



Review Article

The Role and Therapeutic Potential of Interleukin-10 in Immunology

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ABSTRACT

One important anti-inflammatory cytokine that is essential for controlling immune responses and avoiding tissue damage brought on by over-activation of the immune system is interleukin-10 (IL-10). Monocytes, macrophages, and regulatory T cells (Tregs) are among the immune cells that secrete it. IL-10 inhibits the activity of antigen-presenting cells, downregulates the expression of co-stimulatory molecules, and suppresses the production of pro-inflammatory cytokines. According to recent research, IL-10 has substantial therapeutic potential for the treatment of a number of chronic and immune-related illnesses, including cancer, viral infections, and autoimmune disorders, in addition to its role as an immune suppressor. However, since IL-10 may also inhibit advantageous immune responses, its therapeutic use necessitates careful modulation. The objectives of this review are to examine the potential clinical uses of IL-10, highlight its dual role in immune regulation, and talk about the difficulties in using it as a therapeutic agent.

Keywords: Interleukin-10 (IL-10); Immune regulation; Anti-inflammatory cytokines; Autoimmune diseases; Immunotherapy; Cytokine therapy.

Introduction to Interleukin-10

Interleukin-10 (IL-10) is an important anti-inflammatory and regulatory cytokine, and it inhibits the immune response against antigenic stimuli. IL-10 regulates immune responses, irrespective of the environment in which it mediates, to inhibit the stimulation and activation of immune cells. The most pragmatic questions here would be: What does IL-10 do, and why does it do so? To gain an in-depth understanding of the function of IL-10, it would be

interesting to discuss the discovery of this 'new' cytokine. Although initially it was named cytotoxic T-cell lymphocyte inhibitory factor, the physiological effects of IL-10 can be clearly differentiated from those induced by other interleukins. IL-10 is secreted by T-helper-2 cells, Langerhans cells, B1 lymphocytes, B lymphocytes, and monocytes. Many reports suggest that IL-10 can be detected at the lowest concentration in plasma, particularly from healthy patients, and progressively

at higher concentrations in a multitude of immunological conditions such as leukoerythroblastic anemia, infections, leukoerythrodermas, infant dermatitis, particularly in atopic allergy, among many other conditions such as autoimmune, inflammatory, fatty liver syndromes, and orthopedic cases, to name a few. What is intriguing is that candidates where IL-10 is suspected underwent treatment. Furthermore, this response to treatments was quite dynamic; in each of the candidates where IL-10 was suspected to have increased, there were no immediate signs of recovery. Thus, we now understand that IL-10 can implicate pleiotropic syndromes, where immune responses can actually be detrimental to the exigent responses [1-4].

IL-10, also referred to as a cytokine synthesis inhibitory factor, was discovered independently as a molecule that selectively suppresses the expression of T-cell-derived cytokines after being cloned for different reasons. The structure of IL-10, its gene, signaling, receptors, and their intracellular domain have been observed. The most important function of IL-10 was recognized when its capacity to inhibit T-cell proliferation was described. Nevertheless, IL-10 is shown to suppress the expression of MHC class II on the surface of antigen-presenting cells, thereby inhibiting their antigen presentation activities. In addition, it has been demonstrated to inhibit the activation of antigen-presenting cells for the generation of effective immune responses as well [2,5-7].

1.1. Definition and Structure

Interleukin-10 (IL-10) is a cytokine with primary roles in immune regulation. For example, IL-10 inhibits monocytes and macrophages that produce pro-inflammatory cytokines, such as IL-1, IL-6, IL-

12, TNF- α , and IL- β . In addition, it can suppress class II MHC expression in antigen-presenting cells (APC) by inhibiting APC differentiation. It was recently found that IL-10 has an inhibitory effect on Th17 cell differentiation. IL-10 is also a potent inhibitor of T cell function. A recent study shows that the production of IL-10 in dendritic cells (DCs) activated by ATP has an antitumor effect [1, 8, 9].

