
IL-1β	Polymorphisms are associated with increased risk of hepatocellular carcinoma	[77–79]
	Promotes tumorigenesis in DMBA plus obesity-induced liver cancer model	[83]
	Activation downstream of NLRP3 inflammasome activation likely plays a role in HCV-related liver cancer	[84, 85]
	Macrophage-produced IL-1β acts synergistically with EGF to induce IL-6 in macrophages, an important tumor-promoting cytokine in HCC	[87]
IL-1α	Released from ROS-damaged hepatocytes and promotes carcinogenesis in a carcinogen-induced liver cancer model	[80]
Melanoma		
IL-1β	Promotes lung metastasis and adhesion to endothelial cells	[92, 93]
	Macrophage-produced IL-1β signals through fibroblasts and endothelial cells to promote angiogenesis and the upregulation of tumor-promoting factors	[88]
	Promotes invasiveness, metastasis, and angiogenesis in B16 mouse models	[100, 101]
IL-1α	Promotes lung metastasis and adhesion to endothelial cells	[92, 93]
	Critical for oncogenic RAS-induced keratinocyte transformation	[106]
	Inhibits carcinoma formation when overexpressed in keratinocytes	[107]
Colon cancer		
IL-1β	Promotes VEGF expression, EMT, invasion, and growth of human colon cancer cells	[112–115]
	Polymorphisms are associated with recurrence	[117]
IL-1R1	Promotes tumorigenesis and early progression in colon epithelial cells	[18, 123]
	Promotes tumor-elicited inflammation via IL-17 and IL-22 induction in CD4 T-cells and possibly IL-C3	[18]
	Loss in neutrophils increases bacteria-induced inflammation and increased tumor load	[18]

1.2.1 Breast Cancer

1.2.1.1 Human Cancers

Early studies supported a growth-inhibitory role of IL-1β in estrogen receptor (ER)-positive MCF-7 cells, whereas IL-1β has minimal effect on other breast cancer cell lines without ER expression [19, 20]. Interestingly, the inhibitory function of IL-1β in MCF-7 cells is likely due to the crosstalk with downstream signaling mediated by insulin-like growth factor 1 (IGF1) and insulin receptor substrate 1 (IRS-1), leading to the inhibition of phosphatidylinositol 3-kinase/Akt signaling pathway (PI3K/AKT) [21]. Later research using the same MCF-7 cells suggested that IL-1β promotes an aggressive phenotype of MCF-7, i.e., the migration/invasion and a mesenchymal phenotype [22, 23]. This invasive phenotype may be a result of the activation of Src homology (SH) 2-containing phosphotyrosine phosphatase (Shp-2) leading to the expression of matrix metalloproteinase 9 (MMP-9) [22] and the synergistic induction of Erk1/2 activation with epidermal growth factor (EGF) [24]. In a separate study using MCF-7 cells, IL-1β induced a kinase cascade involving NF-κB-inducing kinase (NIK), IKKα, and the consequent activation of NF-κB in a reactive oxygen species (ROS)-dependent manner [25], a possible parallel mechanism for IL-1β-induced aggressive phenotype of MCF-7 cells. Similar promotion of a migratory phenotype by IL-1β was seen in triple-negative breast cancer cells, MDA-MB-231, where IL-1β induces the expression of hypoxic-inducible factor α (HIF-1α) and the CXCR1 chemotaxis pathway [26]. A non-canonical activation of IL-1β-mediated β-catenin signaling was also reported [27] that leads to the onset of epithelial-mesenchymal transition (EMT). The significant induction of EMT by IL-1β also links to another important feature of breast cancer, maintaining the tumor-initiating cells via an NF-κB-dependent mechanism [28]. Interestingly, IL-1β inflammatory response phenotypically locks metastasis-initiating cancer cells (MICs) at a *ZEB1*-positive mesenchymal stage that cannot reverse for the subsequent epithelial colonization process [29]. The dormancy-locked MIC cells can undergo epithelial transition by inhibition of IL-1β pathway to establish macrometastasis [29]. The source of IL-1β is thought to be derived from innate immune cells under inflammatory conditions; however, breast cancer cells can turn on IL-1β expression [30]. The role of IL-1β in breast cancer metastasis is strongly supported by clinical data showing that cancer-cell-intrinsic expression of IL-1β protein significantly correlates with relapse in bone and other sites in a large patient cohort (greater than 1300 patients) with stage II/III breast cancer [30]. IL-1β/IL-1R1 inhibition by anakinra (IL-1RA) or canakinumab (human-specific IL-1β antibody) reduced bone metastasis, likely via a cancer-cell-intrinsic autocrine pathway [30, 31]. In a recent pilot clinical trial involving HER2-negative metastatic patients, anakinra (IL-1RA) treatment modulated transcriptional signature in blood leukocytes leading to decreased IL-1 signaling, NF-κB signaling, and innate immunity but increased genes involved in NK- and T-cell-mediated cytotoxicity. This anakinra-modulated signature, i.e., the IL-1β /IL-1R1-induced gene signature, can faithfully predict breast cancer patients with poor prognosis [32].

The cancer-cell-intrinsic function of IL-1α is much less understood in breast cancer. Limited literature supports that IL-1α may promote human breast cancer progression. Similarly to IL-1β, IL-1α was initially identified as a suppressor for estrogen-induced growth of ER+ MCF-7 cells and downregulated ER protein either alone [33] or in addition to IL-6 [34]. This in vitro inhibitory effect of IL-1α conflicts with an in vivo tumorigenic study where MCF-7 tumors with IL-1α overexpression grew faster than control cells [35], suggesting that IL-1α plays a dominant role in tumor microenvironment in the MCF-7 xenografts. In ER-negative breast cancer cells, IL-1α is preferentially produced by cancer cells with a greater basal or stem cell phenotype [36] and induces downstream activation of NF-κB and IL-6 production to promote cancer progression [37] and other metastatic genes [38]. In agreement, IL-1α protein secretion is correlated with a more malignant phenotype [39] and ER negativity [40]. This may underscore a potential local paracrine and

autocrine role of IL-1α in the maintenance of a more malignant phenotype.

