(REVIEW ARTICLE)

Interleukins: Role in cancer and its immunotherapy

Digna N Patel, Priya C Sharma and Sarat K Dalai *

Institute of Science, Nirma University, Ahmedabad, Gujarat 382481, India.

Abstract

Interleukins are a very important family of cytokines; they are the messengers that assist immune cells to communicate with each other. Interleukins plays a pivotal role in innate and adaptive immune responses by balancing immune cell proliferation, differentiation and regulation. Interleukins aid immune cells in killing cancer cells while simultaneously assisting cancer cells in evading the immune response which leads tumor formation. Some interleukins are very effective at activating effector immune cells to kill cancer cells and also used for cancer immunotherapy. Interleukins are utilized in cancer immunotherapy alone or in combination with other therapies such as CAR-T, checkpoint inhibitors, or chemotherapy. In this review, we will explore the role of different interleukins in cancer and how researchers modified and therapeutically used them to treat cancer (e.g. IL-2, IL-12, IL-15, IL-17, IL-6, IL-18 etc.,).

Keywords: Interleukins, Cancer Immunotherapy; Immune Response; Immune Surveillance; Immune Suppression; Tumor Microenvironment

1 Introduction

The immune system has the ability to protect the body from the infection as well as from damaged/transform cells/tumor cells. The process of identifying the transformed cells and eliminating them through immune cells, prior to the development of clinical tumor is called immunological surveillance. The process of immune surveillance is categorized in three phases: Immune cells Initiation, tumor cell recognition and elimination. However, the immune system promotes the cancer development by sculpting tumor immunogenicity or suppressing host protective immunity. These diverse relation between immune system and cancer development is referred as Immunoediting or immunosuppression.

The tumor microenvironment is a complex network of cells, signalling molecules, and extracellular matrix components that surrounds and interacts with tumor cells. Among various components of tumor microenvironment, immune cells and cytokines play pivotal roles in shaping the immune response against cancer. Immune cells, including lymphocytes, macrophages, dendritic cells, and natural killer cells, infiltrate the tumor microenvironment and interact with tumor cells and stromal cells. Depending on the context and signalling molecules in the tumor microenvironment, these immune cells may promote tumor growth and immune evasion or generate an anti-tumor immune response.

Cytokines are small signalling molecules produced by immune and stromal cells in response to diverse stimuli such as infections, tissue injury, and tumors. Interleukins (ILs) are a type of cytokine that plays an important function in immune surveillance and immunological editing in cancer. Interleukins serve specifically as mediators between distinct immune cells in order to modify immunological activity (Balkwill 2009, Grivennikov, Greten et al. 2010).

The recruitment, activation, and performance of immune cells are all modulated by cytokines in the tumor microenvironment. For instance, certain cytokines, such as interleukin-2 (IL-2) and interferon-gamma (IFN-γ), can

---

* Corresponding author: Sarat K Dalai

promote the activation and proliferation of cytotoxic T cells and natural killer cells, increasing the effectiveness of the immune system's anti-tumor responses (Dunn, Koebel et al. 2006, Rosenberg 2014). On the other hand, cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) might decrease immune cell function and encourage tumor immune evasion (Zou 2006).
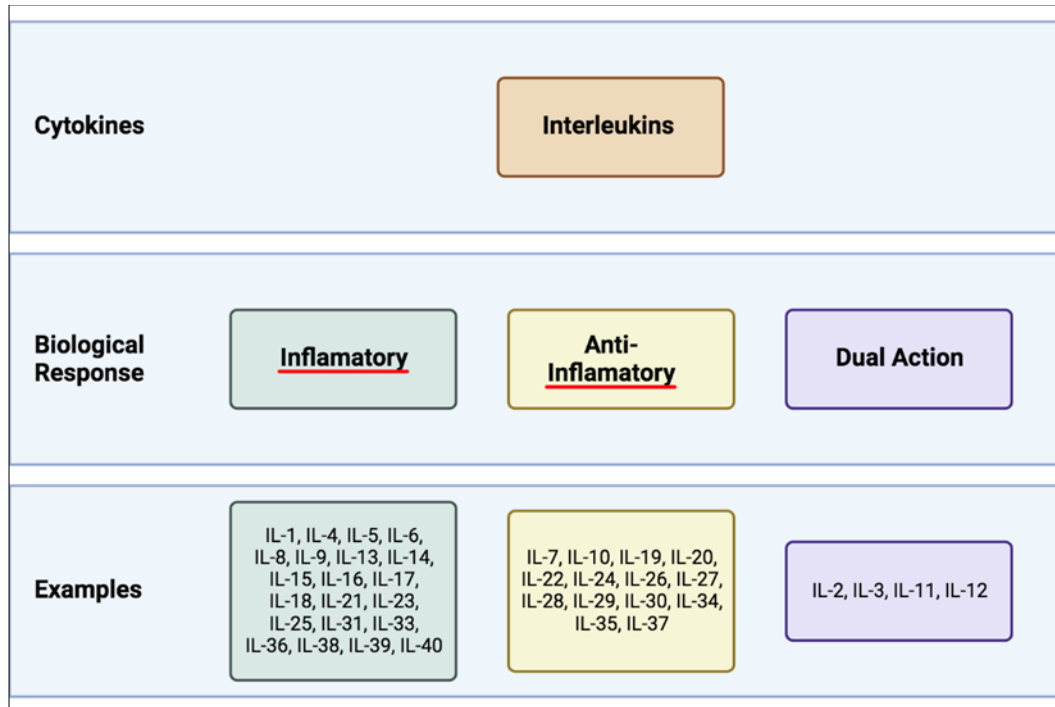

Figure 1 Classification of Interleukins on the basis of their biological response

2   Classification of interleukins

Interleukins are a broad category of cytokines that are essential for controlling immunologic responses and preserving immune system homeostasis. Each interleukin, which ranges in number from IL-1 to IL-38, has a distinct function and binds to a particular receptor. Here is a summary of how interleukins are categorized using various criteria.

