Interleukins in cancer: from biology to therapy

*Daria Briukhovetska1#, Janina Dörr1#, Stefan Endres1,2,3, Peter Libby4, Charles Dinarello5, Sebastian Kobold1,2,3,*\*

**1 Division of Clinical Pharmacology, Department of Medicine IV, Klinikum der Universität München, Munich, Germany, Member of the German Center for Lung Research.**

**2 German Center for Translational Cancer Research (DKTK), partner site Munich, Munich Germany.**

**3 Einheit für Klinische Pharmakologie (EKLiP), Helmholtz Zentrum München, German Research Center for Environmental Health (HMGU), Neuherberg, Germany.**

**4 Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.**

**5 Department of Medicine, University of Colorado Denver, Aurora, CO, USA.**

**\*e-mail: sebastian.kobold@med.uni-muenchen.de**

**#contributed equally**

**Abstract |**

Interleukins and associated cytokines serve as the mean of communication for innate and adaptive immune cells as well as non-immune cells and tissues. Thus, interleukins hold a critical role both in cancer development, progression, and control. Interleukins can nurture an environment enabling and favoring cancer growth while at the same time being essential for a productive tumor-directed immune response. These properties of interleukins can be exploited to improve immunotherapies to promote effectiveness as well as limit side effects. This review aims to unravel some of these complex interactions to guide researchers and clinicians.

**[H1] Introduction**

Advances in tumor biology during the past century have demonstrated the tight interplay between the immune system, healthy and malignant cells. These insights laid the foundation for the concept of immunosurveillance: the ability of the immune system to recognize and eliminate transformed cells. In contrast, immunoediting, describes the reciprocal interaction and shaping of the immune system and cancer cells, eventually culminating in cancer development and progression1,2. The resistance to immune attack and the presence of protumoral inflammation are two of the major hallmarks of cancer3. Highlighting its importance, the immune milieu at the cancer site on presentation (immune contexture) can define the outcome of patients with colorectal cancer (CRC)4,5.

Cytokines mediate key interactions between immune and non-immune cells in the tumor microenvironment (TME). It was recently demonstrated how the TME in, for example, lung adenocarcinoma (LUAD) allows malignant cells to co-evolve with immune responses6. Among cytokines, several interleukins are particularly relevant in the development and progression of cancer. The multitude of cellular sources, receptors, and signaling pathways, and even dose-dependency define the pleiotropic role of interleukins in cancer. Along these lines, interleukin action can be cell-specific and spans cancer initiation, tumor progression and control7.

Delineating the exact mechanisms of tumor immune control and evasion enabled the development of novel, tailored and highly effective therapies. The therapeutic potential of interleukins has been of interest in both basic and translational cancer research in recent years. An increasing number of clinical trials currently underway highlights their value as a therapeutic agent and a target. Cytokines have been tested in clinical trials as singular therapeutic agents date with limited success rates (extensively reviewed in8) and are now undergoing a revival in combinations with synthetic biology, gene, and cellular therapies. In most cases, cytokine classification relies on structural or receptor homology and gene proximity but not necessarily their biological role in cancer which is the purpose of the present work9. In this Review, interleukins will be discussed based on their biological role in cancer rather than family membership. Further information about cytokine classification is presented in Table 1.

This review will cover the milestones of the latest discoveries of interleukin-related mechanisms in cancer, together with their application in clinical practice. We provide a current overview of clinical trials, newly approved therapeutic agents, and breakthrough pre-clinical concepts. Although this paper focuses on cancer, as many of the same principles apply to a host of other diseases, it may prove useful to readers in a broad range of disciplines.

**[H1] Carcinogenesis**

Chronic inflammation has long been established as one of the drivers for carcinogenesis in many cancer entities such as lung, skin, esophageal, gastric, colorectal, pancreatic cancer, and hepatocellular carcinoma4. Some interleukins directly induce signaling in non-immune cells and sustain tissue homeostasis. However, after the oncogenic event, interleukin signaling in cancer cells can become a pathological mechanism of tumor growth, metastatic spread, and cancer progression (Figure 1).

IL-1 has long been implicated in inflammation-induced carcinogenesis10,11. IL-1α and IL-1β, which have more recently gained attention for their role in tumor biology, and its family members (Table 1) are produced by immune (e.g., myeloid) and non-immune (e.g., epithelial) cells in the context of chronic inflammation12.

IL-1α and IL-1β are alarm cytokines (also known as alarmins) that both act through IL-1 receptor (IL-1R) to initiate and amplify local inflammation9. The production of the IL-1β precursor pro-IL-1β occurs rapidly in response to danger- and pathogen-associated molecules by pathogen-recognition receptors (PRRs), such as toll-like receptors (TLRs), C-type lectin (CLRs), or retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) and requires inflammasome activation following proteolytic cleavage by caspase-1 (Cas1) into its active form13. The sensing of DAMPs sensing by RLRs, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and absent in melanoma 2 (AIM2)-like (ALRs) receptors initiates the canonical inflammasome assembly by recruiting and forming pro-Cas1 filaments and activating of Cas1, which in turn cleaves pro-IL-1β and pro-IL-18 releasing their active forms14.

Recent work demonstrated that IL-33 can create a self-amplifying tumorigenic niche that furthers the development of a nascent tumor15. As shown in a model of squamous cell carcinoma, once cells have transformed, they acquired tumorigenic capacity (also known as tumor-initiating cells (TICs)). TICs can secrete IL-33 that in turn attracts infiltration of tumor-associated macrophages (TAM) and promotes transforming growth factor β (TGF-β) signaling that creates a tumorigenic niche15,16.

In the context of chronic inflammation, IL-1α and IL-1β may directly promote the production of carcinogenic mediators, such as nitric oxide (NO) and reactive oxygen species (ROS)12,17. IL-1 triggers the downstream release of pro-inflammatory cytokines, such as IL-6, and mediates the recruitment of innate immune cells triggering a cascade of inflammatory mechanisms12. Here, effects of IL-1 are mediated by phosphorylation of nuclear factor κB (NF-κB) which in turn inactivates the suppressor of cytokine signaling 3 (SOCS3) and potentiates phosphorylation of signal transducer and activator of transcription 3 (STAT3)17,18. Recently, cell-type-specific carcinogenic effects of IL-1 were demonstrated in mice, harboring a deletion of the adenomatous polyposis coli (*Apc*) tumor suppressor in colon epithelial cells where IL-1 secretion was elicited from monocytes, tumor epithelial and stromal cells 19. Acting through IL-1R on epithelial cells, IL-1 directly promoted the malignant transformation of epithelial cells mediated by nuclear accumulation of NF-κB. In addition, IL-1 signaling in T cells triggered the secretion of pro-tumorigenic IL-17 and IL-2219. This observation is in line with the previously reported protumorigenic effects of IL-23 production by myeloid cells and subsequent Th17 responses to microbial products in the same model of colon carcinogenesis20. Similarly, in a mouse model of LUAD myeloid differentiation primary response gene 88 (MyD88)-dependent IL-1 production from myeloid cells acted on γδ T cells to produce an inflammatory loop involving IL-17A and IL-22 secretion that led to the malignant transformation of cells bearing *Kras* and *Trp53* mutations21.

IL-22, which is induced by IL-1 signaling in cancer settings22, has been associated with STAT3 activation and cancer-promoting properties23. IL-22 acts through IL-22R, exclusively expressed on non-hematopoietic cells, to promote wound healing and the production of microbicidal peptides23,24. Recent findings, however, highlight its stage-specific dual properties in carcinogenesis25. Under homeostatic conditions IL-22 is mainly secreted by type 3 innate lymphoid cells (ILC3) and γδ T cells and can repair genotoxic-induced DNA damage in the intestinal epithelium, to prevent the malignant transformation of cells25. However, when its activity is not controlled by IL-22 binding protein (IL-22BP), its natural inhibitor, IL-22 has a pro-tumorigenic effect in a mouse model of colitis-associated colon cancer model26. IL-22-producing T cells were reported to accumulate in nascent lung and colon tumors in mouse and human samples22,27,28. Through STAT3 phosphorylation it provides proliferation and migration signals to transformed malignant cells and/or cells bearing oncogenic mutations, sustaining their stemness through the induction of the SRY (sex-determining region Y)-box (SOX) 2, and NANOG as demonstrated in human colon tissues, and similarly in mouse models of lung, pancreatic and breast cancers 29-32. IL-20 has been shown to act similarly to IL-22 in hepatocellular carcinoma, breast, prostate, and oral cancer, and also induce immune inhibition through PD-1 upregulation in pancreatic cancer33.

Tissue damage and release of alarm cytokines induce IL-6, IL-10, IL-11, and IL-23 expression by sentinel myeloid and tissue cells. Under homeostatic conditions, this results in a self-inhibitory loop to resolve inflammation and promote healing34. In turn, IL-6 and IL-11 are potent orchestrators of innate immune responses and inflammation35,36. Moreover, IL-6 is also a regulator of development and metabolic processes36. These effects are attributed to ubiquitously expressed common transducing gp130 receptor subunit, which can dimerize with membrane IL-6Rα or IL-11Rα to initiate classical cis-signaling or a soluble receptor form resulting in non-classical *trans*-signaling 37-40. Gp130 is associated with activation of Janus kinase 1 (JAK1), JAK2, non-receptor tyrosine-protein kinase 2 (TYK2)38-40, as well as tyrosine-protein phosphatase SH-PTP2 (SHP2) and SRC–Yes-associated protein (YAP)–NOTCH signaling that activates proliferation and tissue regeneration35,36,41. Furthermore, activation of Phosphoinositide 3 kinase (PI3k)-protein kinase B (AKT)-mechanistic target of rapamycin complex 1 (mTORC1) signaling integrates interleukin signaling and the metabolic cell program35,36.