Recombinant IL-10 can be very effective in treating most rodent models of inflammatory diseases, including chronic inflammation, autoimmunity, allergy, summer grass bedding, and sepsis. IL-18 knockout mice produce reduced exogenous IL-10, suggesting that IL-18 may also be an important IL-10-inducible factor. The human IL-10 gene coding sequence is thus instructive for its biological function. IL-10 is encoded by 5 exons; exon 1 is not a coding exon. IFN- γ and IL-10 are initially transfected through plasmids and bacteria. After translation, the purification of recombinant IL-10 was performed using affinity chromatography. The complete translated IL-10 is 178 amino acids. It is secreted as a 35 to 40 kDa protein. Human and mouse IL-10 are 73% identical at the amino acid level; the structure of the two is very similar, and the effect is also conserved [10, 11].

1.2. Biological Functions

The biological functions of interleukin-10 are primarily anti-inflammatory, having a profound dampening of the immune response by decreasing pro-inflammatory cytokine and MHC gene expression. IL-10 is not only linked to innate cells but also to the adaptive response through its promotion of B cell survival and function. If not for IL-10, the body's immune responses would spiral into an out-of-control autoimmune disease state. This anti-inflammatory cytokine is also responsible

for decreased TNF- α production, decreased macrophage, T cell, and dendritic cell activation, and decreased downstream production of interleukin-1, GM-CSF, IFN- γ , and TNF- α . IL-10 also influences CD4⁺ T helper cell differentiation down a TH2 pathway, producing IL-4, IL-5, and IL-13, and acting as a facilitator for the activation and growth of B cells, as well as promoting the differentiation of T regulatory cells. These biological properties contribute to an immune modulatory landscape that allows for the development of many different autoimmune, infectious, and tumor disease states [3, 12, 13].

These biological functions of IL-10 have clear implications for its therapeutic use in the treatment of these chronic immunological diseases. Patients with diseases such as proteinopathies, inflammatory states, and tumor microenvironment states benefit from increased tolerance to therapies that induce the effector immune response. Clinicians are able to inhibit their targets for immune exacerbation therapies by inhibiting multiple systems through IL-10 induced genetic expression of proteins that help promote the immune tolerance effect of the new anti-immune exacerbation target. Immune tolerance is also important in tissue and cell engraftment by preventing the host immune response from attacking the implanted tissues and cells as much. This level of system downregulation through a single clinically targetable genetic control node is only afforded through a heavily homeostatic immune regulator such as interleukin-10. [1,14, 15].

2. Immunomodulatory Mechanisms of Interleukin-10

Balance of pro- and anti-inflammatory responses leads to a normal healing process. Once inflammation progresses out of control, collateral

damage can occur, and in chronic inflammatory disorders, it can lead to permanent tissue damage. IL-10 has emerged as a critical mediator active in

downregulating immune reactions. Interleukin-10, originally described as a cytokine synthesis-inhibitory factor, was classified as an anti-inflammatory cytokine. Subsequent observations have provided more detailed insights into its mode of action and include: the downregulation of the production of pro-inflammatory cytokines, the facilitation of apoptosis in monocytes/macrophages, a decrease in the surface expression of the major histocompatibility complex class II and costimulatory molecules by antigen-presenting cells, effects on T cells via the suppression of their proliferation and expression of T-cell effector functions, and a contribution to the development and maintenance of a tolerogenic microenvironment via the action within mesenchymal stem cells [16- 18].

The protective potential of interleukin-10 in several inflammatory disorders has been demonstrated using different preclinical models and, in some cases, even in clinical trials. Progress has been made in delineating the in vivo mechanisms underlying IL-10-mediated tolerance since its discovery and defining its role in the development of both protective immunity and tolerance. IL-10 action can be further supported by the anti-inflammatory potential of other cytokines in a cooperative manner. Such a mechanistic framework is crucial to understanding the importance of IL-10 in the modulation of the immune response, from the establishment of an anti-inflammatory environment promoting disease progression to protective immunity up to chronic antigenic stimulation. The success of suitable prophylactic and therapeutic

strategies based on IL-10 and IL-10-related administration will partly depend on the modulation of the IL-10 response or application of appropriate adjuvant immunosuppressive strategies [3,18- 21].