There exist a number of publications regarding the polymorphisms of genes encoding for IL-1 family cytokines and their association with breast cancer risk, but the conclusions are unequivocal. Based on a meta-analysis of total 1277 breast cancer cases and 1431 control cases, there is no significant correlation between three IL-1β polymorphisms with breast cancer risk [41, 42]. This lack of correlation between IL-1β polymorphisms with breast cancer is supported by other studies including one in Korean women [43] and another in Caucasian women [44]. Meanwhile, several reports indicate IL-1RN (encoding IL-1R antagonist IL-1RA) polymorphisms are marginally associated with breast cancer risks [44, 45]. Similarly, IL-1α gene polymorphism at the C-terminal untranslated region (rs3783553, TTCA insertion genotype) is significantly associated with a decreased risk of breast cancer [46] due to the differential regulation by miR-122 and reduction in IL-1α expression [47]. An additional IL-1α polymorphism was correlated with increased breast cancer risk based on a multiplex genotyping of 1107 SNPs from 232 candidate genes [48].

1.2.1.2 Mouse Models

In the 4 T1 syngeneic transplant model, tumor-intrinsic IL-1α led to the recruitment of neutrophils and subsequent thymic stromal lymphopoietin (TSLP) production, which in turn promotes tumor cell survival and metastasis [16]. IL-1β can also promote metastasis in *K14cre;Cdh1F/F;Trp53F/F* (KEP), a lobular breast cancer model in an IL-1R1-dependent manner. IL-1 signaling leads to IL-17 production from γδ T-cells, which in turn leads to G-CSF expression and enhanced production and recruitment of metastasis-promoting neutrophils [17]. These neutrophils are critical in suppressing the cytotoxic and antimetastatic activity of CD8 T-cells [17]. In a more recent report, IL-1β was shown to balance the tumor-infiltrating macrophages versus CD11b + dendritic cells (DCs), with IL-1β deficiency leading to increased IL-12-producing CD11b + DCs and prevailing CD8 T-cell-mediated antitumor immunity [49]. Inhibition of IL-1β and an "immune checkpoint" (programmed cell death-1, PD-1) synergistically suppresses breast cancer growth [49]. In obesity, which generally promotes breast cancer in humans and animal models, our group identified that IL-1β is a causal effector molecule that drives obesity-induced breast cancer progression as a downstream effector of the NLRC4 inflammasome activation [50, 51]. Obesity induces an increase in tumor-infiltrating macrophages that produce IL-1β and activate subsequent expression of VEGFA and ANGPTL4 within adipocytes to induce angiogenesis [50, 51]. Genetic and pharmacological inhibition of IL-1β/IL-1R1 signaling suppresses obesity-driven cancer growth and angiogenesis [50, 51]. The NLRP3 inflammasome/IL-1β can also activate within tumor-associated macrophages, leading to angiogenesis and cancer progression [52, 53]. The exact mechanism for NLRC4 inflammasome activation in obesity-driven breast cancer remains not fully understood. Since NLRC4 is only known to sense bacterial products such as flagellin or type III secretion system, it is likely that NLRC4 senses obesity-associated bacterial products either via circulation or from microbiota detected within adipose tissues [54].

All syngeneic models described above focus on the role of IL-1/IL-1R1 signaling in tumor immune microenvironment. In a recent report using the polyoma middle T-antigen mammary carcinoma model (MMTV-PyMT), IL-1α/IL-1R1 signaling pathway was shown to be clearly tumor-suppressive as IL-1R1$^{-/-}$ and IL-1α$^{-/-}$ mice showed significantly elevated tumorigenesis and lung metastasis relative to wild-type and IL-1β$^{-/-}$ mice [55]. The authors did not identify any significant change in major tumor-infiltrating immune cell subtypes, albeit a trend toward increased macrophages in IL-1R1$^{-/-}$ tumors. This tumor-suppressive phenotype is likely due to a direct impact on tumor cells. These findings are further supported by an earlier report that found that tumors in MMTV-PyMT mice do not rely on adaptive immune cells for primary tumor growth but require them for lung metastasis [56]. As PyMT breast cancer

model is clearly defined as luminal breast cancer [57], it is conceivable that IL-1α/IL-1R1-mediated inhibitory effect is via the interaction with ER signaling during early initiation and progression stages, similarly as reported in human ER+ MCF-7 cells [19, 20, 33]. As PyMT tumors lose ER expression in late stages and metastasis, how IL-1α/IL-1R1 signaling suppresses metastasis is yet to be explained. The discrepancy between PyMT model and IL-1α polymorphisms in humans underscores the complex role of IL-1α in breast cancer. There could be a delicate balance between IL-1α-mediated immunosurveillance and IL-1α-induced cancer cell survival and proliferation.

1.2.2 Sarcoma

1.2.2.1 Human Cancers

Human data related to IL-1α and IL-1β is relatively sparse. The expression of both IL-1 ligands has been reported in human sarcoma cells [58, 59]. Using the osteosarcoma line MG-63, signaling through IL-1α induces a panel of genes involving protein synthesis (*S6K*, increased 22-fold), signaling proteins (*PP2A*), antiapoptotic gene (cIAP1 or *BIRC2*, increased 20-fold), cell cycle (*CDC42BPB*, increased 16-fold), and inflammation (MIP2β or *CXCL3*, increased sevenfold) [60]. Collectively, the IL-1α-induced expression changes indicate various potential functions in cell cycle, viability, and inflammation. IL-1α also induces matrix metalloproteinase 3 (MMP-3), IL-6, BMP-2, and Cox2 production in the SW1353 chondrosarcoma line [61, 62], indicating possible functions in tissue remodeling, inflammation, and invasion. A similar set of genes were also regulated by IL-1β in sarcoma cell lines [63–67], in addition to its regulation on microRNAs [68, 69]. At the mechanistic level, IL-1 induces classic NF-kB and MAP kinase activation to regulate downstream gene expression pattern [64, 65, 70]. There is only a single report using 120 patients finding that two IL-1β polymorphisms are associated with risk of osteosarcoma [71].