Classical IL-6 signaling is considered essential for homeostatic processes whereas *trans-*signaling was specifically demonstrated to amplify the inflammation and promote inflammation-induced carcinogenesis 42-44. Excessive activation of STAT3 by the overabundance of IL-6 and IL-11combined with oncogenic driver mutations licenses the development of malignant tumors such as colon and gastric45-48, pancreatic 49,50, and lung51 cancers. IL-1 and IL-6 released by myeloid cells induce PI3k-AKT-mTOR signaling that via activation of hypoxia-inducible factor 1-alpha (HIF1α) that shifts their metabolism towards glycolysis and decreases oxidative phosphorylation, which leads to amplification of IL-1 and IL-6 production and exacerbated inflammation-induced carcinogenesis52,53. Deregulated IL-6 and IL-1 signaling is also a contributor to cancer-induced cachexia (see Box 2).

Importantly, IL-6 also induces angiogenesis and tumor vascularization mediated by vascular endothelial growth factor (VEGF)34. Further, classical IL-6 signaling via IL-6R in lymphocytes promotes proliferation of T cells and lineage commitment to Th17 and T follicular helper (Tfh) cells43. IL-6 suppresses forkhead box P3 (Foxp3) limiting the ability of TGF-β to promote regulatory T (Treg) cell development, which enables Th17 differentiation and amplifies pro-inflammatory response, as demonstrated in a mouse melanoma model of Th17 adoptive cell transfer (ACT)54.

IL-23 is another interleukin produced in response to danger-associated molecular patterns (DAMPs) at epithelial barriers20. Typically, it counteracts the anti-tumor action of IL-12, but it was also demonstrated to directly promote tumor incidence and growth. IL-23 triggers IL-17 production from ILC3 and committed Th17 cells, synergizing with IL-6 in the amplification of inflammation, and prompting epithelial cells to acquire stemness and undergo malignant transformation20,55-57. IL-23 together with IL-1, IL-6, and IL-21 are capable of inducing IL-17 production independently of T cell receptor (TCR) signaling12,18,58. During chronic inflammation, an abundance of microbial antigens may drive IL-17 and subsequent aberrant wound healing that results in tumorigenesis, as seen in murine models of skin and colon cancers59-62. In skin stem cells, IL-17A signaling can recruit and transactivate epidermal growth factor receptor (EGFR) which induces expansion and migration of these cells62,63. Hence, the inflammatory responses initiate cellular programs in conditions of uncontrolled chronic activation may provide a direct link to tumorigenesis.

**[H1] Cancer growth and progression**

Malignant tumors possess several characteristic traits termed by Hanahan and Weinberg hallmarks of cancer64. Importantly, several of these traits namely sustained proliferation, inflammation, angiogenesis, active invasion, and migration are also the hallmarks of wound healing, and therefore may maliciously utilize cytokine signaling aimed at tissue repair (Figure 2)65,66.

Thus, it was demonstrated that IL-1 not only promotes inflammation-induced carcinogenesis but also contributes to tumor invasiveness and angiogenesis67. Although activation of for example NLR family pyrin domain containing 3 (NLRP3) inflammasome is reported ubiquitously in cancer, consequences of NLRP3 activation and release of IL-1β and its family member IL-18 range from antitumor activity to cancer growth and metastasis68,69. As such, IL-18 was demonstrated to promote angiogenesis through the activation of NF-κB which triggers the secretion of VEGF from cancer cells, induces their proliferation and invasion and prevents apoptosis, and may also induce programmed cell death 1 (PD-1)-dependent immunosuppression of natural killer (NK) cells70-73.

In addition to its ability to amplify pro-carcinogenic chronic inflammation, IL-6 drives tumor-intrinsic mechanisms of cancer progression that recapitulate most of these hallmarks74. IL-6 induces PI3K-AKT, mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK), NF-κB, and STAT3 signaling. These pathways augment the expression of anti-apoptotic proteins (B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-x(L)), induced myeloid leukemia cell differentiation protein (Mcl-1), Baculoviral inhibitor of apoptosis domain (IAP) repeat-containing protein 5 (BIRC5, also known as Survivin), evade growth control, activate metabolism, and induce angiogenesis via VEGF production (reviewed in 74). STAT3 phosphorylation in cancer cells is also induced by other cytokines, such as IL-22, exacerbating cancer-promoting pathways22,27,29,75.

Furthermore, chronic STAT3 activation in cancer cells induces proliferation, expression of matrix metalloproteinases (MMP), and migration, thereby increasing aggressiveness of carcinomas34,76,77. These effects are typically associated with epithelial-to-mesenchymal transition (EMT), which is orchestrated by EMT transcription factors (EMT-TF), such as zinc finger E-box-binding homeobox (ZEB), SNAI1 and 2, SLUG and TWIST, and enables cell detachment, metastatic spread, and invasiveness78-80. EMT induced by the integrated network of IL-1β, IL-6, IL-17, IL-22, and IL-23 mediates the invasiveness of many cancer types. For example, STAT3 activation by IL-22 was found to upregulate EMT markers in mouse models of pancreatic ductal adenocarcinoma (PDAC) and breast carcinoma30,32. Moreover, chronic exposure to IL-1β induces MAPK (ERK and c-Jun N-terminal kinase (JNK)) – activating protein 1 (AP-1) engagement that results in epigenetic modifications that cause long-lasting EMT phenotypes including SLUG and ZEB2 transcription in lung cancer81,82. Similarly, EMT is promoted by IL-6 and IL-11 mediated paracrine activation of STAT3 in invasive PDAC, IL-13 mediated activation of STAT6 by in CRC and IL-35 in breast cancer49,83-85. IL-23 utilizes the Wnt/β-catenin pathway to induce EMT in oesophageal cancer86, whereas NF-κB activation induced by IL-17 directly promotes ZEB1 in lung cancer87. IL-8 induces EMT through PI3K-AKT and rat sarcoma (RAS)-rapidly accelerated fibrosarcoma (RAF)-mitogen-activated protein kinase (MEK)-ERK in various cancers88. However, permanent activation of ZEB1 by IL-1β in breast cancer cells entraps them in a mesenchymal state and prevents metastatic colonization, hence, cancer cells require mesenchymal-epithelial transition (MET) for further progression82. Taken together, this provides a rationale for the therapeutic neutralization of these cytokines to reduce EMT-mediated cancer progression.

**[H1] Cancer immunosurveillance**

***[H2] Innate immunity***

Despite the plethora of oncogenic factors that constantly induce malignant transformation of cells, our immune system recognizes and eliminates most of these transformed cells through immunosurveillance2. Innate immune cells, namely NK, natural killer T (NKT) cells, and γδ T cells, possess a wide array of the evolutionarily conserved “altered self” and activation receptors that can recognize and eliminate transformed cells2. This process depends on perforin, granzyme B, and interferon-gamma (IFN-γ) production in these cells89. The latter directly induces apoptosis in tumor cells and triggers a cascade of chemokines to initiate the recruitment of innate immune cells and induce the production of pro-inflammatory anti-tumoral cytokines (Figure 3)2.

Proliferation, maturation, and cytotoxic effector functions of innate immune cells are tightly controlled by IL-2 family cytokines, namely IL-2, IL-7, IL-15, and IL-21, that utilize heteromeric receptors and share a common γc receptor subunit8 (Table 1). IL-15 is the primary cytokine to regulate the biology of NK cells, which have particular importance for the control of hematological malignancies90. Unlike other IL-2 family members, IL-15 is typically presented in conjunction with IL-15Rα subunit on the surface of antigen-presenting cells (APC)8. To elicit signaling, the IL-15:IL-15Rα complex binds a heterodimeric IL-2Rβ:γc receptor complex shared with IL-28,91. Upon binding to its receptor on NK cells, IL-15 triggers a cascade of reactions resulting in phosphorylation of serine-threonine kinase AKT. Consequently, it causes accumulation and translocation of the transcription factor X-box binding protein 1 (XBP1s) into the nucleus, where T-box protein expressed in T cells (T-bet) is recruited, the essential transcription factor for cytotoxicity of NK cells and differentiation of Th1 cells90,92. T-bet, in turn, induces transcription of granzyme B and genes, responsible for proliferation, maturation, and survival of NK cells90. Importantly, the activity of AKT kinase downstream of IL-15 induces homeostatic priming in NK cells and cytotoxic lymphocytes (CTL)93.

NK-cell secreted IFN-γ primes APCs, such as dendritic cells (DC) and macrophages, to produce IL-12, which shares one of its subunits, p40, with IL-238,56. Importantly, APCs serve as a bridge between the innate and adaptive immune responses, and their recruitment, maturation, and activation are governed by cytokines94. IL-12 secreted from APCs, in turn, amplifies IFN-γ production in NK cells (requires priming by IL-15 and/or IL-1891,95) and thereby anti-tumor responses96.