2.1. Regulation of Inflammatory Responses

Interleukin-10 (IL-10) is a key factor in the regulation of the inflammatory response, which is initiated by many environmental, infectious, or genetic triggers. This remnant capacity to modulate the extensive network of cells, cytokines, chemokines, and intracellular signaling molecules that initiate the immune response is important for the resolution and restoration of homeostasis during the reactive immune response. IL-10 exerts its biological activities mainly via the negative regulation of the production of many pro-inflammatory cytokines, chemokines, and enzymes, and also takes part in enhancing humoral responses. The upregulation of the immune response by IL-10 mainly occurs through the induction of co-stimulatory molecules, production of stabilizing factors, and inhibition of negative signal transcription factors [8,18, 22].

In contrast to the opposite activities induced by IL-10, pathological changes leading to the chronification of the inflammatory-immune response with irreparable tissue damage are primarily due to dysregulated production of IL-10. These new insights into the role of IL-10 in chronic inflammatory conditions have led us to search for this cytokine as an important target in future therapeutic interventions in treating allergies and autoimmune diseases. The expression of IL-10 is restricted to specific immune response cells and is not seen in resident cells of the organs [2, 23].

2.2. Suppression of T Cell Activation

Interleukin-10 suppresses the activation and proliferation of various T cell subsets. It has been shown that IL-10 inhibits the secretion of IL-2, IFN-gamma, and TNF-alpha, whereas other cytokines such as IL-5, IL-13, or IL-4, as well as the expression of the high-affinity IL-2 receptor on resting and activated peripheral blood T cells, are not affected. Two ways in which IL-10 could interact with the T-cell receptor and the major histocompatibility complex, with either the CD3 zeta-associated or the JAK-STAT pathway, have been analyzed. Signaling has been shown to be dependent on MHC, even though it is said to be distinct regarding CD4+ and CD8+ T cells [24, 25]. The blockade of the p38-mitogen-activated protein kinases has also been suggested for the inhibitory effect of IL-10 on T cells. Further treatment with a compound that decreases ERK-1/2 and Raf-1 activities, as well as the addition of another compound, has been shown to affect IL-10 signaling that inhibits T cells among pre-B acute lymphoblastic leukemia cells. However, the addition of a compound that blocks the activity of the c-Jun-N-terminal kinases has no effect on the suppressed effects of IL-10 on T cells [26]. On the whole, the in vitro and in vivo data suggest that IL-10 suppresses T-cell responses by directly acting at least on T-cell receptor signaling and its downstream pathways. Because an ongoing balance between activation and tolerance is mandatory and tissue damage during autoimmune reactions needs to be prevented, the suppressive effects of IL-10 on T cells also come naturally. Other than its anti-inflammatory effects during the early immune response, the T-cell effect of IL-10 also suggests that this cytokine can control hypersensitivity and chronic inflammatory diseases. In several studies, increased IL-10 expression has been shown to be associated with good clinical control [27- 29].

1. 3. Interleukin-10 in Infectious Diseases

Interleukin-10, balancing the immune response to functionally relevant pathogens, is essential for the homeostasis of the human immune system. The immunological effects of IL-10 clearly affect infectious diseases. Numerous studies have shown a beneficial role for IL-10 in infectious diseases, with individual counter-regulation of the immune response of the host being essential for protection, while a dysregulation of the immune response was associated with a poor prognosis. In many cases, there is a balance to be struck when it comes to the role of IL-10 in the immune response to an infection. [12, 30]. Regarding viral infections, classical antiviral immune responses, CD8⁺ and bearing virus-specific CTL, are closely related to the severity and prognosis of the infection and might be subject to inhibition by IL-10 in severe cases. Studies in several viral infections linked an increase in IL-10 levels to high virus loads and a fulminant infection [31].