1.2.2.2 Mouse Models

Using mouse fibrosarcoma cell lines, IL-1α and IL-1β have very distinct roles in sarcoma progression. IL-1α overexpression in fibrosarcoma is located at the plasma membrane and transduces an antitumor immunity from cell surface to effector immune cells, evidenced by increased mononuclear immune cells in the tumor sites, as well as increased CD8 T-cell and IFNγ production [72]. IL-1β production in the same cells led to a more aggressive tumor growth with increased angiogenesis [72]. Fibrosarcomas with IL-1α deficiency grew more aggressive tumors, whereas those with IL-1β deficiency grew smaller tumors when using immunodeficient Nu/Nu mice [73] and immunocompetent mice [74]. The above cancer-cell-intrinsic IL-1α and IL-1β production is limited to tumor and its microenvironment. Using whole-body knockout mice, Krelin et al. used the 3-methylcholanthrene (3-MCA)-induced fibrosarcoma model in IL-1β$^{-/-}$, IL-1α$^{-/-}$, IL-1α/β$^{-/-}$ (double knockout), and IL-1Rα $^{-/-}$ mice with the Balb/C genetic background and found IL-1β, but not IL-1α, was able to promote tumorigenesis and invasiveness [75]. There is an observation of strong inflammatory response related to IL-1β-induced tumorigenesis that can be blocked by anakinra, suggesting a proinflammatory microenvironment is essential for tumorigenesis and progression in this model [75]. Though IL-1α did not exhibit a role in the MCA-induced primary fibrosarcomagenesis, it is critically involved in immunoediting of cancer cells that prevents the cancer cells from T-cell- and, to a lesser extent, NK-cell-dependent immunosurveillance [76]. These data suggest that both cancer-cell-intrinsic and host productions of IL-1 β play a role in the promotion of sarcoma, whereas IL-1α has a more complicated function depending on the location.

1.2.3 Liver Cancer

1.2.3.1 Human Hepatocellular Carcinoma (HCC)

A recent epidemiological study from South Korea identified IL-1β polymorphisms are significantly associated with HCC, with two polymorphisms

associated with decreased risk and one with increased HCC risk [77]. In the same study, no IL-1α or IL-1RA polymorphisms were associated with HCC risk [77]. A similar result was shown in HCC with preexisting HCV infection in a Japanese cohort [78] and an Egyptian cohort [79], with IL-1β polymorphisms associated with HCC risk but not in IL-1RA or TNFα genes. A separate study using two large cohorts of Chinese HCC patients identified an insertion/deletion polymorphism at the miRNA-122 binding site of IL-1α 3′ untranslated region increased the risk of HCC development. The relevant polymorphism disrupts the binding of miR-122 to mRNA, resulting in an increase in IL-1α expression and HCC risk [47]. The same polymorphism is also associated with a risk of breast cancer [46], indicating a general tumor-promoting function of IL-1α in various cancer types. These data suggest IL-1/IL-1R signaling transduction may play a critical role during human HCC development.

1.2.3.2 Mouse Models

In a procarcinogen diethylnitrosamine (DEN)-induced liver cancer model [80], DEN induces HCC via the induction of massive hepatocyte killing, recruitment of myeloid cells, and the production of proinflammatory cytokines that stimulate compensatory proliferation of remaining mutated hepatocytes [81, 82]. IL-1α is one of the cytokines that is released by hepatocyte damage upon the accumulation of excessive ROS, which in turn promotes hepatocyte proliferation and survival via IL-1R1- and Myd88-mediated signal transduction [80]. This process does not involve IL-1β, as deficiency in IL-1β or its major activator Casp-1 did not promote DEN-induced HCC development [80]. Interestingly, under certain conditions, such as 7,12-dimethylbenzathracene (DMBA) plus obesity-induced liver cancer in neonates, IL-1β is important for liver cancer development via regulating a senescence-related secretion phenotype (SASP) [83]. This suggests that obesity-associated chronic inflammation, similarly to what we have seen in breast cancer [50], relies on IL-1β to transmit tumor-promoting inflammation. Chronic infection of hepatitis C virus (HCV), one of the major epidemiological factors for human HCC, also activates NLRP3 inflammasome and IL-1β within hepatic macrophages to induce chronic inflammation and likely contributes to HCV-related HCC in humans [84, 85]. One of the mechanisms of liver-macrophage-produced IL-1β is the synergy with EGFR-mediated IL-6 production [86], one of the critical proinflammatory cytokines that promote HCC [87] and may account for sex differences of HCC patients [82].

1.2.4 Melanoma/Skin Cancer

1.2.4.1 Human Melanomas

IL-1R1 is mainly expressed by tumor-associated endothelial cells and fibroblasts, whereas IL-1β is mainly expressed by tumor-associated macrophages [88]. There are inconsistent reports whether human melanoma cell lines express IL-1β using various reagents, but several reports conclude that melanoma cell lines are not the major source of IL-1β protein due to the lack of inflammasome components [88, 89]. IL-1α is expressed uniformly in nevi, primary tumors, and metastases [90, 91]. Early studies have shown that IL-1α/β induces experimental lung metastasis in A375 xenografts [92] and promotes tumor cell adhesion to endothelial cells [93]. The IL-1β/IL-1R1 signaling cascade seems to be initiated by cancer cells, via an unknown mediator, to induce IL-1β transcription and processing in macrophages [88, 89]. Fibroblasts and endothelial cells propagate the signal from macrophage-produced IL-1β, leading to cancer-promoting factors and angiogenesis [88]. The autocrine IL-1β/IL-1R1 signaling cascade within macrophages is also important to promote DNA methylcytosine dioxygenase Tet2, which sustains immunosuppressive function and promotes melanoma progression [94]. Although IL-1R1 is generally expressed below detectable levels in human melanoma, IL-1 can induce downstream signaling activation using human melanoma cell lines [95] and invasiveness via upregulation of adhesive molecules from both cancer cells and endothelial cells in human xenografts [96, 97]. Limited genetic information indicates that IL-1β

polymorphism is marginally associated with invasive phenotype [98] and IL-1RA genotype is associated with patient survival [99].