IL-18 acts through its receptor highly expressed in NK cells and trigger IFN-γ production, cytotoxicity, and Fas ligand (FasL) expression12. In addition to the reported ability to directly promote the proliferation and migration of cells in certain types of cancer, tumor-infiltrating NK and CD8 T cells express high levels of IL-18R73,97. However, IL-18 activity is moderated by IL-18 binding protein (IL-18BP), a soluble receptor that acts as a decoy for IL-18 and inhibits anti-tumoral and anti-viral activities of NK cells and CTL97,98. Moreover, mouse and human NK cells have high expression of IL-1R8, another member of the IL-1 receptor family, that together with IL-1R5 (IL-18Rα) binds IL-37, known for its anti-inflammatory properties12,99. IL-1R8 could inhibit IL-18-dependent mTOR and JNK signaling pathways that are essential for NK cell metabolism, differentiation, and activation, as demonstrated in mouse models of liver carcinogenesis, hematogenous liver and lung metastasis 99.

Recently, eosinophils, another pleiotropic innate immune cell type primarily known for anti-helminth and allergic response, have received attention due to their distinct anti-tumor mechanisms in hepatocellular carcinoma and breast cancer100,101. IL-5, which together with IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) constitute a family of hematopoietic cytokines, is a key regulator of eosinophil differentiation, maturation, expansion, and survival101. Recruited by the tumor-released alarmin IL-33, eosinophils can directly exert cytotoxicity but also aid anti-tumoral Th1 cell responses100.

IL-28A, IL-28B, and IL-29 are cytokines distantly related to the IL-10 family, but also interferons and therefore also termed type III or λ interferons. They typically mediate innate immune antiviral activity but also directly induce apoptosis of malignant cells102,103.

***[H2] Adaptive immunity***

Upon immunogenic cancer cell death, antigens released by tumor cells are taken up by APCs, primarily DCs, and enter draining lymph nodes to initiate the development of antigen-specific adaptive immune responses. There, the cytokine milieu plays a fate-defining role for T cells2,104 (Figure 2). Proliferation, survival, differentiation, and termination of T cell responses are mainly governed by IL-2, IL-7, and IL-158, whereas IL-3 is necessary for survival and proliferation of lymphocyte progenitors105,106. IL-2 binds with intermediate affinity to γc:IL-2Rβ inducing the clonal expansion of T cells, but also for termination of the T cell responses through FAS/FASL-mediated apoptosis of T cells8. IL-2Rα chain (CD25) expressed mainly in Tregs, increases the affinity of the IL-2 receptor, mediates FOXP3 expression, and is essential for self-tolerance8.

CTL and effector Th1 cells are the primary mediators of anti-tumoral adaptive immunity107. IL-12 derived from DCs provides an essential signal that drives expression of T-bet, and thus the differentiation of effector Th1 cells, and CTL104,107,108. Successful anti-PD1 immunotherapy relies on IL-12 dependent crosstalk between T cells and DCs to promote tumor cell killing109. Similar to signaling in NK cells, IL-2, IL-15, and IL-18 synergize with IL-12 to trigger IFN-γ production and direct cytotoxicity in CTL and Th1 cells8,107. Thus, soluble IL-15/IL-15 receptor α (IL-15Rα) complexes produced by myeloid cells were shown to be essential for establishing NK and CTL populations in tumors in mouse models of melanoma and colon cancer110. In addition, priming of T cells by IL-18 activates NF-κB, augments STAT4 activation by IL-12, and enables TCR-independent production of IFNγ18. Despite its ability to suppress IL-12 production and resolve inflammation, IL-10 also potently induces CTL cytotoxicity towards tumors with potential for clinical application111.

The plasticity of the interleukin-dependent T cell transcriptional profile is essential for tailoring immune responses and necessary effector mechanisms112. Th9 cells and their prototypical cytokine IL-9, despite being closely related to the Th2 lineage that typically antagonizes Th1 responses, can serve as persistent anti-tumor effectors that resist exhaustion and can be exploited in cellular therapy 113. Th9 cells are typically induced by IL-4 and TGF-β, and experiments have shown that IL-1β could replace TGF-β to promote the Th9 lineage. Th9 cells induced that way mounted a persistent response and possessed potent anti-tumoral properties secreting IL-9, IL-21, and granzyme114-117. IL-21, besides its typical role in B cell responses, enhances cytotoxicity and improves persistence of NK cells and CTL in tumors as demonstrated in a melanoma mouse model of ACT118,119. Secretion of IL-21 can also be induced in T cells by IL-27, and limits differentiation of Tregs, enhances proliferation of NK and CD8+ T cells but also triggers the exhaustion program in these cells as also recently investigated in a mouse model of melamoma120,121. Th2 cells, typically seen as antagonists to anti-tumoral Th1 responses, can cause remodeling of tumor vasculature thus leading to tumor starvation and regression122.

**[H1] Cancer immunoevasion**

Despite the potent action of cancer immunosurveillance and immunoediting, malignant cells may evolve to evade anti-tumoral responses and exploit extrinsic immunoinhibitory mechanisms for progression6,123. In this way, they may secrete substances that enable domination cell types that suppress anti-tumor immunity, such as Tregs, ILC3, Th17 cells, Th2 cells, M2 macrophages, and myeloid-derived suppressors, and induce anergy of anti-tumor cells through their metabolic reprogramming, tipping the balance towards cancer progression.

***[H2] Tregs***

High-affinity IL-2 signaling together with TGF-β induces *Foxp3.* FOXP3 drives Treg differentiation and IL-10 production, thereby establishing an immunosuppressive TME4,8,15. Besides its role in creating a macrophage-dependent tumorigenic niche, IL-33 may directly promote TGF-β-elicited Treg differentiation, suppress IFN-γ, and promote Treg stability in the tumor124,125.

The regulatory role of Tregs in the TME is largely mediated by the secretion of IL-10, IL-35 and TGF-β126. IL-10 is anti-inflammatory and relies on its ability to suppress B lymphocyte-induced maturation protein-1 (Blimp-1) dependent cytokine secretion and regulate cytotoxic effector function, whereas IL-35 induces inhibitory TCRs (including PD-1, lymphocyte-activation gene 3 (LAG3), T cell immunoglobulin and mucin domain 3 (TIM3), T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains (TIGIT), 2B4 (CD244)) and limits the formation of T cell memory as demonstrated in mouse models of melanoma126. Mechanistically, IL-10 may also directly reduce TCR sensitivity upon increased cell membrane glycosylation127. Tregs further limit the availability of IL-2 to CD4 T cells in the TME causing deficiency of granzyme B expression in these cells and uncontrolled tumor outgrowth as demonstrated in a mouse sarcoma model128.

***[H2] Th17 responses and myeloid suppressors***

In response to IL-1β stimulation, Th17 and γδ T cells produce IL-17, which recruits a large number of immunosuppressive granulocytes (reviewed in 60,129), which was demonstrated to promote lung metastasis in a murine breast cancer model130. Moreover, in lung cancer, IL-23 converts type 1 innate lymphoid cells (ILC1) cells into IL-17-producing ILC3 cells that promote IL-17 mediated tumor cell proliferation131. Similarly, IL-8 (also known as chemokine (C-X-C motif) ligand 8, CXCL8) provides a chemotactic signal for myeloid cells in breast cancer patients and confers resistance to immunotherapy 132,133. Similarly, IL-18 produced upon inflammasome activation drives generation of myeloid-derived suppressor cells (MDSCs) in multiple myeloma, conferring a mechanism of immunosuppression 134.

***[H2] Th2 responses***

Tumor and stromal cells may secrete factors to promote Th2 and macrophage type 2 (M2) polarization, which suppress anti-tumoral Th1 polarization and responses135,136. In the same way, IL-33 induced type 2 ILCs were demonstrated to antagonize NK cell function in a mouse model of melanoma137. In turn, IL-33, secreted by cancer-associated fibroblasts (CAFs) in breast cancer, is a potent enhancer of type 2 innate lymphoid cells (ILC2) and Th2 responses, may induce TCR-independent secretion of IL-13 and recruitment of immunosuppressive granulocytes58,135. Moreover, IL-33 activates intrinsic signaling in Treg cells necessary for their immunosuppressive action in cancer124.

***[H2] Immune cell metabolic reprogramming***

Cancer cells can induce metabolic reprogramming of immune cells in the TME and systemic changes in metabolism which can induce the transition from pro-inflammatory to immunosuppressive responses53. Glycolytic switch in effector T cells dependent on NF-κB-inducing kinase (NIK) signaling was recently demonstrated pivotal for anti-tumor immunity in a mouse melanoma model138. The accumulation of glycolysis-derived lactate in the TME can increase oxidative phosphorylation and together with IL-4 induces anti-inflammatory reprogramming (involving M2 polarization of macrophages and secretion of IL-10 and TGF-β)53. In addition, accumulation of lactate and depletion of amino acids and glucose, in the TME in combination with TGF-β signaling can induce Treg polarization, amplify immunosuppression and T cell exhaustion thereby rendering tumors resistant to immunotherapy (reviewed in 53). As such, in PDAC, it was shown that stromal cells released IL-6 that increased glycolysis and lactate efflux from the tumor cells leading to M2 polarization of macrophages and reducing the efficacy of anti-PD-1 treatment139.

Hence, the accumulation of tumor-derived substances together with chronic inflammatory responses renders anti-tumor immunity unable to restrain tumor growth and progression resulting in an uncontrolled tumor outgrowth, distant metastasis, and limiting the efficacy of targeted therapies.

**[H1] Interleukins in cancer therapy**

As some interleukins regulate immunosurveillance and thereby tumor control, clinicians have tried to utilize them for cancer therapy in the past decades. However, cancer treatment by interleukins proved to be challenging as it, so far, did not live up to its expectations in terms of effectiveness while also encountering serious toxicities in some cases. Because interleukins also nurture cancer progression, neutralization of their activity has emerged as a potential avenue.