Classical Interleukins: Interleukin-1, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-15, and IL-17 are the classical interleukin molecules. These interleukins have been thoroughly researched and have clearly defined functions in immunological control. Inflammation, immune cell differentiation, proliferation, and effector activities are all modulated by their actions on different immune cells. (O'Shea and Paul 2010, Dinarello 2013)

Hematopoietin Receptor Family: Interleukins that are members of the hematopoietin receptor family have related receptor subunits. IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) are members of this family. These interleukins primarily affect hematopoietic cells and control eosinophil differentiation and activation as well as hematopoiesis. (Wang, Lupardus et al. 2009).

Factors that Induce Interferon: This group of interleukins includes IL-12, IL-18, IL-23, and IL-27. The control of Th1 and Th17 immune responses as well as the activation of natural killer cells depend on them. These interleukins regulate the synthesis of interferon-gamma (IFN-γ) and other immunological mediators, increasing immune defence against infections and tumors. (Sun, He et al. 2015, Jorgovanovic, Song et al. 2020)

Anti-inflammatory Interleukins: Some interleukins, such IL-10 and IL-37, have strong anti-inflammatory effects. They reduce tissue damage, suppress immunological responses, and encourage immune tolerance. These interleukins are essential for keeping the immune system in balance and avoiding excessive inflammation and autoimmune disease. (Ouyang and O'Garra 2019)

Interleukin-1 Family: IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra), and IL-18 are all members of the interleukin-1 family. In contrast to IL-1Ra, which functions as a competitive inhibitor of their signalling, IL-1α and IL-1β are pro-

inflammatory cytokines. Inflammation and immunological reactions are influenced by IL-18. IL-1 family members' dysregulation has been linked to a number of inflammatory illnesses and autoimmune conditions. (Sims and Smith 2010, Mantovani, Dinarello et al. 2019)

These are only a few instances of how interleukins are categorized according to their roles and receptor specialization. The classification is continually changing as additional interleukins are found and their functions are understood.

3   Mechanism of action of Interleukins in TME

Interleukins (ILs) and immune cells interact with one another in the tumor microenvironment through a number of different pathways and mechanisms. The main processes and pathways involved in the interaction between ILs and immune cells in the tumor microenvironment are described in depth here;

IL Production and Secretion: The tumor microenvironment contains a variety of cell types, including immunological, stromal, and tumor cells, all of which can release interleukins. Following their release, these ILs enter the tumor microenvironment. For example, tumor-associated fibroblasts (TAFs) and immune cells invading the tumor can release IL-6, whereas regulatory T cells (Tregs) and tumor-associated macrophages (TAMs) can release IL-10. (Yang, Guo et al. 2020, Shah, Mallik et al. 2022)

IL Receptor Engagement: ILs bind to particular receptors on the surface of immune cells after being secreted. When IL receptors are activated, intracellular signalling pathways are triggered, which modify immune cell function. Different ILs interact with various receptor subunits, activating subsequent signalling cascades. IL-2, for example, binds to the IL-2 receptor (IL-2R) on T cells and natural killer (NK) cells, whereas IL-6 binds to the IL-6 receptor (IL-6R) on a variety of immune cell types. (Nelson 2004, Sansone and Bromberg 2012)

Signal Transduction Pathways: Engagement of the IL receptor starts the intracellular signalling cascades that control immune cell responses. These pathways include the nuclear factor-kappa B (NF-κB) pathway, the mitogen-activated protein kinase (MAPK) pathway, the phosphoinositide 3-kinase (PI3K)-Akt pathway, and the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. Immune cell gene expression, cytokine secretion, proliferation, and survival are all altered when these pathways are activated. (Morris, Kershaw et al. 2018)

Immune Cell Activation and Effector Functions: ILs are essential for stimulating immune cells and regulating their ability to perform effector activities. For example, IL-2 is known to drive T cell proliferation and cytotoxicity, IL-12 boosts the production of IFN-gamma (IFN-γ) by NK cells and T cells, IL-15 supports the development of memory T cells and NK cell survival, and IL-17 activates neutrophils and causes inflammation. (Leonard and O'Shea 1998, Trinchieri 2003, Boyman and Sprent 2012)

Immune Cell Trafficking and Infiltration: The migration and infiltration of immune cells into the tumor microenvironment are regulated by ILs. They cause immune cells to express adhesion molecules and chemokine receptors, boosting the cell's migration to the tumor location. This encourages immune cell infiltration, which results in the immediate destruction of tumor cells and the start of adaptive immune responses. For example IL-8, can attract neutrophils and other immune cells to the tumor microenvironment. (DJJ 2008)

Modulation of Immune Suppression and Tumor Immune Evasion: The immune system is suppressed in the tumor microenvironment largely because of ILs. Immunosuppressive cell populations like Tregs and TAMs can differentiate and function more effectively when certain ILs, such IL-10 and IL-6, are present. These cells hinder the anti-tumor immune response, resulting in the development of the tumor. (Zou 2006)

Feedback Regulation: Through feedback loops, IL signalling and immune cell responses in the tumor microenvironment are closely controlled. Negative regulators can reduce IL signalling pathways to stop an excessively active immune response, such as suppressor of cytokine signalling (SOCS) proteins. Additionally, immunosuppressive elements present in the tumor microenvironment, such as prostaglandin E2 (PGE2) and transforming growth factor-beta (TGF-β), can suppress IL production and immune cell responses. (Yoshimura, Naka et al. 2007, Massagué 2008)

The complex interplay between ILs and immune cells in the tumor microenvironment is mediated by a variety of pathways and mechanisms, highlighting the complexity of the immune response to cancer and offering potential targets for cancer immunotherapy.