1.2.4.2 Mouse Models

Most IL-1-related mouse models of melanoma are from syngeneic transplantation of B16 mouse melanoma cell line. This model provides excellent resources for host IL-1 signaling in cancer immunity, inflammation, and angiogenesis. Early studies defined the role of IL-1β as required for invasiveness, metastasis, and angiogenesis via the induction of VEGFA and lymphotoxin [100, 101]; IL-1α has a similar function with a weaker phenotype [100]. IL-1β has also been shown to promote hepatic metastasis of melanoma via upregulation of vascular cell adhesion molecule-1 (VCAM-1) [102], presumably via retention of cancer cells to endothelial cells. Treatment of B16 melanoma with IL-1RA reduces tumor growth and lung metastasis [103], suggesting that IL-1 signaling may be a viable target for melanoma therapy.

Conflicting results have been reported in the two-stage 7,12-dimethylbenzanthracene/12-O-tetradecanoylphorbol-13-acetate (DMBA/TPA)-induced skin cancer model. The DMBA/TPA model has limitations but currently is the only model used for studying IL-1 signaling in carcinogen-induced skin cancer model. Drexler et al. reported the critical role of IL-1R1 and Casp-1 in tumor progression, with whole-body deletion of IL-1R1 or Casp-1 leading to less tumorigenesis relative to the wild-type controls [104]. Similar result was also seen in a separate study using genetic knockout of IL-1R1 and MyD88 [105]. The involvement of Casp-1 strongly indicates the involvement of IL-1β, not IL-1α, in the DMBA/TPA-induced skin cancer. However, the involvement of IL-1α is vital in the mediation of the oncogenic RAS-induced keratinocyte transformation via IL-1R1- and MyD88-mediated signaling transduction [106]. Interestingly, the transgenic expression of IL-1α under the keratin-14 promoter, which drives IL-1α expression from keratinocytes, completely inhibits papilloma and carcinoma formation, suggesting a tumor-suppressive/immunosurveillance phenotype of IL-1α overexpression [107].

1.2.5 Colon Cancer

1.2.5.1 Human Colorectal Cancer (CRC)

Expressions of IL-1α and IL-1β are detectable in colonic epithelial cells, with Casp-1 and IL-1β largely diminished within colon cancer cells [108]; however, both Casp-1 and IL-1β are elevated in CRC tumors versus normal tissues likely due to tumor-infiltrating immune cells. IL-1α is maintained in colon cancers and can be induced further by proinflammatory stimuli, like prostaglandin E2, to boost inflammation and likely carcinogenesis [109] or to induce angiogenesis and IL-8 production in endothelial cells [110, 111]. IL-1β, presumably mainly from myeloid cells, directly works on human colon cancer cells to promote VEGF expression for angiogenesis [112, 113], Zeb1 for EMT, stemness and invasion [114], Wnt signaling for cancer growth [115], and COX2 for inflammation [116]. This is largely in agreement with the role of IL-1/IL-1R1 signaling in promoting CRC development and progression. Polymorphisms of IL-1β and IL-1RA have been shown to be associated with tumor recurrence in stage II colon cancer [117], and IL-1RA genotype is associated with colorectal cancer risk [118].

1.2.5.2 Mouse CRC-Colitis-Associated Colorectal Cancer (CAC) by AOM/DSS and CRC by CPC-APC

The impact of IL-1/IL-1R1 signaling transduction is very perplexing in colon cancer mouse models, as shown initially in a lack of discernable phenotype in IL-1R1$^{-/-}$ mice with azoxymethane/dextran sodium sulfate (AOM/DSS)-induced early colitis and CAC [119], as well as in *CDX2Cre-Apcf/wt* (CPC-APC) mouse model of conditional monoallelic APC loss in the colon to induce CRC [18]. IL-1 signaling has been shown to be important in stimulating IL-17 production and Th17 differentiation, two key events that are

known to promote CRC [120, 121]. Upon the availability of the recently made IL-1R1 conditional knockout mice [122], the Grivennikov group performed elegant work to dissect the roles of IL-1R1 on colonic epithelial cells, T-cells, and myeloid cells. In epithelial cells, IL-1R1 promotes initial tumor outgrowth and early progression [18], likely due to the antiapoptotic role of the major downstream IKKβ-mediated NF-kB activation [123]. In CD4 T-cells, IL-1R1-mediated signaling transduction is critical for eliciting IL-17 and IL-22 production [18] and maintaining tumor-elicited inflammation, hence driving CRC progression particularly via activation of STAT3 [124–126]. In contrast, IL-1R1 in myeloid cells plays an opposite role in tumor-elicited inflammation and CRC progression [18]. Neutrophil-specific IL-1R1 depletion leads to a deficit in neutrophil-mediated bacterial killing, thus increasing bacteria-induced tumor-elicited inflammation [18]. As a result, there is a larger tumor load in mice with neutrophil-specific IL-1R1 depletion. Within myeloid lineages, neutrophils are the dominant cell type to mediate IL-1R1 signaling since CX3CR1-Cre-mediated IL-1R1 deletion in the intestinal and tumor-associated macrophages did not yield any significant phenotype, while broader Il-1R ablation in myeloid populations using CD11b-Cre or LysM-cre demonstrated the same phenotype as in Ly-6G-Cre-mediated-neutrophil-specific deletion of IL-1R1. This neutrophil-mediated bacterial killing is enhanced by IL-1β treatment in vitro [18], indicating an anti-inflammatory role of IL-1β/IL-1R1 when encountering microbes in colon. IL-1α and IL-1β are not created equal in controlling colonic inflammation prior to carcinogenesis. In DSS-induced colitis, IL-1α is released by DSS-induced necrosis of intestinal epithelial cells as an alarmin to initiate limited colon inflammation and repair; IL-1β, on the other hand, plays a major role in colon repair [127], likely via an indirect neutrophil activation, microbial control, and/or direct pro-survival pathways in colonic epithelial cells to maintain the integrity of the barrier. Absence of IL-1β leads to severe colitis, a similar phenotype as IL-1R1$^{-/-}$ mice [127], indicating IL-1β-mediated myeloid activation and bacterial killing play a predominant role in preventing colitis in this DSS-induced mouse colitis model.