Reports suggesting interleukins as biomarkers exist for several interleukins74,140-143, but so far no interleukin has been implemented as a biomarker in the food and drug administration (FDA) guidelines for oncologic therapeutics and their potential overall value has been extensively reviewed143.

Here, we summarize recent advances in the translation of therapeutic exploitation of interleukins, covering therapeutic neutralization of interleukins as well as the use of their recombinant and engineered forms (Figure 4).

***[H2] Therapeutic neutralization***

**[H3] Interleukin-1**

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) provided the strongest evidence for the potential of IL-1-neutralisation in cancer so far. The study enrolled patients with stable coronary artery disease on the standard of care, but with persistent elevation of high sensitivity C-reactive protein (hsCRP). Patients were treated with the anti-IL-1β antibody canakinumab and were not diagnosed with cancer at the time of enrollment. Canakinumab not only reduced hsCRP but also significantly lowered overall cancer mortality compared to the placebo group, especially concerning lung cancer144. This finding likely reflected the ability of IL-1β to impede invasion and metastasis of existing subclinical cancers rather than cancer initiation due to the median duration of the trial of 3.7 years145. In support of this, a substantial number of patients diagnosed with lung cancer had already circulating tumor DNA at the time point of enrollment146. These findings spawned several clinical trials blocking IL-1β and other inflammatory interleukins in cancer with expected primary completion dates until 2024.

In 2018, a phase 3 trial of canakinumab in monotherapy compared to placebo started in non-small-cell lung cancer (NSCLC) patients (NCT03447769)147. Similarly, a phase 2 trial studying canakinumab monotherapy in myelodysplastic syndrome (MDS) and chronic myelogenous leukemia (CML) was initiated in 2020 (NCT04239157)148. Also in 2018, a phase 3 trial using canakinumab in combination with pembrolizumab and chemotherapy in NSCLC (NCT03631199)149, and in 2019 a phase 3 trial with canakinumab and chemotherapy alone (NCT03626545) was started150. Several additional studies have been initiated between 2016 and 2020 (see Supplementary Table 1).

Anakinra is an IL-1R antagonist in clinical trials for cancer therapy. In a phase 2 trial, 47 patients with smoldering myeloma were treated with anakinra alone for 6 months. If a patient did not achieve a minor response (MR) or better, anakinra was combined with dexamethasone. 3 out of 47 patients achieved an MR to anakinra alone, highlighting the need for a combinatorial approach. Upon addition of dexamethasone, 5 partial responses (PR) and 4 MR were achieved151,152. Anakinra is also under investigation in several other clinical trials in multiple cancer types in mono- and combination therapy (see Supplementary Table 1).

**[H3] Interleukin-6**

While the anti-IL-6 antibody siltuximab reduced tumor growth in a xenografted cholangiocarcinoma model153, it only achieved small effects in multiple myeloma as monotherapy154, in combination with the proteasome inhibitor bortezomib155 and with bortezomib, the cytostatic agent melphalan and the anti-inflammatory glucocorticoid prednisone156. Siltuximab was also not effective in solid tumors as monotherapy. In prostate cancer, the best outcome achieved was stable disease (SD)157, in renal cell carcinoma (RCC) the best outcome was a single PR158 and no clinical efficacy was observed in a group of mixed solid tumors159. Furthermore, several clinical trials observed treatment-associated side effects, such as higher rates of infections upon siltuximab treatment154-156, which overall does not support a benefit of siltuximab therapy.

IL-6 can protect cancer cells from therapy-induced DNA damage, oxidative stress, and apoptosis and is known to induce immunosuppression and maintains highly therapy-resistant cancer stem cell populations74. Thus, IL-6 neutralization might reverse resistance to conventional cancer therapy. In combination with chemotherapy, the anti-IL-6R antibody tocilizumab yielded the first positive results160. However, combining IL-6 neutralization with immune checkpoint inhibitors (ICIs) has engendered controversy. While IL-6 neutralization might enable patients to continue receiving ICIs by countering cytokine release syndrome (CRS, see Box 1), IL-6 inhibition was shown to suppress the expression of PD-1 and programmed death-ligand 1 (PD-L1). This might decrease the effectiveness of ICIs161. As preclinical studies mainly demonstrate the synergy between IL-6 neutralization and ICIs, several clinical trials have been initiated to test the combination in a clinical setting (see Supplementary Table 1).

Publications highlight the potential of blocking IL-6 *trans*-signaling in hepatocellular carcinoma (HCC)162 and CRC163 by comparing carcinogenesis in wild-type mice and mice transgenic for soluble gp130Fc, which consists of gp130 fused to a human IgG1 domain164. These data may lead to clinical trials for olamkicept (soluble gp130Fc) in cancer patients in the future.

**[H3] Interleukin-8**

HuMax-IL-8 is an antibody neutralizing IL-8. While no objective responses (OR) were observed in monotherapy, no dose-limiting toxicities were observed and 73 % of patients with solid tumors had SD165. IL-8 induces resistance to several chemotherapeutic agents and ICIs, summarized elsewhere133,140,166. Therefore, several clinical trials explore the effect of HuMax-IL-8 in combination with nivolumab (NCT03400332167, NCT04123379168, and NCT04050462169), nivolumab and degarelix (NCT03689699170), and the anti-PD-1 antibody nivolumab with stereotactic body radiotherapy (SBRT) (NCT04572451171).

**[H3] Interleukin-17**

Blocking IL-17 in a murine model of gastric cancer led to a reduction of tumor growth and in combination with anti-PD-1 therapy to tumor rejections in 80 % of the mice172. It also decreased the development of prostate cancer173. IL-17 can accelerate the progression of multiple myeloma174 and another study showed that IL-17 neutralization indeed can lead to a reduction in multiple myeloma growth175. A clinical trial started in 2017 (NCT03111992176) now explores the efficacy of the anti-IL-17A antibody CJM112 in multiple myeloma.

**[H3] Interleukin-23**

In the context of castration-resistant prostate cancer (CRPC), MDSC-derived IL-23 was shown to activate the androgen receptor pathway, thereby supporting survival and proliferation of cancer cells under androgen-deprived conditions. Neutralization with an anti-IL-23 antibody significantly reduced tumor growth and extended survival of mice177. This suggests anti-IL-23 therapy might support anti-androgen therapy regimens. To assess the potential of this, the anti-IL-23 antibody tildrakizumab is now tested in a phase 1/2 trial in CRPC patients in combination with abiraterone acetate, an inhibitor of androgen synthesis (NCT04458311178).

**[H3] Interleukin-33**

It was shown in a preclinical study that IL-33 may directly act on tumor cells, inducing polyploidy, rapid proliferation, and causing therapy resistance. Using a specific IL-33-blocking antibody could restore the efficacy of anti-PD-1 therapy in an otherwise ICI-resistant subclone of the B16F10 melanoma model179.

***[H2] Recombinant and engineered interleukins***

IL-2 was the first interleukin to be approved for cancer treatment, although its use entails major safety concerns180. Recent advances focusing on modifying interleukins to improve toxicity and efficacy of treatment with recombinant and/or engineered interleukins might help to overcome this issue.

**[H3] Interleukin-2**

Although high dose therapy with IL-2 induced durable complete responses (CR) in some melanoma and RCC patients, it comes with potentially life-threatening adverse events. Therefore, low dose IL-2 schedules were evaluated in several trials. However, in low abundance, IL-2 binds preferentially to its high-affinity receptor expressed on Tregs, potentially leading to immune evasion. Thus, several IL-2 variants with an increased affinity towards the IL-2Rβ:γc complex expressed by CTLs are in development.

A non-α IL-2 variant already in clinical trials is bempegaldesleukin, a pegylated IL-2 variant. In addition to increasing its half-life, the polyethylene glycol (PEG)-residues coupled to IL-2 block its binding site to the high-affinity IL-2Rα subunit. Over time, the PEG groups are lost and continually release the active form of bempegaldesleukin, thereby minimizing overdosing181. Bempegaldesleukin was evaluated as monotherapy in phase 1 clinical trial in patients with metastatic solid tumors, predominantly consisting of patients with melanoma or RCC. The best overall responses observed were SD182, which is disappointing in comparison to the 7 % and 9 % durable CR achieved by conventional IL-2 therapy in melanoma and RCC180,182. Nevertheless, bempegaldesleukin showed a favorable safety profile, encouraging combination with ICIs. A phase 1 study on bempegaldesleukin in combination with nivolumab in metastatic solid tumors achieved a 19 % CR183. Several other clinical trials in combination with ICIs including phase 3 clinical trials in patients with bladder cancer (NCT04209114184), RCC (NCT03729245185), or melanoma (NCT03635983186) are currently ongoing. Other non-α IL-2 variants are tested in clinical trials in combination with ICIs. ALKS 4230 is a circularly permuted IL-2 and IL-2Rα designed to selectively activate the intermediate-affinity IL-2R that is tested in 4 clinical trials in patients with advanced solid tumors or non-cutaneous squamous cell carcinoma of head and neck alone and in combination with pembrolizumab (see Supplementary Table 1). THOR707 is an engineered non-α IL-2 tested in patients with solid tumors alone and in combination with an unspecified ICI or with an anti-EGFR antibody (NCT04009681187).

NARA1leukin is a fusion construct that consists of human IL-2 engineered into the anti-IL-2 antibody NARA1. NARA1 is thereby permanently masking the CD25-binding site of IL-2 and thus abolishing the CD25-mediated Treg development while mediating potent anti-tumor responses in a murine melanoma model188.