4   Role of Interleukins in immune surveillance

Interleukins (ILs) play a critical role in cancer immune surveillance, which refers to the body's ability to find and get rid of cancer cells before they develop into clinically evident tumors. As essential signalling molecules, interleukins shape the immune response to cancer by mediating the intricate interactions between immune cells and tumor cells. Interleukins such as interleukin-2 (IL-2), interleukin-12 (IL-12), interleukin-15 (IL-15), and interleukin-17 (IL-17) have all been linked to cancer immune surveillance. By coordinating immune cell actions, these interleukins aid in the identification, activation, and destruction of cancer cells.

For example, a crucial cytokine in the activation and growth of immune cells such cytotoxic T cells and natural killer (NK) cells is IL-2. These immune cells are essential for identifying and destroying cancer cells (Boyman and Sprent 2012). T helper 1 (Th1) cells, which are essential for initiating cell-mediated immune responses against cancer, are stimulated to differentiate by IL-12. It encourages the synthesis of interferon-gamma (IFN-γ), which activates a variety of immune effector cells, including natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), and causes the killing of tumor cells (Trinchieri 2003). Memory CD8+ T cells, NK cells, and T cells—all of which are crucial for tumor surveillance—all depend on IL-15 for maintenance and survival. IL-15 increases these immune cells' cytotoxic activity and encourages their infiltration into tumors, which leads to an increase in the detection and eradication of cancer cells (Steel, Waldmann et al. 2012). IL-17, which is produced by a subset of T cells known as Th17 cells, can help with tumor immune surveillance by attracting immune cells to the tumor microenvironment and increasing the release of immune mediators that promote tumor cell death (Kryczek, Wu et al. 2011).

These interleukins improve cancer immune surveillance through a variety of methods. They can increase the synthesis of pro-inflammatory cytokines, chemokines, and immune effector molecules, which aid in the activation and recruitment of immune cells to tumor sites. Furthermore, they increase immune cell cytotoxicity, trigger IFN-γ production, and encourage the formation of memory T cells, all of which are necessary for long-term tumor surveillance.

Understanding the function of interleukins in cancer immune surveillance is critical for developing successful immunotherapeutic methods. Therapeutic approaches that target interleukins or their downstream signalling pathways have the potential to improve anti-tumor immune responses.

5   Role of Interleukins in immune suppression

Interleukins (ILs) play an important role in cancer immune suppression, helping to create an immunosuppressive milieu that promotes tumor growth and development. Within the tumor microenvironment, interactions between tumor cells, immune cells, and cytokines determine the immunological response to cancer. Interleukins have immunosuppressive effects in this environment, preventing effective anti-tumor immune responses.

Interleukins such as interleukin-10 (IL-10), interleukin-6 (IL-6), and interleukin-1 (IL-1) have all been linked to cancer immune suppression. IL-10 is an immunosuppressive cytokine that impairs immune responses against tumor cells by inhibiting the activity of antigen-presenting cells and effector T cells. IL-6 enhances the survival and proliferation of immunosuppressive cell types such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), hence inhibiting anti-tumor immunity. IL-1 helps to inhibit the immune system by stimulating the production of immunosuppressive factors and establishing an inflammatory milieu that promotes tumor growth. (Balkwill 2009, Gabrilovich and Nagaraj 2009, Sansone and Bromberg 2012)

These interleukins influence critical immunological pathways implicated in cancer immunosuppression. They have the ability to induce the synthesis of immunosuppressive molecules such as indoleamine 2,3-dioxygenase (IDO), programmed cell death ligand 1 (PD-L1), and transforming growth factor-beta (TGF-), which limit immune cell activity and facilitate tumor immune evasion. Interleukins can also alter immune cell development and function, favoring the establishment of immunosuppressive cell populations while limiting the activity of cytotoxic T cells and natural killer cells. (Grivennikov, Greten et al. 2010, Gao, Souza-Fonseca-Guimaraes et al. 2017)

Interleukins play an essential role in cancer immune suppression in a variety of cancer forms. IL-6 has been demonstrated to stimulate the proliferation of Tregs in colorectal cancer, leading to immune suppression and tumor progression. IL-10, which is generated by both tumor and immune cells, suppresses the activity of immune effector cells in melanoma, contributing to immune evasion and tumor progression. IL-1β mediated inflammation has been linked to the development of immunosuppressive cell populations and a poor prognosis in breast cancer. (Mumm, Emmerich et al. 2011, Li, Wang et al. 2012)