1.2.6 Other Cancers

Data from IL-1-related GEM models is lacking in most other cancer types. Research based on cancer cell lines or genetic data suggests that IL-1 signaling is critical for other cancers as well, including association of polymorphisms with risks [128–134], the promotion of aggressiveness in cancer by working on either cancer cells or microenvironment, and angiogenesis. For example, neutrophils can produce IL-1β in an inflammasome-independent manner, which is critical to mediate lung cancer resistance to IKK/NF-κB inhibition [15]. The same process is likely important for driving oncogenic KRAS-NF-κB addiction in malignant pleural effusion, a critical process for metastasis in lung cancer and other solid cancers [135]. In castration-resistant prostate cancer, IL-1RA upregulation by a combined immune checkpoint blockade and myeloid-derived suppressor cell (MDSC)-targeted therapy is critical to reduce MDSC infiltration [136]. Treatment with anakinra, the IL-R1 antagonist, provides an immune-permissive microenvironment that sensitizes castration-resistant prostate cancer to immune checkpoint blockade [136]. Based on all the information related to mouse and human data, the prevailing function of IL-1/IL-1R1-mediated signaling transduction in cancer is to promote cancer progression, and targeting IL-1/IL-1R1 signaling pathway could potentially benefit a large cancer patient population.

1.3 IL-1 Signaling Pathway in Different Cell Types Within Tumor Microenvironment: A Brief Summary

1.3.1 Cancer Cells

Cancer cells can be the primary target for IL-1 signaling that mostly transmits from IL-1/IL-1R1/IL-1RAcP to downstream IKK/NF-κB or

MAP kinase (JNK/p38). Those pathways are critical for the pro-survival and pro-invasive function of carcinoma cells. In addition, IL-1 can work on cancer cells to produce other factors such as VEGF for angiogenesis, IL-6 and TNF for tumor-induced inflammation, and other chemokines, cytokines, and growth factors to promote cancer progression. JNK and p38 activation, however, can initiate apoptosis under certain conditions, without the counteraction from IKK/NF-κB pro-survival function. The net signaling outcome can be suppressive for cancer cell growth. As cancer cells are not the primary focus of this chapter, we will not get into details here.

1.3.2 Fibroblasts

Fibroblasts can produce IL-1 and propagate IL-1 signaling. It has been shown that herpes simplex virus 1 (HSV-1) infection induces activation of NLRP3 inflammasome and consequent IL-1β activation in fibroblasts [137]. G-protein-coupled estrogen receptor (GPER) can induce IL-1β transcription and activation (presumably via NLRP3 activation) in cancer-associated fibroblasts (CAFs) [138]. Fibroblasts have been shown to relay macrophage-derived IL-1β signaling to induce cancer-promoting factors and angiogenesis [88]. In CAF cells, IL-1α has been shown to induce leukemia inhibitor factor (LIF) via a non-canonical JAK/STAT pathway, which contributes to the generation of inflammatory CAF and shapes CAF heterogeneity in pancreatic cancer [139]. IL-1 has been shown to induce PD-L1 and COX-2 in melanoma-associated fibroblasts, which is critical to induce immunosuppression in oncogenic BRAF melanoma [91]. Cellular senescence of fibroblasts has been shown not only to inhibit tumorigenesis early in life but to promote cancer in aged organisms [140]. Membrane-bound IL-1α serves as a critical upstream regulator of senescence-associated secretory phenotype (SASP) in senescent fibroblasts [141], where IL-1α mRNA is induced by NF-κB-mediated transcription and its protein is translated by mTOR-mediated mechanism [142].

1.3.3 Adipocytes

Adipocytes are integral components among several cancer types such as pancreatic and breast cancers. Cancer-associated adipocytes are known to produce IL-1β that can interact with other cell types within tumor microenvironment [143–145]. Adipose tissue is among the top expressers for IL-1R1 based on human protein atlas, indicative of its capability to receive IL-1 signaling transduction. Unsurprisingly, we found adipocytes are the major effector cells of myeloid IL-1β in obese animals carrying breast cancer [50, 51]. IL-1β induces various angiogenic factors including VEGF and ANGPTL4 to promote cancer progression [50, 51].

1.3.4 Endothelial Cells

Endothelial cells have long been known to be a direct or indirect target of IL-1 signaling. Many cell types, including endothelial cells, within tumor microenvironment can produce VEGF upon IL-1 activation, the growth factor for endothelial cells during angiogenesis. In turn, IL-1 and VEGF synergize to promote angiogenic response, and both factors are required for angiogenesis [101]. An interesting observation from a nontumor model defines a role of IL-1β in mobilizing endothelial progenitor cells, a process that could be potentially important for IL-1β-induced angiogenesis in cancer [146]. Endothelial cells have been thought to be one cellular source for CAFs via EMT [147], which has been demonstrated in vivo to contribute to cardiac fibrosis [148]. IL-1β is an important factor to promote this process via FGF-2 or other factors [149].

1.3.5 Immune Cells

IL-1β is one of the best-studied cytokines in inflammation and has been known to be one of the major cytokines involved in innate immunity and inflammation [2–6]. Activation of IL-1β is mostly studied in macrophages under infection or