Another approach is the de novo design of Neo-2/15, a hyper stable interleukin that mimics only the binding site to IL-2Rβ:γc, but otherwise structurally independent from IL-2 and IL-15. Therefore, it can mediate IL-2 and IL-15 signaling independent of IL-2Rα or IL-15Rα and showed superior therapeutic activity compared to IL-2 in mouse models of melanoma and colon cancer189.

Several attempts have been made to couple IL-2 to tumor-targeting antibodies to reduce side effects caused by high systemic concentrations while improving the efficacy by concentrating IL-2 at the tumor. Some of those IL-2-antibody fusion constructs reached the stage of clinical trials190. However, no breakthrough results have emerged so far (see Supplementary Table 1).

**[H3] Interleukin-10**

IL-10 has anti-inflammatory as well as CTL-stimulating properties, which led to its exploration as an anti-cancer therapeutic. The pegylated IL-10 variant pegilodecakin can induce systemic immune activation, an increase of immunostimulatory cytokines as well as a reduction of TGF-β in patients with solid cancer. Additionally, PRs and prolonged SD were observed upon pegilodecakin treatment191. In a follow-up trial, in a mixed group of solid cancers expansion and activation of intratumoral CTL in response to treatment were observed192. First clinical data on the combination of pegilodecakin with ICIs was promising as well193, however, two follow-up trials testing pegilodecakin in combination with nivolumab (NCT03382912194) and the anti-PD-1 antibody pembrolizumab (NCT03382899195) have been terminated early due to an unfavorable risk-benefit ratio.

An agent still in the preclinical investigation is CmAb-(IL-10)2, a bispecific fusion protein with one arm derived from the anti-EGFR antibody cetuximab and the other arm containing an IL-10 dimer. It has shown superior anti-tumor activity compared to IL-10 fused to a non-tumor-targeting antibody196.

**[H3] Interleukin-12**

IL-12 is an interleukin that demonstrates striking immune activation and tumor control but causes severe adverse effects in the doses necessary to induce an anti-tumor effect. However, targeted delivery strategies to achieve high concentrations at the tumor site while avoiding high systemic amounts led to a renaissance of IL-12 cancer therapy197.

Gene therapy allows to better control the localization and amount of interleukins in a therapy regimen. Tavokinogene telseplasmid, an IL-12 encoding plasmid electroporated into melanoma lesions, achieved an overall response rate of 36 % with a CR rate of 18 % in a phase 2 trial. Of note, 46 % of patients also showed regression in at least one uninjected lesion and 25 % had a net regression in all uninjected lesions198, suggesting the induction of systemic anti-tumor immunity. In combination with pembrolizumab, the overall response rate could be increased to 41 % with 36 % CR199. Several follow-up trials have been initiated between 2017 and 2020 in triple-negative breast cancer (TNBC) (NCT03567720200), head and neck squamous cell carcinoma (HNSCC, NCT03823131201), and melanoma (NCT04526730202, NCT03132675203).

Other therapeutic strategies using IL-12 have been extensively discussed elswhere107,197 and recent clinical trials are listed in Supplementary Table 1.

CBD-IL-12 is a fusion protein consisting of IL-12 and a collagen-binding domain. It accumulates in the tumor due to exposed collagen in the disordered tumor vasculature and demonstrates anti-tumor effects superior to IL-12 by a broad activation of the immune system at the tumor site204.

Li et al. designed multifunctional oncolytic nanoparticles with the intent to send several different signals triggering anti-tumor responses at once. They show that the composition of nanoparticles containing self-replicating RNA can induce immunogenic cell death of tumor cells, as the contained RNA serves as a signal for PRRs as well as coding IL-12 to further enhance the induced immune response. When delivered intratumorally, control of large tumors is achieved in several tumor models205.

**[H3] Interleukin-15**

In contrast to IL-2, IL-15 does not lead to Treg expansion while having similar immunostimulatory properties. However, monotherapy with IL-15 and several engineered variants was ineffective, although there are several promising combination therapies in clinical trials206.

An example of this is ALT-803, consisting of recombinant IL-15 with an N72D mutation linked to the Sushi-domain of IL-15Rα fused to an immunoglobulin G (IgG) Fc-fragment. While the N72D mutation increases binding to IL-15Rβ, the Sushi-domain provides the IL-15Rα part and the Fc-fragment increases its half-life. However, ALT-803 had only limited effect as monotherapy in patients with solid tumors207 and showed responses in only 19 % of patients with hematologic malignancies208. Strikingly, in combination with intravesical bacillus Calmette-Guérin (BCG) therapy, CRs could be achieved in 9 out of 9 patients with bladder cancer209, which led to the expansion of the trial to enroll nearly 600 patients (NCT02138734210).

Other IL-15-based therapeutic strategies include combination with ICIs and tumor-targeting antibodies (Supplementary Table 1) and approaches for IL-15 in combination therapy of cancer have been extensively reviewed206,211.

**[H3] Interleukin-18**

IL-18 therapy has shown little preclinical efficacy, potentially due to IL-18BP, a high-affinity IL-18 decoy receptor. Using direct evolution, the authors developed decoy-resistant IL-18 (DR-18) that maintains signaling potential and unlike IL-18 exerted potent anti-tumor responses in mice, by supporting effector T cell development, reducing T cell exhaustion, and enhancing activity and maturation of NK cells97.

**[H3] Interleukin-23 and Interleukin-36**

IL-36γ together with IL-23 can be successfully employed in combination with OX40 ligand to promote acute inflammation for efficient tumor control212 and is currently under investigation in a clinical trial (NCT03739931213).

***[H2] Complementing adoptive cell transfer***

Interleukins play a key role in ACT, a breakthrough achievement in cancer therapy of the past decade. Interleukins such as IL-2, IL-7, and IL-15 have been widely used to improve *in vitro* expansion and differentiation of adoptive cells and to complement ACT therapy in humans by co-administration or by genetically engineering them into the transferred cells.

**[H3] Interleukin-2**

Treatment of patients with IL-2 to support ACT has been studied with variable success in several cancer types. Among others, IL-2 was combined with tumor-infiltrating lymphocytes (TIL) in melanoma214. While some of those trials yielded benefits, for example, a correlation of chimeric antigen receptor (CAR) T cell engraftment with IL-2 concentrations215, this approach still faces toxicity problems similar to those of using interleukins alone.

A strategy to overcome the toxicity of systemic IL-2 treatment while retaining its ability to support ACT therapy is orthogonal IL-2/IL-2 receptor pairs. The designed *ortho*IL-2 cannot bind to the wild-type IL-2 receptor but transfers native IL-2 signaling when binding to the designed *ortho*IL-2Rβ, which was transduced into T cells. This creates a system where only the ACT product reacts to the *ortho*IL-2 treatment and systemic toxicity is avoided. *Ortho*IL-2 showed efficacy in a mouse melanoma model with the enhanced expansion of *ortho*IL-2Rβ ACT product and negligible toxicity. These data might indicate a potential advantage for clinical use in ACT216.

**[H3] Interleukin-8**

A quite different approach is to use tumor-associated interleukins, such as IL-8, to improve CAR T cell infiltration into the tumor by overexpressing their respective receptors. The expression of the IL-8 receptors CXC motif chemokine receptor (CXCR)1 or CXCR2 in CAR T cells markedly enhanced migration and persistence in the tumor and induced complete regression and long-lasting immunological memory in preclinical models of glioblastoma, ovarian and pancreatic cancer217.

**[H3] Interleukin-12**

Another strategy currently pursued in several trials is the expression of certain interleukins by cellular therapy products. In this manner, the interleukins should only be expressed locally at the tumor site, thereby avoiding systemic toxicity and recruiting additional immune cells to establish immune responses against CAR-antigen negative tumor cell populations. In the case of T cells, this approach was named ‘T cells redirected for antigen-unrestricted cytokine-initiated killing’ (TRUCK). The first interleukin used as a proof of concept for TRUCKs was IL-12218 and by now other interleukins, such as IL-7, IL-15, and IL-23 have been used to engineer T cells as well.

In preclinical testing, IL-12 expression by CAR T cells led to the recruitment and activation of macrophages critical for the elimination of cancer cells with antigen-loss that would normally escape from CAR-induced killing218. The first in-human trial was a study expressing IL-12 under control of a nuclear factor of activated T-cells (NFAT)-inducible promotor in TILs from patients suffering from metastatic melanoma. However, the study had to be terminated due to severe toxicities likely caused by excessive IL-12 release219. Recently, several clinical trials have been started using IL-12-expressing CAR T cells, trying to avoid uncontrolled IL-12 release by the more restricted activation of CARs compared to polyclonal TIL and by using safety switches (see Supplementary Table 1).

Another approach is to induce only transient expression of IL-12 by electroporating *IL-12* mRNA into ovalbumin-specific OT-I TCR transgenic CD8+ T cells. Injected intratumorally, but not intravenously, these cells led to complete rejections of injected and distant lesions in a B16-ova tumor model. The authors claim that the transient expression was likely helpful to restrict IL-12 induced adverse events, but do not show any data to prove this assumption220.

A recent clinical trial using intratumorally injected activated DCs (aDCs) showed that successful DC therapy was associated with higher expression of IL-12p40 and IL-8221. This may indicate a favorable interplay between DC- and interleukin therapy.