Understanding the role of interleukins in cancer immune suppression is critical for creating ways to counteract immunosuppression and boost anti-tumor immune responses. In preclinical and clinical investigations, therapeutic methods that target interleukins or their downstream signalling pathways have showed promise in disrupting immunosuppressive mechanisms and restoring efficient immune surveillance against cancer. Additionally, interleukins promote immunosuppressive pathways, impede immune cell activity, and favour the growth of suppressive cell populations, all of which contribute to cancer immune suppression. Interleukins and related immunosuppressive systems can be targeted to improve cancer immunotherapy.
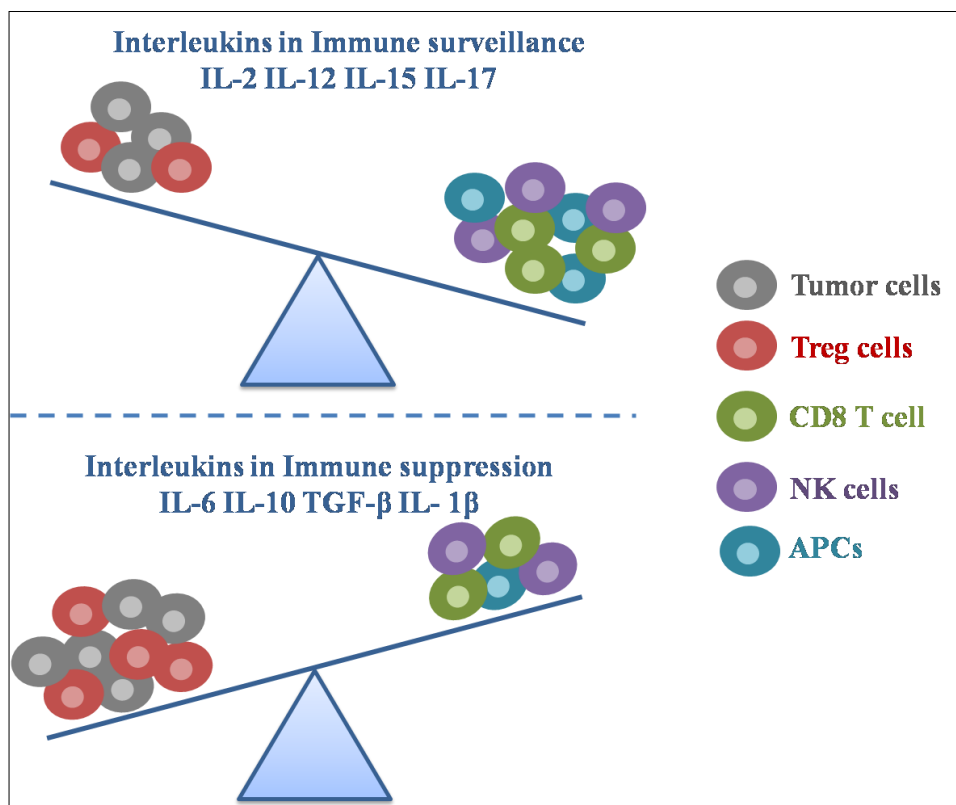

Figure 2 Interleukins role in balance between immune response and tumor development

5.1 Cancer immunotherapy

Cancer immunotherapy has emerged as a promising technique in cancer treatment, utilising the immune system's ability to recognize and eliminating tumor cells. Interleukins are a type of cytokine that has a variety of immunomodulatory effects. They have been extensively investigated and used in cancer immunotherapy. Interleukins have critical roles in immune response regulation, anti-tumor immunity promotion, and the efficacy of immunological-based treatments.

5.2 IL-2

IL-2 (Interleukin-2) is a cytokine that regulates immunological responses, namely the activation and proliferation of T cells and natural killer (NK) cells. IL-2 functions by attaching to IL-2 receptors on the surface of immune cells. IL-2 acts by attaching to its receptor, which is made up of three subunits: IL-2 receptor alpha (IL-2Rα/CD25), IL-2 receptor beta (IL-2Rβ/CD122), and the common gamma chain (γc/CD132). IL-2 activates intracellular signalling cascades, including the JAK-STAT pathway, leading to the activation of several downstream immune response genes. (Rosenberg 2014)

IL-2 is primarily a growth factor for T and NK cells. It encourages the growth and development of effector T cells, which results in greater cytotoxicity against target cells. IL-2 also promotes a proliferation and activation of natural killer (NK) cells, improving their ability to eradicate target cells such as cancer cells. Furthermore, IL-2 increases the formation and maintenance of regulatory T cells (Tregs), which are involved in immunological tolerance. (Boyman and Sprent 2012)

IL-2-based cancer immunotherapy includes a wide range of IL-2 variations and techniques that have been studied for their ability to boost anti-tumor immune responses. Recombinant IL-2 (rIL-2) is a genetically modified type of IL-2 that

has undergone substantial research. Early research found that systemic rIL-2 treatment could boost anti-tumor immune responses by boosting the growth and activation of effector T and NK cells. However, rIL-2 therapy was linked to serious side effects, including vascular leak syndrome (Carmenate, Pacios et al. 2013). Following work concentrated on creating IL-2 variants with enhanced safety characteristics.

IL-2 receptor agonists are IL-2 variations that focus primarily on binding to effector T cells' high-affinity IL-2 receptor while sparing regulatory T cells. Aldesleukin (recombinant IL-2) and NKTR-214 are two of these variations that have demonstrated encouraging outcomes in preclinical models and clinical studies. (Charych, Hoch et al. 2016) By preferentially activating effector T cells and NK cells, IL-2 receptor agonists seek to strengthen anti-tumor immune responses, improving tumor management. To maximise the therapeutic potential of IL-2, combination treatments based on IL-2 have also been investigated. In preclinical models and in clinical studies for many cancers, combining IL-2 with immune checkpoint inhibitors, adoptive cell therapy, or other immunomodulatory drugs has demonstrated synergistic effects. (Atkins, Lotze et al. 1999, Atkins, Kunkel et al. 2000)

In addition to these IL-2 variations, researchers have created fusion proteins and Immunocytokines based on IL-2. These designs combine IL-2 with tumor-targeting antibodies or antibody fragments, allowing IL-2 to be delivered to tumor cells selectively. Immunocytokines improve the anti-tumor immune response while minimising systemic damage by localising IL-2 to the tumor microenvironment. Preclinical investigations utilising IL-2-based fusion proteins in several malignancies, including melanoma and renal cell carcinoma, have provided promising results. (Hodi, O'day et al. 2010, Yu, Liu et al. 2019)

In conclusion, IL-2-based cancer immunotherapy provides a variety of options for enhancing anti-tumor immune responses. In preclinical and clinical investigations, IL-2 variations such as rIL-2 and IL-2 receptor agonists, as well as IL-2-based combination treatments and IL-2 based fusion protein, have showed promise. These approaches attempt to improve the efficacy and safety profile of IL-2-based immunotherapies, opening up new possibilities for cancer treatment.

5.3   IL-12

IL-12 (Interleukin-12) is a cytokine that plays an important role in immune response regulation, particularly in boosting the activation and proliferation of natural killer (NK) cells and T cells. Antigen-presenting cells produce IL-12, which acts on multiple immune cells to boost the immune response to infections and tumors.