sterile inflammation [2–6]. Myeloid cells are also one of the major producers of IL-1β in tumor microenvironment. Among the tumor-associated innate immune cells, IL-1β has been shown to work on all different cell types and elicit various functions. IL-1β is known to recruit and activate neutrophils that can either suppress microbiota-induced colonic inflammation and inhibit CRC [18] or promote inducible nitric oxide synthase (iNOS) production in neutrophils to inhibit CD8 T-cells in the setting of breast cancer metastasis [17]. IL-1β has been shown to induce CCL2 expression from various cellular sources and recruit tumor-associated macrophages and other myeloid lineages such as monocytic and granulocytic MDSCs [150]. In turn, these immune cells can be the cellular targets of IL-1 signaling to initiate immunosuppressive and pro-angiogenic signaling during cancer progression. IL-1β is also produced by the NLRP3 inflammasome in a subset of DCs in the presence of necrotic cancer cells during cancer progression and/or therapy [151], which is important for DC-mediated T-cell activation and cancer clearance by certain chemotherapy. DC-derived IL-1α, in a nontumor setting, promotes the proliferation of CD8 T-cells [152]. Interestingly, the DC-derived IL-1β activation requires a feed-forward mechanism from CD8 T-cells, in a specific antigen-dependent manner [153–155]. Likely depending on different cytokine milieu or DC subtypes, IL-1β has been shown to balance the presence of tumor-associated macrophages or $CD11b^+$ DC [49]. Tumors from wild-type animals favor IL-10 producing immunosuppressive tumor-associated macrophages, whereas tumors from the IL-1β-deficient host have increased $CD11b^+$ DC that can mount an antitumor Th1 and CD8 responses [150]. Among the innate lymphoid cells (ILCs), the role of IL-1 in cancer-associated NK-cells (group 1 ILCs) is largely unknown, and earlier studies indicate a role of IL-1 in promoting NK-cell activity toward tumoricidal effects [156]. Further literature supports this notion and found that co-treatment of IL-1β and IL-12 enhances the production of IFNγ and GM-CSF from a subset of human NK-cells [157]. On the other hand, IL-1β is critical to promote the development and maintenance of ILC3 cells [158, 159], and IL-1β is able to inhibit NK-cells from acquiring IFN-γ production and degranulation [158], indicative of an IL-1β-dependent suppression of NK effector function. IL-1β can also stimulate the activation of ILC3 cells that initiates antigen-specific CD4 T-cell responses [160] but also can induce production of often pro-tumorigenic cytokines such as IL-17A and IL-22. Distinct function of IL-1 signaling on ILC is yet to be established under different cancer contexts.

Among the adaptive immune cells, IL-1 has been shown to work on both αβ T-cells and γδ T-cells during cancer progression. In the latter, γδ T-cells in lung metastasis can be activated by IL-1β to express IL-17, a key cytokine that can induce G-CSF. G-CSF and IL-1β collectively lead to the successful neutrophil recruitment and polarization, which results in the production of immunosuppressive iNOS to inhibit CD8 T-cells [17]. The direct impact of IL-1 on CD4 T-cells was recently established in a CRC model where IL-1 signaling promotes a Th17 phenotype and potentiates tumor-elicited inflammation and progression [18]. This result is in agreement with the discovery that IL-1β promotes Th17 lineages when combined with IL-6 [161] or with IL-23 [162–164]. The IL-1β-dependent Th17 commitment could also be due to the alteration of plastic Tregs into Th17 [165–167]. In addition, IL-1β directly acts on a mixed memory CD4 T-cell population to induce IL-22 production [18, 168]. Both IL-17 and IL-22 have been reported to promote cancer progression in different cancers [18, 168]. IL-1β and IL-4 have been shown to promote the differentiation of Th9 cells in the absence of TGFβ, resulting in a superior antitumor CD4 Th9 population that is less exhausted with cytotoxic gene signatures [169]. In nontumor setting, there are many outstanding cases in which IL-1β can enhance antigen-specific CD4 and CD8 T-cell proliferation and activation, as well as memory responses of these T-cells, mostly likely via direct IL-1β/IL-1R1 signaling [170–172].

The various effector cell types dictate a careful evaluation of tumor microenvironment, which defines the dominant role of IL-1 signaling within

the tumor microenvironment. Treating cancers with IL-1 antagonists should be carefully evaluated using a comprehensive approach. For example, lung cancers or metastasis may benefit from IL-1 inhibition due to the role of IL-1 in recruiting cancer-promoting neutrophils and subsequent CD8 suppression. In CRC, however, neutrophils are critical to eliminate cancer-penetrating bacteria and thus control the tumor-elicited inflammation and tumor progression. Another concern is how to best use the antitumorigenic role of IL-1 signaling in DC activation and antigen-specific CD8 T-cell priming and activation, a process that requires DC to sense ATP release from necrotic cancer cells and NLRP3 activation. Thus, it would likely be detrimental to use IL-1 inhibitors under these conditions.

1.4 Clinical Implications and Perspectives

1.4.1 Clinical Studies

Due to the complex role of IL-1 signaling in immunity and physiology, clinical development of IL-1-targeted therapy is mostly related to autoimmune diseases such as the development of anakinra in rheumatoid arthritis and canakinumab (IL-1β-specific antibody) for several rare inflammatory diseases. Recently, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), initially designed to prevent heart attack, stroke, or cardiovascular death in patients with elevated C-reactive protein using different doses of canakinumab, identified a significant reduction in lung cancer mortality and risk in the cohort receiving canakinumab relative to placebo controls (> 50% risk reduction) [173]. This was extremely exciting in the field of cancer therapy, and Novartis immediately followed up with several trials to combine canakinumab with chemotherapy and immune checkpoint inhibitor in lung cancers, including a phase III CANOPY-2 study evaluating the efficacy and safety of canakinumab in combination with docetaxel in non-small cell lung cancers (Clinicaltrials.gov Identifier: NCT03626545).

In breast cancer, a pilot trial in HER2-negative metastatic breast cancer patients defines an anakinra-regulated gene signature from the leukocyte transcripts, mostly related to IL-1 family (IL-1B, IL-1R1, IL-1R2, IL-1RAP, IL-1RN, IL-6, IL-6R), NF-KB signaling (NF-KB2, NF-KBIZ), and innate immune sensing (TLR1, TLR2, TLR4, TLR5, TLR8, NOD2) molecules. The anakinra-regulated signature from blood leukocytes can faithfully predict patient outcome. In particular, the gene signature is enriched in the aggressive basal-like breast cancer subtype that could potentially benefit from IL-1/IL-1R1-targeted therapy [32]. In addition to blocking the role of IL-1 in cancer-associated inflammation, anakinra administration in this pilot trial led to elevated cytotoxic signatures from NK- or CD8 T-cells, indicative of activation. This phenomenon was recently explained using animal models where IL-1 blockade leads to increased DC-mediated antigen presentation and CD8 T-cell activation [49], which provides the rationale to combine immunotherapy in patients with TNBC with canakinumab (Clinicaltrials.gov Identifier: NCT03742349).