**[H3] Interleukin-7**

Over time, the idea to express interleukins in the ACT product has spread from IL-12 to other interleukins. IL-7 and chemokine (C-C motif) ligand 19 (CCL19) are essential for the maintenance of T cell zones in lymphoid organs. In a preclinical setting, CAR T cells engineered to express IL-7 and CCL19 were superior in tumor killing in comparison to conventional CAR T cells. Histopathological analysis showed increased infiltration of DCs and CAR T cells as well as endogenous T cells into the tumor. The depletion of endogenous T cells dampened the therapeutic effect of IL-7 CCL19 CAR T cells. Together with the observation of abundance of memory CAR T cells and endogenous T cells in the spleen, this suggests co-expression of IL-7 and CCL19 by CAR T cells can initiate a CAR-independent immune response222. Four clinical trials evaluating the effect of CAR T cells overexpressing IL-7 and CCL19 have been initiated between 2017 and 2020 (see Supplementary Table 1).

**[H3] Interleukin-15**

Preclinical studies showed that the expression of IL-15 in NKT cells led to a decreased expression of exhaustion markers, enhanced in vivo persistence, increased localization at the tumor site, and improved tumor control223. In CAR T cells, membrane-bound IL-15 led to an increase in T memory stem cells with long persistence and potent rejection of CD19+ leukemia224. This led to a collection of still ongoing clinical trials engineering IL-15 into CAR T and NKT cells (Supplementary Table 1). An interim analysis showed that anti-GD2 CAR-NKT cells expressing IL-15 did not cause any dose-limiting toxicities in three heavily pretreated children with neuroblastoma. CAR-NKT cells were shown to be present at the tumor sites and one patient achieved regression of bone metastatic leasions225.

Recently, a novel approach to reduce the toxicity of IL-15 has been reported. Tang et al. designed a cell-surface conjugated nanogel that can be loaded with large quantities of protein drugs226. The nanogel is designed to release its cargo upon an increase in T cell surface reduction potential, which is induced by T cell-antigen encounter. Thereby, the drug release is limited to places of TCR activation, predominantly the tumor site. The authors also show that the system is translatable to CAR T cells. The potential to expand this method to other cytokines and protein drugs, maybe even combinations thereof, makes this system especially noteworthy, although the approach is inherently self-limiting as the nanogels will be depleted of their drugs over time226.

**[H3] Interleukin-23**

A very recently published alternative to potentially toxic interleukins like IL-12 and IL-15 is IL-23. A preclinical study showed that engineering CAR T cells with the IL-23 subunit p40 led to autocrine IL-23 signaling promoting the selective proliferation of activated T cells with improved anti-tumor capacity. Additionally, side effects seemed diminished compared to IL-18 or IL-15227.

**[H1] Future outlook** Limited understanding of the impact of interleukin therapy on carefully balanced systems in the TME, as well as the Janus-likes functions of some interleukins, rendered the therapeutic exploitation of interleukins difficult to predict. This caused much disappointment in the field of interleukin therapy of cancer, as life-threatening side effects occurred while most therapeutic strategies did not live up to the expectations concerning effectiveness.

One example is the targeting of one of the first interleukins to be discovered (IL-1β), in which case neutralization could yield either disease exacerbation or improvement. Recent developments have pointed out that neutralization of this key pathway at a time point where the disease is already present might have therapeutic activity in cancer patients. Also, IL-2 monotherapy in melanoma and RCC achieved durable CR, highlighting the potential of interleukin therapy.

However, in general, interleukin monotherapy so far still faces major limitations and new strategies have emerged recently to tackle those problems. Thus, the trend is moving away from applying native forms of interleukins and goes towards sophisticated engineering approaches. Most investigated strategies in the past years were altering the receptor affinity to the only target selected cell populations or designing tumor-targeting fusion constructs to increase the efficacy and reduce systemic toxicities.

Additionally, to improve the application of interleukin therapy, combination approaches are gaining more and more importance. New insights on how interleukins shape tissue repair, cancer progression, and immune evasion will greatly help to identify how interleukins are involved in the resistance against established therapies like chemotherapy or ICI treatment. Thereby, interleukin therapy could unleash the unused potential of other therapeutics and thus help otherwise therapy-resistant patients to benefit thereof.

Another hypothesis on the low efficacy of interleukin monotherapy is the idea that delivering a single immunostimulatory signal is not sufficient to mount a durable immune response that can eliminate the tumor. Hence, strategies combining several immunostimulatory signals have been fast approaching recently. A strategy often pursued in this regard is the combination of interleukin therapy to support ACT, either by combining ACT with regular interleukin therapy or by the development of TRUCKs. ACT showed remarkable success in hematologic malignancies but lacks efficiency in solid tumors due to poor infiltration and proliferation of the ACT product as well as a highly immunosuppressive TME impairing its function. Interleukins may support ACT by overcoming all of those hurdles and the amount of clinical trials in this fashion highlights the expectations set in the idea.

**[H1] Conclusion**

In conclusion, interleukins comprise key elements that orchestrate the TME and govern tumor-immune cell crosstalk, as they are important players in large cytokine networks. Although interleukin or interleukin-targeted therapy still has significant hurdles to overcome on its path to the clinic, the intensive foundational research conducted on interleukins in cancer biology in the past decade will help to better understand the mechanisms of interleukin therapy and thereby contribute to the development of new strategies. Also, there is a rich pipeline of exciting new preclinical and clinical studies on interleukin therapy of cancer that will yield interesting results in the upcoming years.

Table 1 | **Interleukin families and their role in cancer**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Interleukin** | **Receptors** | **Function in cancer** | **Potential therapeutic strategy** | **Ref.** |
| ***IL-1 superfamily*** | | | | |
| *IL-1 subfamily* | | | | |
| IL-1α | IL-1R1:IL-1R3  sIL-1R3 | Pleiotropic: promotes inflammatory carcinogenesis and anti-tumor immunity | Therapeutic neutralization to manage cachexia in clinical trials | 12,228 |
| IL-1β | IL-1R1:IL-1R3  IL-1R2:IL-1R3  sIL-1R2  sIL-1R3 | Pleiotropic: promotes inflammation-induced carcinogenesis, but recruits anti-neoplastic cells, may block metastatic outgrowth | Therapeutic neutralization to manage CR syndrome in ACT, cancer prevention and treatment (CANTOS trial) | 12,229 |
| IL-33 | IL-1R3:IL-1R4  sIL-1R4 | Protumor: tumorigenic niche, Tregs function, Th2 polarization | Preclinical neutralization | 15,124 |
| *IL-18 subfamily* | | | | |
| IL-18 | IL-1R5:IL-1R7  IL-18BP | Mostly antitumoral: activates lymphocytes to produce IFN-γ, induces apoptosis | Preclinical engineered rIL-18 or in combination with ACT, hampered by IL-18BP | 97 |
| IL-37 | IL-1R8:IL-1R7 | NK cell function checkpoint, but has some anti-tumor properties | Not explored | 230 |
| *IL-36 subfamily* | | | | |
| IL-36α, β, and γ | IL-1R6:IL-1R3 | Anti-tumoral: promotes Th1 inflammation, inhibited by IL-36Ra | Preclinical rIL-36γ as a tolerable alternative to IL-1 | 231 |
| IL-38 | IL-1R6:IL-1R9 | Has not been explored, evidently immunosuppressive | Not explored | 232,233 |
| ***IL-2 (common γ chain) family*** | | | | |
| IL-2 | sIL-2Rα  IL‑2/15Rβ:γc  IL‑2Rα:IL‑2/15Rβ:γc | Anti-tumoral: T and NK cell growth factor, but terminates T cell responses by the maintenance of T regs and induction of AICD | rIL-2 approved for monotherapy. Further engineered to avoid side effects and is used in ACT | 8,234 |
| IL-4 | IL-4Rα:γc  IL-4Rα:IL-13Rα1 | Protumoral: promotes Th2 inflammation and Th9 polarization. IL-4R, when overexpressed, promotes cancer growth | Targeting IL-4R bearing cancer cells, blocking signaling. Producing anti-tumoral Th9 cells for ACT | 235 |
| IL-7 | IL-7Rα:γc  sIL-7Rα | Anti-tumoral: T and NK cell growth factor | rIL-7 or analogs in combination with ILs or ACT | 236 |
| IL-9 | IL-9R:γc | Pleiotropic: context-dependent | Preclinical Th9 cells in ACT | 114 |
| IL-15 | IL-15:IL15Rα +  IL-2/15Rβ:γc | Anti-tumoral: activates lymphocytes to produce IFN-γ | rIL-15 or analogs in combination with ILs or ACT | 8 |
| IL-21 | IL-21R:γc | Anti-tumoral: enhances cytotoxicity of CTLs | Combination therapies with rIL‑21 in clinical trials | 8 |
| ***IL-3 family*** | | | | |
| IL-3 | IL-3Rα:βc | Hematopoietic factor, promotes hematologic malignancies | Fused to toxins to target CD123-bearing cells | 105,106 |
| IL-5 | IL-5Rα:βc | Pleiotropic: via eosinophils and Th2 | Preclinical neutralization | 101 |
| ***IL-6 family*** | | | | |
| IL-6 | IL-6Rα:gp130 (classic)  sIL-6Rα:gp130 (trans) | Protumoral: activates carcinogenesis, tumor outgrowth, mediates CRS, promotes cachexia | Neutralization to manage CRS in ACT, cachexia | 36,37,44 |
| IL-11 | IL-11Rα:gp130 (classic)  sIL-11Rα:gp130  (trans) | Protumoral: promotes inflammation induced carcinogenesis and cancer progression | Preclinical neutralization and gp130 common receptor blockade | 38,39 |
| IL-31 | IL-31Rα:OSMRβ | Th2 cytokine, evidently tumorigenic | Not explored | 237 |
| ***IL-10 family*** | | | | |
| IL-10 | IL-10Rα:IL-10Rβ | Pleiotropic: promotes cytotoxicity,  but inhibits anti-tumor responses | rIL-10 to increase cytotoxicity in trials | 192,238 |
| IL-19 | IL-20Rα:IL-20Rβ | Understudied, evidently protumoral | Not explored | 239 |
| IL-20 | IL-20Rα:IL-20Rβ  IL-22Rα1:IL-20Rβ | Protumoral: directly promotes carcinoma outgrowth, induces PD-1 | Preclinical neutralization | 33,240 |
| IL-22 | IL-22Rα1:IL-10Rβ  IL-22Rα2 (IL-22BP) | Protumoral: promotes progression of carcinomas | Preclinical neutralization | 77,238 |
| IL-24 | IL-20Rα:IL-20Rβ  IL-22Rα1:IL-20Rβ | Anti-tumoral: induces apoptosis and autophagy of cancer cells | Preclinical rIL-24 combined with oncolytic virus | 241,242 |
| IL-26 | IL-20Rα:IL-10Rβ | Protumoral via Th17 and neutrophils | Preclinical neutralization | 243,244 |
| ***IL-12 family*** | | | | |
| IL-12 | IL-12Rβ1:IL-12Rβ2 | Anti-tumoral: the main driver of Th1 immunity, initiates and amplifies IFN-γ production | rIL-12 has severe side effects, thus engineered, or combined with other ILs and ACT in trials | 8,245 |
| IL-23 | IL-23R:IL-12Rβ1 | Mainly protumoral: direct and indirect effect via Th17 and Th22 | Neutralization in trials, enhance CAR T cell cytotoxicity | 212,227,245 |
| IL-27 and  IL-30  (also known as IL-27p28) | IL‑27Rα(WSX‑1):gp130 | Pleiotropic: induces NK and CTL cytotoxicity, but enhances Treg activity and T cell exhaustion | Neutralization and engineered rIL-27 in trials | 120,121,246,247 |
| IL-35 | IL-12Rβ2:gp130  IL-12Rβ2:IL-12Rβ2  gp130:gp130  IL-27Rα:IL-12Rβ2 | Protumoral: Treg mediated suppression of T cell responses and exhaustion of T cells. Promotes metastatic colonization | Preclinical neutralization in combination with checkpoint inhibitors and other therapies | 83,126 |
| ***IL-17 family*** | | | | |
| IL-17A/F | IL-17RA:IL-17RC | Protumoral: carcinogenesis, immunosuppression, EMT | Neutralization in clinical trials | 60,129 |
| IL-17B | IL-17RB | Mostly protumoral, but antitumoral properties are also reported | Not explored, scarce preclinical evidence | 248 |
| IL-17C | IL-17RA:IL-17RE | 249 |
| IL-17D | unknown | 250 |
| IL-25 (also known as IL-17E) | IL-17RA:IL-17RB | 63 |
| ***IFN-λ family (type III interferons)*** | | | | |
| IL-28A and B | IL-28Rα(IFNLR1):IL-10Rβ | Anti-tumoral: induces apoptosis of malignant cells | Preclinical gene therapy using IL-28 and IL-29 | 102,103,251 |
| IL-29 | IL-28Rα:IL-10Rβ |
| ***Other interleukins*** | | | | |
| IL-8 (also known as CXCL8) | CXCR1, CXCR2  ACKR1/DARC | Protumoral: attracts neutrophils, mediates suppressive environment | Therapeutic neutralization in clinical trials | 132 |
| IL-13 | IL-13Rα1:IL-4Rα  IL-13Rα2 | Protumoral: Th2 cytokine | Targeting or blocking IL-13R | 235 |
| IL-14α and β | IL-14R | B cell growth factor, also in lymphoma, not explored | Not explored | 252 |
| IL-16 | CD4 | Evidently protumoral: lymphoma proliferation, chemoattractant | Not explored, scarce preclinical evidence | 253 |
| IL-32  (Also known as NK4) | unknown | Pleiotropic: depending on isoform (α to s) and cancer type | Preclinical anti-tumor effects in combination | 254 |
| IL-34 | CSF1R | Protumoral: cancer progression, immune suppression, and therapeutic resistance | Preclinical neutralization to alleviate protumor effects | 255,256 |