IL-12 works by attaching to its receptor, which is made up of two subunits: IL-12 receptor beta 1 (IL-12Rβ1) and IL-12 receptor beta 2 (IL-12Rβ2). (Van De Vosse, Lichtenauer-Kaligis et al. 2003) When IL-12 binds, it initiates a signalling cascade that results in the activation of STAT proteins, specifically STAT3 and STAT4. IL-12 stimulation of the JAK-STAT pathway results in the development of T helper 1 (Th1) cells, which play an important role in initiating cell-mediated immune responses against cancer and intracellular pathogens. (Athie-Morales, Smits et al. 2004) These Th1 cells produce IFN- γ, which boosts immune responses by activating immunological effector cells such as natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), resulting in tumor cell death. Furthermore, IL-12 can activate and proliferate memory T cells, resulting in long-term immunological memory. (Pearce and Shen 2007)

IL-12-based cancer immunotherapy includes a variety of IL-12 variances that have been studied for their ability to boost anti-tumor immune responses. Recombinant IL-12 (rIL-12), IL-12 gene therapy, and different mutant IL-12 Immunocytokines are examples of these variants. Each has distinct advantages and has been studied in preclinical and clinical research in various forms of cancer.

Recombinant IL-12 (rIL-12) is a genetically modified type of IL-12 that has undergone substantial research. rIL-12 has been shown in preclinical and clinical trials to generate strong immune responses against tumors by activating natural killer (NK) cells and T cells. (Colombo, Trinchieri et al. 2002) However, systemic injection of rIL-12 was linked to serious side effects, limiting its therapeutic relevance.

In IL-12 gene therapy, the IL-12 gene is directly delivered to tumor cells or the tissue around them. Through continuous local IL-12 production, the tumor is targeted by the immune system in this strategy. Preclinical research utilising lentiviruses and adenoviruses as viral vectors has produced potential anti-tumor effects. Clinical trials have assessed the security and effectiveness of IL-12 gene therapy in treating melanoma and prostate cancer, among other cancers. (Mazzolini, Prieto et al. 2003, Tandle, Blazer et al. 2004)

Clinical trials have been conducted on these IL-12-based immunotherapies to assess their safety and effectiveness in treating various cancers. For instance, a phase I trial looked at the use of rIL-12 in patients with advanced solid tumors and found some clinical responses as well as tolerable effects. Prostate cancer and melanoma has both been the subject of IL-12 gene therapy clinical trials, with encouraging results in terms of safety and anti-tumor efficacy. Also in patients with HER2-positive lymphoma and breast cancer have shown disease stabilisation and objective responses in trials with IL-12 based immunotherapy. (Atkins, Robertson et al. 1997, Tarhini, Millward et al. 2009)

IL-12-based cancer immunotherapies improve anti-tumor immune responses. Clinical trials have shed light on the potential effectiveness and safety of IL-12-based immunotherapies, opening the path for further research and improvement.

5.4   IL-15

IL-15 (Interleukin-15) is a cytokine that plays a critical role in regulating immune responses, particularly in the activation and proliferation of natural killer (NK) cells, CD8+ T cells, and memory T cells. IL-15 functions by attaching to a receptor complex made up of the IL-15 receptor alpha (IL-15Rα), IL-2 receptor beta (IL-2Rβ), and the common gamma chain (γc). (Giri, Kumaki et al. 1995) When IL-15 binds to its receptor complex, it recruits and activates JAK1 and JAK3, which are linked with the cytoplasmic regions of the receptor subunits. Further, STAT3 and STAT5 are phosphorylated by JAKs, resulting in transcriptional activation of target genes involved in diverse cellular processes such as cell survival, proliferation, and differentiation. (Waldmann 2006)

The survival, proliferation, and activation of immune cells involved in anti-tumor responses are encouraged by the action of IL-15. The expansion and activation of NK cells are boosted by IL-15, increasing their cytotoxicity towards target cells like tumor cells. Additionally, it encourages memory CD8+ T cell survival and growth, which aids in long-term immunological memory and offers defence against tumor recurrence. Furthermore, by raising the synthesis of perforin and granzyme B, two essential effector molecules involved in killing target cells, IL-15 can improve the cytotoxic activity of CD8+ T cells and NK cells. (Klebanoff, Finkelstein et al. 2004)

Cancer immunotherapy based on IL-15 has drawn a lot of interest as a viable strategy to boost the anti-tumor immune response. Recombinant IL-15 (rIL-15), a sort of IL-15 variation created by genetic engineering, is one example. Early research found that systemic treatment of rIL-15 could boost NK cell and CD8+ T cell activation and expansion, hence enhancing anti-tumor immune responses. (Conlon, Lugli et al. 2015) However, the therapeutic effectiveness of rIL-15 was constrained by its relatively short half-life. As a result, efforts have been made to create other IL-15 versions with better pharmacokinetic characteristics.

IL-15 superagonists are a type of IL-15 variation that has been genetically modified to increase the potency and duration of IL-15 signalling. These superagonists, such as ALT-803 and N-803, have shown substantial anti-tumor action in preclinical settings by increasing NK cell and memory T cell growth and activation. (Conlon, Lugli et al. 2015) IL-15 superagonists have been studied in clinical studies for their safety and efficacy in a variety of cancers, including melanoma, renal cell carcinoma, and non-small cell lung cancer. (Romee, Cooley et al. 2018, Wrangle, Velcheti et al. 2018)

Furthermore, IL-15-based combination therapies have been investigated in order to maximise IL-15's therapeutic potential. Combinations of IL-15 with immune checkpoint inhibitors, adoptive cell therapy, or other immunomodulatory drugs have demonstrated synergistic effects in preclinical models and are now being tested in clinical trials for a variety of cancer types. (O'Sullivan Coyne, Conlon et al. 2018, Zhou, Husman et al. 2022)

In conclusion, IL-15-based cancer immunotherapy provides promising techniques for improving anti-tumor immune responses. In preclinical and clinical trials, rIL-15 and IL-15 superagonists, as well as combination treatments, have showed promise. These approaches aim to improve the efficacy and duration of immune responses against cancer, opening up new possibilities for the development of successful immunotherapies.