Bermekimab (MABp1, an IL-1α-specific monoclonal antibody) was recently used in a phase III trial to treat metastatic CRC with predicted poor outcomes. This study used defined primary endpoints including lean body mass (stable or increased body weight) and criteria QLQ-C30 (fatigue, pain, and anorexia; at least two of these are improved) from European Organisation for Research and Treatment of Cancer (EORTC). The bermekimab treatment significantly increased percentage of patients reaching the primary endpoints (33% versus 19%) but did not increase adverse events relative to placebo controls (23% versus 33%) [174]. In a similar setting, when pretreatment levels of serum IL-1RA were taken into account, patients with lower baseline IL-1RA levels responded better to bermekimab treatment with increased response rate [175]. There was no overall survival benefit from this trial, suggesting that inhibition of IL-1α should be intended for improving patient quality of life, like cancer-associated cachexia [174, 175]. One of the advanced phase III trials using

bermekimab to treat metastatic CRC was terminated due to inability of the study to reach futility boundary of the primary endpoint (Clinicaltrials.gov Identifier: NCT01767857).

In addition to these advances in clinical studies, outstanding literature provides a strong rationale to target this pathway for cancer therapy. We have shown that anakinra or IL-1R1 antibody can inhibit obesity-associated angiogenesis in breast cancer [50]. Chimeric antigen receptor (CAR) T-cell therapy targeting CD19 has been an outstanding approach for refractory B cell malignancies but commonly associated with severe cytokine storms. Anakinra can ameliorate the severe adverse effect [176] and is worthwhile to explore its role in CAR T-cell-treated patients. IL-1β has been shown to induce antigen presentation from DC and induce cancer-antigen-specific priming of CD8 T-cells, which indicates a role of IL-1β in chronic activation of CD8 T-cells in tumor microenvironment and provides a rationale to combine IL-1 inhibition with immune checkpoint blockage during cancer therapy [49].

1.4.2 Consideration for Clinical Studies

It is important to use caution for human clinical studies. For example, IL-1 signaling has been shown to inhibit mammary tumor growth and metastasis in luminal type of breast cancer [55] associated with "cold" immune microenvironment that is unresponsive to immune checkpoint blockage [177, 178]. IL-1α inhibits the conversion of papilloma to carcinoma in skin cancer [107]. There are also occasional reports that IL-1 treatment can inhibit cancer cell growth in vitro from various cancer types [19, 20, 33, 34, 179, 180] that may not be the best cancer types to target IL-1 signaling pathway for therapy. In addition, there are some controversial results related to the role of IL-1β in DC activation/T-cell priming. Earlier reports have shown that DC can receive ATP from dying tumor cells via the P2X7 purinergic receptors, leading to the activation of NLRP3 inflammasome and downstream IL-1β processing and secretion. IL-1β, in turn, propagates the signal from DCs to prime $CD8^+$ T-cells and induces IFNγ for cancer cell killing. This process is critical to mediate chemotherapy-induced cancer cell killing in an adaptive immune-dependent manner. In breast cancer patients with loss-of-function mutations in P2X7, that is, unable to activate NLRP3 inflammasome, doxorubicin treatment leads to faster metastasis and resistance to treatment [151]. This is further supported by another study showing that IL-1β is critical to mediate the efficacy of doxorubicin treatment in an adaptive immune-dependent manner [181]. The disagreement on the role of IL-1β in DC activation and CD8 T-cell priming [49, 151, 181] warrants careful evaluation of DC subtypes within tumor microenvironment and draining lymph nodes. IL-1RA, produced by CD11b + Gr-1+ myeloid cells, can antagonize senescence in cancer and promote PTEN-loss-mediated cancer initiation [182]. Many anticancer drugs that induce senescence of cancer cells also increase IL-1 production as summarized in a recent outstanding review article [183]. The decision to combine IL-1 inhibition and other therapy requires further understanding of the tumor immune microenvironment including the major immune cell subtypes, role of IL-1 on these immune cells, and the nature of therapeutic agents to be used.

1.4.3 Using Publicly Available Genetic Information for Assessing the Role of IL-1 Signaling in Cancer Progression

Among the Cancer Genome Atlas (TCGA) Pan-Cancer data across 30 cancer types, we analyzed the correlation between mRNA expression of IL-1α, IL-1β, IL-1R1, and IL-1RA and overall survival. Due to the inefficiency of IL-1 signaling in eradicating tumors from most preclinical research, targeting IL-1 pathways should only be considered to facilitate other established therapeutics. We found some very interesting information and summarized here (Fig. 1.2):