**Abbreviations |** Interleukin (**IL**), complete response (**CR**), adoptive cell transfer (**ACT**), Canakinumab Anti-inflammatory Thrombosis Outcomes Study (**CANTOS**), interferon-γ (**INF-γ**), IL-18 binding protein (**IL-18BP**), natural killer cell (**NK**), activation-induced cell death (**AICD**), cytotoxic T lymphocyte (**CTL**), cytokine release syndrome (**CRS**), programmed cell death-1 (**PD-1**), IL-22 binding protein (**IL-22BP**), epithelial-to-mesenchymal transition (**EMT**)

Diagram

Description automatically generated

**Figure 1 | Interleukins in carcinogenesis.** Persistent inflammation in response to pathogen- and danger-associated molecular patterns (PAMP and DAMP) triggers activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which primes pro-IL-1β production and NLR family pyrin domain containing 3 (NLRP3) inflammasome activation that causes the release of active IL-1β from fibroblasts, epithelial and myeloid cells such as dendritic cells (DCs), monocytes and macrophages (MΦ). In turn, IL-33 derived from tumor-initiating cells (TIC) recruits macrophages (MΦ) that upon activator protein 1 (AP-1) signaling produce transforming growth factor-beta (TGF-β) which suppresses the function of cytotoxic lymphocytes (CTL). IL-1β induces production of nitric oxide (NO) and reactive oxygen species (ROS) by epithelial cells that may cause DNA damage and promotes the production of IL-6 and IL-11 from epithelial and myeloid cells, and IL-22 from type 3 innate lymphoid cells (ILC3) and γδ T cells. Under homeostatic conditions, IL-22 facilitates DNA repair caused by bacterial genotoxins, but in transformed cells, IL-6 and IL-11 together with IL-22 rapidly induce phosphorylation (P) of signal transducer and activator of transcription 3 (STAT3). Activation of STAT3 signaling is observed in multiple types of cancer and induces proliferation, survival, stemness, epithelial-mesenchymal transition and migration of transformed cells. IL-1β together with TGFβ induces differentiation of T helper 17 (Th17) cells, which upon IL-23 stimulation from DCs secrete IL-17A and IL-17F (IL-17A/F). IL-17, which typically activates NF-κB to mediate wound-healing signaling and may exacerbate nascent tumor outgrowth.

Diagram

Description automatically generated

**Figure 2 |** **Tumour microenvironment.** Immunoevasion and tumor progression rely on cancer cell-intrinsic and extrinsic cytokine signaling. Several cancer types were demonstrated to overexpress certain cytokines, for example IL-6 or IL-11, which may act in an autocrine manner to activate phosphoinositide 3-kinase (PI3K)-[protein kinase B](https://en.wikipedia.org/wiki/Protein_kinase_B) (AKT)-mTOR signaling to upregulate glycolysis and induce metabolic reprogramming, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), RAS-RAF-MAPK and activator of transcription 3 (STAT3). These pathways in turn can lead to epithelial-mesenchymal transition (EMT), increased proliferation, reduced apoptosis, increased migration and production of cytokines, such as IL-8, metalloproteinases and vascular endothelial growth factor (VEGF) which induces angiogenesis. Other cytokines, such as IL-1β, IL-13, IL-17, IL-22, IL-23, IL-35 can also induce EMT and, thus, tumor progression. Tumor-secreted IL-8, in turn, induces recruitment of polymorphonuclear leukocytes (PMN), which together with monocytes differentiate into myeloid-derived suppressor cells (MDSC), which inhibit Th1 responses and together with tumor-associated macrophages (TAM) and M2 macrophages, polarized by T helper 2 (Th2) cytokines, contribute to the pool of transforming growth factor-beta (TGF-β) to shape an immunosuppressive microenvironment. In turn, TGF-β together with IL-33 promote differentiation of T regulatory cells (Treg), which bear a high-affinity IL-2 receptor and are a major source of IL-10 that under chronic conditions suppresses anti-tumor responses. Alternatively, together with IL-6, TGFβ promotes the differentiation of Th17 cells to produce IL-17 and promote further MDSC recruitment and differentiation.

Diagram

Description automatically generated

**Figure 3 | Interleukin-based cancer control.** Natural killer (NK) cells bear a set of receptors that allow the recognition and elimination of transformed cells. Danger-associated molecular patterns (DAMP), such as high-mobility group protein B1 (HMGB1), that are released from malignant cells, are processed by resident antigen-presenting cells, such as dendritic cells (DC), and macrophages (MΦ). In turn, these cells produce IL-12 and IL-15 to promote the cytotoxic activity of NK cells and cytotoxic lymphocytes (CTL) and induce Interferon-γ (IFN-γ) release. Resident and recruited monocytes upon priming differentiate into macrophage-like cells and contribute to IL-12 and IFN-γ pool. DCs loaded with tumor antigens migrate into the draining lymph nodes (LN), where they present processed antigens together with [major histocompatibility complex](https://en.wikipedia.org/wiki/Major_histocompatibility_complex) class II (MHCII) to naïve T cells. Naïve T cells originate from the lymphoid progenitors in the bone marrow (BM), where they require an IL-3 proliferation signal, and further IL-7 promoted development in the thymus. IL-12 secreted by DCs in the LN triggers expression of T-box transcription factor (T-BET, also known as TBX21) that defines T helper 1 (Th1) polarization. Upon stimulation, Th1 and CTL migrate to the tumor site and produce IL-2 that leads to rapid lymphocyte proliferation (represented by a circular arrow) and amplification of antigen-specific responses. CTLs and Th1 cells use perforin and granzymes to kill tumor cells and release IFN-γ that can directly induce apoptosis of tumor cells and primes M1 macrophage polarization, that together with DCs produce IL-12 nesessary to sustain Th1 polarization and amplify IFN-γ production. Cytotoxic effects may be also enhanced by IL-10 secreted by M1 macrophages, IL-27 from macrophages and DCs and IL-21 from T helper 17 (Th17) and T follicular helper (Tfh) cells.