5.5   IL-17

IL-17 (Interleukin-17) is a cytokine that is involved in the promotion of inflammation and immunological responses. It is predominantly produced by Th17 cells, a subset of T cells, as well as other immune cells such as innate lymphoid cells (ILCs) and T cells. IL-17 operates on a variety of cell types via its receptor complex, which includes IL-17 receptor A (IL-17RA) and IL-17 receptor C (IL-17RC). (Kolls and Lindén 2004) IL-17's mode of action involves attaching to its receptor complex and activating intracellular signalling pathways such as the NF-κB and MAPK signalling pathways. This causes

downstream transcription factors to be activated, as well as the generation of different pro-inflammatory cytokines, chemokines, and antimicrobial peptides. (McGeachy and Cua 2008)

IL-17 is important in both host defence against infections and the pathophysiology of inflammatory disorders. Its role in cancer, however, is complex and context-dependent. While IL-17 can promote inflammation and tumor growth in some circumstances, it can also boost anti-tumor immune responses in others. (Kryczek, Wu et al. 2011)

Cancer immunotherapy based on interleukin-17 (IL-17), a pro-inflammatory cytokine released by diverse immune cells, is used to treat cancer. IL-17 has a complex function in tumor genesis and progression, and its therapeutic targeting in cancer immunotherapy shows promise. Although IL-17-based therapeutics are still in their infancy, numerous techniques have been investigated in preclinical investigations and clinical trials.

One strategy is to utilise neutralising antibodies that target IL-17 or its receptor. These antibodies seek to inhibit the IL-17 signalling pathway, which can promote tumor growth and immune evasion. Preclinical investigations have shown that IL-17 neutralising antibodies can decrease tumor growth and improve anti-tumor immune responses. Modulating the balance of IL-17 and regulatory T cells (Tregs) in the tumor microenvironment is another technique. Tregs have the ability to block anti-tumor immune responses, whereas IL-17 promotes pro-inflammatory responses. (Murugaiyan and Saha 2009) Strategies for decreasing Treg activity and raising IL-17 production have been investigated in preclinical animals, with promising results for improving anti-tumor immunity.

Combination therapy based on IL-17 has also been studied. In preclinical investigations, combining IL-17 inhibition with other immunotherapeutic drugs, such as immune checkpoint inhibitors, demonstrated synergistic results. This combined approach attempts to boost anti-tumor immune responses by concurrently targeting numerous immunological checkpoints. (Zhang, Chandra et al. 2020) While IL-17-based cancer immunotherapy is still in its early stages, it has the potential to improve anti-tumor immune responses. The above-mentioned therapeutic methods, such as IL-17 neutralising antibodies, Treg and IL-17 balance management, and combination therapies, provide possible paths towards developing successful IL-17-based immunotherapies for cancer treatment.

5.6   IL-6

IL-6 (Interleukin-6) is a cytokine that regulates the immune system and causes inflammation. In reaction to infection, tissue damage, or other stimuli, it is produced by a variety of cells, including immune cells, fibroblasts, and endothelial cells. IL-6 functions via attaching to its receptor complex, which is made up of the IL-6 receptor alpha (IL-6Rα) and glycoprotein 130 (gp130). When IL-6 binds to the IL-6 receptor complex, it activates intracellular signalling pathways such as the JAK-STAT and MAPK pathways. This results in the phosphorylation and activation of transcription factors like STAT3, which control the expression of target genes involved in immune responses and inflammation. (Scheller, Chalaris et al. 2011, Hunter and Jones 2015)

IL-6 affects a variety of cell types, including immune cells, hepatocytes, and endothelial cells. It has the ability to induce the production of acute-phase proteins, regulate immune cell differentiation and activation, and cause inflammation. IL-6 is critical in the coordination of the immune response to infection and tissue injury. Cancer immunotherapy based on interleukin-6 (IL-6) entails targeting this cytokine, which plays a complex role in cancer growth and immune regulation. Several techniques to targeting IL-6 signalling for cancer immunotherapy have been investigated, however clinical translation is still in the works.

Tocilizumab, a monoclonal antibody that targets IL-6 or its receptor, is one strategy. These antibodies are designed to suppress IL-6 signalling and its pro-tumorigenic effects. (Dimitriou, Hogan et al. 2021) Clinical trials including the use of IL-6 antibodies in cancer patients have yielded promising outcomes, especially when combined with other treatments. Tocilizumab in combination with immune checkpoint inhibitors, for example, has been demonstrated to improve outcomes in some cancer types, such as renal cell carcinoma and lung cancer. (Ando, Takahashi et al. 2014)

Another strategy is to target IL-6-activated downstream signalling pathways, such as the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. To disrupt IL-6 signalling, small molecule inhibitors of JAK or STAT proteins have been developed. (Schwartz, Kanno et al. 2017) JAK inhibitors, such as ruxolitinib and baricitinib, are now being studied in clinical studies for their efficacy in various malignancies. While IL-6-based cancer immunotherapy is still in its early stages, targeting IL-6 and its signalling pathways as a treatment method has promise.