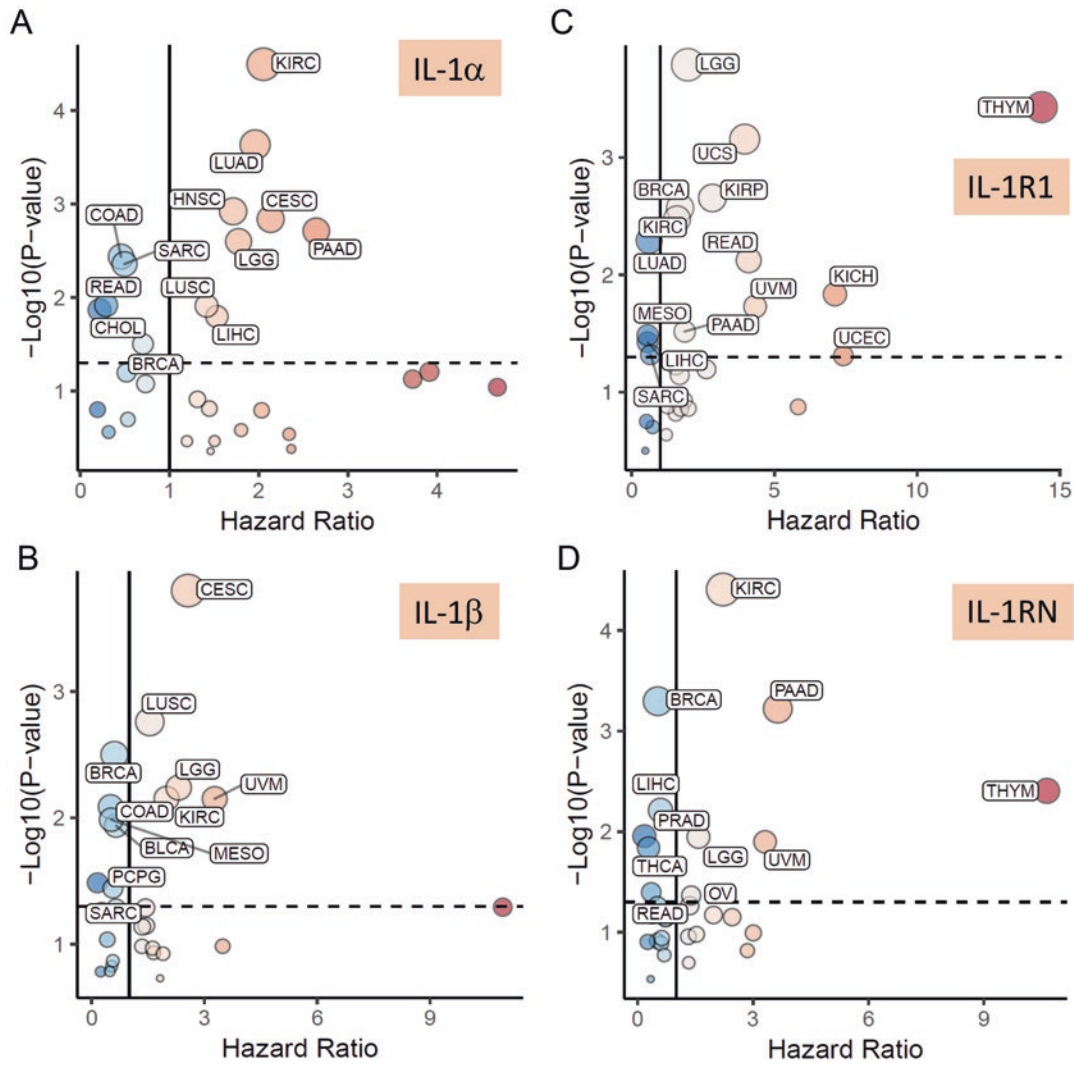

Fig. 1.2 The use of TCGA data to predict the correlation between mRNAs from IL-1 pathway and prognosis

IL-1R1, the major mediator of IL-1 signaling, is mostly correlated with poor overall prognosis (11/30 versus 4/30). Since most TCGA specimens have very restricted cancer cell content (e.g., BRCA specimens should have at least 80% carcinoma cells) [184], it is presumably that most IL-1R1 mRNA comes from cancer cells and mediates cancer progression via cancer-cell-intrinsic mechanisms.

IL-1RA, the antagonist for IL-1 ligands, is correlated with poor prognosis in six cancers, among which five are shared with IL-1R1 group. This suggests that IL-1 signaling activation often induces a negative feedback by turning on IL-1RA [7, 8].

Two cancer types (kidney renal clear cell carcinoma, KIRC, and low-grade glioma, LGG) exhibit a correlation between poor prognosis and mRNAs of all four factors, suggesting that IL-1 signaling may play a critical role in disease progression and could be targeted in these cancers. In particular, KIRC is known to have relatively low mutational burden but responds to immune checkpoint therapy [185]. A combination of anakinra and immune checkpoint blockage to inhibit both IL-1α and

IL-1β may be a better choice to treat KIRC patients by alteration of immunosuppressive microenvironment as well as inhibition of cancer growth [186, 187].

Two cancer types (uveal melanoma, UVM, and thymoma, THYM) exhibit a correlation between poor prognosis and mRNAs of IL-1β, IL-1R1, and IL-1RA, not IL-1α. Using IL-1β-specific antibody such as canakinumab could be a choice to boost immunotherapy and leave IL-1α-mediated immune surveillance arm intact.

Pancreatic adenocarcinoma (PAAD), a known immune-cold cancer type, is a difficult cancer to treat and shows elevated mRNA levels of IL-1α, IL-1R1, and IL-1RA, not IL-1β, among the patient specimens with poor prognosis. Literature has shown that cancer cell-derived IL-1α is critical for cancer cell adhesion [188], growth [189], and Treg cell infiltration [190]. These patients may benefit from IL-1α-specific treatment such as using bermekimab (MABp1) in combination with other therapies.

Both IL-1α and IL-1β are correlated with poor prognosis in cervical squamous cell carcinoma/endocervical adenocarcinoma (CESC) and lung squamous cell carcinoma (LUSC), supporting a role of common IL-1R1 signaling in squamous cell carcinomas that may benefit from anakinra co-treatment. The CANTO trial did not have enough non-small cell lung squamous cell carcinoma (LUSC) patients to determine if canakinumab reduces the risk of LUSC [173].

IL-1α, but not IL-1β, is correlated with poor prognosis in lung adenocarcinoma (LUAD), suggesting the role of IL-1α in promoting cancer progression in lung adenocarcinoma. Considering the role of canakinumab (IL-1β) in reducing LUAD risk and prolonging patient survival, the clinical trial mentioned above (Clinicaltrials.gov Identifier: NCT03626545) may benefit from comparing anakinra and canakinumab in non-small cell lung cancer patients.

Please note the above data are based on mRNA expression and the information provided above is by no means the guide on how to design clinical research and how to choose target patient populations. All known literature should be comprehensively analyzed to justify the most rational design for human studies. There are also many other drugs targeting IL-1 signaling transduction, including FDA-approved rilonacept (a soluble decoy receptor for neutralizing both IL-1 ligands) and others in development such as gevokizumab and LY2189102 (anti-IL-1β), AMG 108 (anti-IL-1R1), and AX-765 (long-lasting Casp-1 inhibitor). These agents are potential drugs to be repurposed for cancer therapy [191].

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