**Figure 4 | Mechanisms of interleukin therapy.** a|Recombinant and engineered cytokines. Increased persistence: Prolonging half-life and controlling interleukin toxicity by the progressive release of the active drug from conjugated polymers or Fc-tags. Targeted toxicity: Interleukin-toxin fusion proteins target the toxin to cells bearing the interleukins receptor leading to cell death. Gene therapy: To avoid systemic toxicity, the interleukin is expressed directly at the tumor site. Selective receptor affinity: interleukins can be engineered to alter their receptor affinity, thereby increasing efficacy or reducing side effects. Targeted interleukin delivery: By coupling interleukins to tumor-targeting antibodies, they reach higher concentrations at the tumor site while decreasing side effects associated with high systemic concentrations. b|Complementing adoptive cell therapy (ACT). T cells redirected for antigen-unrestricted cytokine-initiated killing (TRUCKs): Expression of interleukins by ACT cells leads to an accumulation of the interleukin at the tumor site, thereby avoiding systemic toxicity and mounting non-ACT immune responses by the activation of endogenous T cells (tumour infiltrating T cells, TILs) for targeted cancer cell killing, as well as macrophages that can also mount an innate immune response against cancer cells that do not express antigen. Sensitizing chimeric antigen receptor (CAR) T cells to IL: Expression of interleukin receptors (for example, IL-7R) on ACT cells increases the likelihood of signaling at low interleukin concentrations. DC vaccine adjuvant: DC vaccination can be accompanied by therapy with interleukins (for example, IL-2) enhancing the activation of DC-primed T cells. ACT adjuvant: Improving persistence, survival, proliferation, and activation of ACT by interleukin therapy (for example, IL-2 or IL-15).

Box 1 | **Cytokine release syndrome**

While CAR T cell therapy is effective in hematological malignancies, severe cytokine release syndrome (CRS) is a potentially lethal side effect of the treatment. In the first case reports about CAR T cell therapy febrile neutropenia, hypotension, acute vascular leakage syndrome, and acute respiratory distress syndrome occurred in a patient but could be successfully treated with a single course of anti-cytokine therapy257. It was confirmed that IL-6 is among a group of 7 cytokines significantly elevated in patients' serum that is predictive of CRS258. Further research in mice showed that the severity of CRS is not due to CAR T cells, but to macrophages releasing IL-1 and IL-6259,260. Tumor-CAR T cell interaction triggered the recruitment and activation of myeloid cells. Direct activation of macrophages by CAR T cells via the CD40L/CD40 axis was proposed as an additional mechanism260. The time-course analysis revealed that IL-1 preceded IL-6 release by 24 hours259, thereby making it an attractive target for CRS therapy. This hypothesis was further supported by the exclusive upregulation of IL-1R1 in tumor-associated myeloid cells but not splenic cells260. Treatment of CRS with the IL-1R antagonist anakinra proved to be effective in both preclinical studies259,260. In 2019 and 2020 three clinical trials started to evaluate the ability of anakinra to alleviate CAR-induced CRS in different leukemias. Anakinra is also evaluated in a study for the treatment of COVID-19 induced CRS.

Box 2 | **Cancer-induced cachexia treatment involving interleukins**

IL-6 leads to cellular and systemic metabolic reprogramming capable to induce cachexia in patients with cancer. Preclinical studies show that the anti-IL-6R antibody tocilizumab can reduce the bodyweight drop associated with cachexia induced by the transplanted tumor in a mouse lung cancer model261. The anti-IL-6 antibody clazakizumab was used to treat patients with non-small cell lung cancer (NSCLC) and weight loss of more than 5 % of their body weight in the last three months. Although one serious adverse event was likely connected to the therapy, clazakizumab treatment improved the lung symptom score and reversed fatigue. Furthermore, the loss of lean body mass was reduced from -1,5 kg on placebo to -0,19 kg on clazakizumab262.

Moreover, ubiquitous expression of gp130 enables IL-6 signaling in the liver that reduces ketogenesis via suppression of peroxisome proliferator-activated receptor alpha (PPAR-α) and causes hypoketonemia, which, then triggers glucocorticoid secretion, immunosuppression and contributes to cachexia263. In advanced cancer, IL-1α together with IL-6 influence energy metabolism and induces autophagy in the muscle, liver, and adipose tissue, which indicates a potential avenue in managing cachexia264,265. Bermekimab, an antibody that neutralizes IL-1α, was also used to treat cancer patients suffering from cachexia. Bermekimab did not improve survival but increased lean body mass and improved quality of life in patients with NSCLC and CRC266,267. However, marketing authorization for Europe was refused by the European Medicines Agency (EMA) due to safety and efficacy concerns.   
A recent preclinical study reveals the potential of tumor-derived IL-8 to induce cachexia by inducing myotube atrophy, which could be inhibited by the use of CXCR2 antagonists268. Also, treatment of cancer-induced cachexia with IL-4 promoting protein synthesis and rescuing myogenesis was proposed to be a promising avenue recently269.

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Author contributions

S.K., D.B., J.D. contributed equally to all aspects of the article. S.E., P.L. and C.A.D. contributed to researching literature for the article, discusion of the content, and reviewed or edited the manuscript before submission.

**Competing interests**

S.K and S.E are inventors of several patents in the field of immuno-oncology unrelated to the present work. S.K and S.E received research support from TCR2 Inc and Arcus Bioscience for work unrelated to this manuscript. SK and SE have licensed IP to TCR2 Inc, SK has received honoraria from GSK and Novartis.

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**Glossary**

Adoptive Cell Transfer

Treatment of patients with ex vivo expanded or modified immune cells usually derived from the patient itself.

Antigen-Presenting Cell

Dendritic cells, macrophages, and B cells that present non-self peptide antigens to T cells via MHC II molecules.

Checkpoint inhibition

Therapeutic neutralization of signaling pathways that activate immune checkpoints, which normally lead to the inhibition of immune cell function to keep immune responses under control.

Danger-associated molecular patterns and alarmins

Endogenous, constitutively expressed, chemotactic, and immune-activating proteins and peptides that are released upon degranulation, cell injury, or death or in response to immune induction.

ΓΔ T Cells

A subset of T cells differing from conventional T cells by expressing a distinct γδ T cell receptor in contrast to the usual αβ T cell receptor. They do not depend on MHC presentation and possess properties of both innate and adaptive immunity

Group 2 Innate Lymphoid Cells

Cells with characteristics of lymphoid cells but without rearranged antigen-specific surface receptors. Similar to CD4+ T cells, they produce type-2 cytokines and are also referred to as natural or innate helper cells.

Group 3 Innate Lymphoid Cells

Cells with characteristics of lymphoid cells but without rearranged antigen-specific surface receptors are crucial for maintaining homeostasis in the gut microbiota.

Immunotherapy

Treatment of patients with factors shaping an immune response to enable the patient's immune system to react to the disease.

M1 Macrophages

A macrophage subtype associated with inflammation that is characterized by the secretion of the pro-inflammatory cytokines IL-1, IL-6, and TNFα.

M2 Macrophages

An inhibitory macrophage subtype associated with tissue remodeling and repair that secrete anti-inflammatory cytokines like IL10 and TGFβ.

Myeloid-Derived Suppressor Cells

A heterogeneous group of myeloid cells often recruited by tumor cells that lead to pronounced immunosuppression by inhibiting a wide range of inflammatory immune cells.

Natural Killer Cells

Cytotoxic lymphocytes can eliminate virus-infected or tumor cells by the recognition of non-self antigens presented on MHC I molecules of the target cell.

Natural Killer T Cells

A subset of T cells exhibiting antigen-specific immunity via a restricted TCR recognizing CD1-presented lipid antigens, but also sharing NK cell functions in terms of its independence of MHC.

Pathogen-associated Molecular Patterns

Molecules associated with pathogens like lipopolysaccharide that get released upon infection and lead to a response of the immune system.

Th1 Response

Proinflammatory response inducing killing of intracellular pathogens and tumor cells mainly mediated by IFNγ.

Th2 Response

The immune response against mainly extracellular antigens mediated by the IL-4, IL-5, and IL-13 induced the production of antibodies.

Tumor-associated Macrophages

Macrophage subtype that is highly abundant in tumors and associated with immunosuppression, tumor progression, and metastasis.

Tumor-infiltrating Lymphocytes

Lymphocytes that migrated into the tumor and can be isolated, expanded, and re-infused into the patient as therapy.

Regulatory T cell

A subtype of T cells maintaining self-tolerance and preventing excessive immune responses, mainly by the inhibition of proliferation and activation of cytotoxic T cells.

**Table of content summary**

This review provides an update of interleukins in tumor biology, covering the milestones of the latest discoveries of interleukin-related mechanisms in cancer, together with their application in clinical practice. It includes an overview of current clinical trials, newly approved therapeutic agents, and breakthrough pre-clinical concepts.

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