5.7　IL-18

IL-18 is a pro-inflammatory cytokine that is important in boosting the immune response to tumors. It acts by binding to its receptor complex, which is made up of IL-18 receptor alpha (IL-18Rα) and IL-18 receptor beta (IL-18Rβ) subunits found on numerous immune cells. (Dinarello, Novick et al. 2013) IL-18's mechanism of action involves the activation of both innate and adaptive immune responses. When IL-18 binds to its receptor complex, it initiates a signalling cascade that activates downstream pathways such as the NF-κB and MAPK signalling pathways. T cells, natural killer (NK) cells, and other immune cells respond by producing pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). (Okamura, Kashiwamura et al. 1998)

Several techniques towards IL-18-based immunotherapy have been investigated. One approach is to use recombinant IL-18 (rIL-18) as an adjuvant therapy with other treatments, such as immune checkpoint inhibitors. (Ma, Li et al. 2016) Preclinical research has shown that rIL-18 can boost the anti-tumor immune response, resulting in better therapeutic outcomes. Another strategy is to use IL-18-based gene therapy, which involves delivering the IL-18 gene directly into tumor cells or surrounding tissue. The goal of this technique is to generate persistent local synthesis of IL-18, thereby triggering a targeted immune response against the tumor. (Nagai, Horikawa et al. 2002) In preclinical trials, IL-18 gene therapy demonstrated excellent results, showing its potential for boosting anti-tumor immune responses.

Immunotherapy based on IL-18 has the potential to improve the immune response to cancer. The use of rIL-18 as adjuvant therapy and IL-18 gene therapy has the potential to improve therapeutic outcomes in cancer patients

6　Conclusion

In conclusion, due to their ability to influence the immune system and boost anti-tumor response, interleukins may become a promising arm in the field of cancer immunotherapy. Interleukins can encourage immune surveillance, tumor detection, and killing by activating immune cells such as T cells and Natural killer cells (NK), which can result in tumor regression and long-term remission. Furthermore, interleukin-based immunotherapy has been optimized, minimizing side effects and maximizing therapeutic efficacy, leading to the finding of novel genetic and structural modification and combination therapies. Even though there are still obstacles to overcome, such as the need for more research into the complex interactions between interleukins and the tumor microenvironment, ongoing studies and clinical trials continue to provide insightful analysis and cutting-edge approaches for utilizing interleukins' potent anticancer effects. Interleukin-based cancer immunotherapy has the potential to transform the way cancer is treated and enhance patients' lives with further advancements.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1]　Ando, K., et al. (2014). "Tocilizumab, a proposed therapy for the cachexia of Interleukin6-expressing lung cancer." 9(7): e102436.

[2]　Athie-Morales, V., et al. (2004). "Sustained IL-12 signaling is required for Th1 development." 172(1): 61-69.

[3]　Atkins, M. B., et al. (2000). "High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update." 6: S11-14.

[4]　Atkins, M. B., et al. (1999). "High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993." 17(7): 2105-2105.

[5]　Atkins, M. B., et al. (1997). "Phase I evaluation of intravenous recombinant human interleukin 12 in patients with advanced malignancies." 3(3): 409-417.

[6]　Balkwill, F. J. N. r. c. (2009). "Tumor necrosis factor and cancer." 9(5): 361-371.

[7]　Boyman, O. and J. J. N. R. I. Sprent (2012). "The role of interleukin-2 during homeostasis and activation of the immune system." 12(3): 180-190.

[8]　Carmenate, T., et al. (2013). "Human IL-2 mutein with higher antitumor efficacy than wild type IL-2." 190(12): 6230-6238.

[9]   Charych, D. H., et al. (2016). "NKTR-214, an engineered cytokine with biased IL2 receptor binding, increased tumor exposure, and marked efficacy in mouse tumor models." 22(3): 680-690.

[10]   Colombo, M. P., et al. (2002). "Interleukin-12 in anti-tumor immunity and immunotherapy." 13(2): 155-168.

[11]   Conlon, K. C., et al. (2015). "Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15 in patients with cancer." 33(1): 74.

[12]   Dimitriou, F., et al. (2021). "Interleukin-6 blockade for prophylaxis and management of immune-related adverse events in cancer immunotherapy." 157: 214-224.

[13]   Dinarello, C. A. (2013). Overview of the interleukin-1 family of ligands and receptors. Seminars in immunology, Elsevier.

[14]   Dinarello, C. A., et al. (2013). "Interleukin-18 and IL-18 binding protein." 4: 289.

[15]   DJJ, W. J. C. C. R. (2008). "The interleukin-8 pathway in cancer." 14: 6735-6741.

[16]   Dunn, G. P., et al. (2006). "Interferons, immunity and cancer immunoediting." 6(11): 836-848.

[17]   Gabrilovich, D. I. and S. J. N. r. i. Nagaraj (2009). "Myeloid-derived suppressor cells as regulators of the immune system." 9(3): 162-174.

[18]   Gao, Y., et al. (2017). "Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells." 18(9): 1004-1015.

[19]   Giri, J. G., et al. (1995). "Identification and cloning of a novel IL-15 binding protein that is structurally related to the alpha chain of the IL-2 receptor." 14(15): 3654-3663.

[20]   Grivennikov, S. I., et al. (2010). "Immunity, inflammation, and cancer." 140(6): 883-899.

[21]   Hodi, F. S., et al. (2010). "Improved survival with ipilimumab in patients with metastatic melanoma." 363(8): 711-723.

[22]   Hunter, C. A. and S. A. J. N. i. Jones (2015). "IL-6 as a keystone cytokine in health and disease." 16(5): 448-457.

[23]   Jorgovanovic, D., et al. (2020). "Roles of IFN-γ in tumor progression and regression: a review." 8: 1-16.

[24]   Klebanoff, C. A., et al. (2004). "IL-15 enhances the in vivo antitumor activity of tumor-reactive CD8+ T cells." 101(7): 1969-1974.

[25]   Kolls, J. K. and A. J. I. Lindén (2004). "Interleukin-17 family members and inflammation." 21(4): 467-476.

[26]   Kryczek, I., et al. (2011). "IL-17+ regulatory T cells in the microenvironments of chronic inflammation and cancer." 186(7): 4388-4395.

[27]   Leonard, W. J. and J. J. J. A. r. o. i. O'Shea (1998). "Jaks and STATs: biological implications." 16(1): 293-322.

[28]   Li, Y., et al. (2012). "IL-1β promotes stemness and invasiveness of colon cancer cells through Zeb1 activation." 11(1): 1-13.

[29]   Ma, Z., et al. (2016). "Augmentation of immune checkpoint cancer immunotherapy with IL18." 22(12): 2969-2980.

[30]   Mantovani, A., et al. (2019). "IL-1 and related cytokines in innate and adaptive immunity in health and disease." 50(4): 778.

[31]   Massagué, J. J. C. (2008). "TGFβ in cancer." 134(2): 215-230.

[32]   Mazzolini, G., et al. (2003). "Gene therapy of cancer with interleukin-12." 9(24): 1981-1991.

[33]   McGeachy, M. J. and D. J. J. I. Cua (2008). "Th17 cell differentiation: the long and winding road." 28(4): 445-453.

[34]   Morris, R., et al. (2018). "The molecular details of cytokine signaling via the JAK/STAT pathway." 27(12): 1984-2009.

[35]   Mumm, J. B., et al. (2011). "IL-10 elicits IFNγ-dependent tumor immune surveillance." 20(6): 781-796.

[36]   Murugaiyan, G. and B. J. T. J. o. I. Saha (2009). "Protumor vs antitumor functions of IL-17." 183(7): 4169-4175.

[37]   Nagai, H., et al. (2002). "Gene transfer of secreted-type modified interleukin-18 gene to B16F10 melanoma cells suppresses in vivo tumor growth through inhibition of tumor vessel formation." 119(3): 541-548.

[38]   Nelson, B. H. J. T. J. o. I. (2004). "IL-2, regulatory T cells, and tolerance." 172(7): 3983-3988.

[39] O'Sullivan Coyne, G. H., et al. (2018). Phase I study of recombinant interleukin-15 in combination with checkpoint inhibitors nivolumab and ipilimumab in subjects with refractory cancers, American Society of Clinical Oncology.

[40] O'Shea, J. J. and W. E. J. S. Paul (2010). "Mechanisms underlying lineage commitment and plasticity of helper CD4+ T cells." 327(5969): 1098-1102.

[41] Okamura, H., et al. (1998). "Regulation of interferon-γ production by IL-12 and IL-18." 10(3): 259-264.

[42] Ouyang, W. and A. J. I. O'Garra (2019). "IL-10 family cytokines IL-10 and IL-22: from basic science to clinical translation." 50(4): 871-891.

[43] Pearce, E. L. and H. J. T. J. o. I. Shen (2007). "Generation of CD8 T cell memory is regulated by IL-12." 179(4): 2074-2081.

[44] Romee, R., et al. (2018). "First-in-human phase 1 clinical study of the IL-15 superagonist complex ALT-803 to treat relapse after transplantation." 131(23): 2515-2527.

[45] Rosenberg, S. A. J. T. J. o. I. (2014). "IL-2: the first effective immunotherapy for human cancer." 192(12): 5451-5458.

[46] Sansone, P. and J. J. J. o. C. O. Bromberg (2012). "Targeting the interleukin-6/Jak/stat pathway in human malignancies." 30(9): 1005.

[47] Scheller, J., et al. (2011). "The pro-and anti-inflammatory properties of the cytokine interleukin-6." 1813(5): 878-888.

[48] Schwartz, D. M., et al. (2017). "JAK inhibition as a therapeutic strategy for immune and inflammatory diseases." 16(12): 843-862.

[49] Shah, K., et al. (2022). "Targeting tumor-associated fibroblasts in cancers." 12: 908156.

[50] Sims, J. E. and D. E. J. N. R. I. Smith (2010). "The IL-1 family: regulators of immunity." 10(2): 89-102.

[51] Steel, J. C., et al. (2012). "Interleukin-15 biology and its therapeutic implications in cancer." 33(1): 35-41.

[52] Sun, L., et al. (2015). "Interleukin 12 (IL-12) family cytokines: Role in immune pathogenesis and treatment of CNS autoimmune disease." 75(2): 249-255.

[53] Tandle, A., et al. (2004). "Antiangiogenic gene therapy of cancer: recent developments." 2(1): 1-20.

[54] Tarhini, A. A., et al. (2009). "A phase 2, randomized study of SB-485232, rhIL-18, in patients with previously untreated metastatic melanoma." 115(4): 859-868.

[55] Trinchieri, G. J. N. R. I. (2003). "Interleukin-12 and the regulation of innate resistance and adaptive immunity." 3(2): 133-146.

[56] Van De Vosse, E., et al. (2003). "Genetic variations in the interleukin-12/interleukin-23 receptor (β1) chain, and implications for IL-12 and IL-23 receptor structure and function." 54: 817-829.

[57] Waldmann, T. A. J. N. R. I. (2006). "The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design." 6(8): 595-601.

[58] Wang, X., et al. (2009). "Structural biology of shared cytokine receptors." 27: 29-60.

[59] Wrangle, J. M., et al. (2018). "ALT-803, an IL-15 superagonist, in combination with nivolumab in patients with metastatic non-small cell lung cancer: a non-randomised, open-label, phase 1b trial." 19(5): 694-704.

[60] Yang, Q., et al. (2020). "The role of tumor-associated macrophages (TAMs) in tumor progression and relevant advance in targeted therapy." 10(11): 2156-2170.

[61] Yoshimura, A., et al. (2007). "SOCS proteins, cytokine signalling and immune regulation." 7(6): 454-465.

[62] Yu, C., et al. (2019). "Combination of immunotherapy with targeted therapy: theory and practice in metastatic melanoma." 10: 990.

[63] Zhang, Y., et al. (2020). "Interleukin-17–induced neutrophil extracellular traps mediate resistance to checkpoint blockade in pancreatic cancer." 217(12).

[64] Zhou, Y., et al. (2022). "Interleukin 15 in cell-based cancer immunotherapy." 23(13): 7311.

[65] Zou, W. J. N. R. I. (2006). "Regulatory T cells, tumor immunity and immunotherapy." 6(4): 295-307.