The role of IL-10 regarding a bacterial infection is considered more controversial. Increasing cytokine levels and immunopathology were linked to mortality in severe bacterial infections, and in a setting with limited medical resources, the negative impact of TNF- α on the systemic inflammatory response driven by IL-10 has been demonstrated. Additionally, experimental infections and the treatment with recombinant IL-10 inhibitors have shown an improved survival associated with Th1/Th2 activity in mice [2,32, 33]. The immunological response mediated by IL-10 might also represent a potential target for medical treatment in infectious diseases. The concept of interfering with the immunological response in IL-10 in a complicated malaria infection, for example, is

intensively discussed and is in some cases already clinically tested. The non-beneficial role of recombinant IL-10 treatment during a Plasmodium infection was demonstrated in a study, challenging the use of recombinant IL-10 in the treatment of complicated malaria. The possible therapeutic implications for immunosuppression developed during sepsis have been summarized [34, 35].

3.1. Role in Viral Infections

When faced with a viral pathogenesis, the antiviral immune response is primarily responsible for eliminating the virus and the infected cells to fend off an infection of the host organism. Pathogen-associated patterns, such as the incorporation of viral proteins into the plasma membrane of infected body cells or the replication and release of viral DNA and RNA in the cytoplasm, are among the most important chemical signals for dendritic cells and macrophages. This activated antigen-presenting cell is consequently 'activated' and presents the viral antigen to T lymphocytes on its surface via an MHC signaling protein, with the help of a co-stimulation ligand. This occurs through the docking of the T cell receptor with its antigen on the active-presenting macrophage. Interleukin-10 can also serve as a feedback regulator for the size and duration of the specific immune response, for example, to prevent an aggressive, unwanted immune reaction to an additional viral pathogen during the respective induction [3,25, 36]. Pathogenic states or previously injected pathogens can trigger the currently present immune cascade in an already inflamed and intolerant immune system. In the acute inflammatory phase, the production of IL-10 accelerates the overall degradation process of the IL-10 protein. In the increasing surrounding production in specific immune cells, it primarily acts selectively to dampen

the reactivated proteins. The consequence of IL-10 production is pushing. If one integrates IL-10 during the mild reinfection phase of the immune reaction, it attaches to the specific MHC II receptors on cells, overlapping with the parasites. Cytotoxic T cells and anti-unified Tc-NK are completely unable to exterminate the less dangerous virally infected cells. The idea of an additional infection is to eradicate the harmful ones as quickly as possible [37, 38].

3.2. Role in Bacterial Infections

Interleukin-10 has a prominent role in regulating the immune responses to bacterial pathogens. Its inhibitory effects on T cell priming, maturation, and the function of antigen-presenting cells promote immune tolerance and, therefore, promote tissue homeostasis in the presence of pathogens. However, during active bacterial infections, the extent of immune regulation must be carefully managed. As a consequence, an intense focus on the role of IL-10 function has been performed in the context of bacterial diseases. Several early studies showed that high IL-10 levels were predictive of poor outcomes in bacterial infections such as septicemia, meningitis, and shigellosis, except when IL-10 was considered together with IFN- γ [33, 39].

The protective effect of IFN- γ has been further exploited by researchers who showed that high IL-10:IFN- γ ratios are associated with poor outcomes in bacterial sepsis. IL-10 acts, directly or indirectly via IL-10- and/or STAT-3-dependent pathways, to limit inflammation in bacterial diseases, as typically evidenced by inhibitory effects on pro-inflammatory cytokine production. Recent progress has demonstrated that gene polymorphisms that augment IL-10 production have been described in vaccinated subjects who are also at greater risk of disease. This observation may also hold true in the context of acute

infections, e.g., pneumococcal infections, in which the IL-10 allele has been shown to be associated with neutropenia. Therefore, in certain bacterial diseases, IL-10 is likely to be an important host factor that sets the balance of outcomes. A sustained IL-10 response allows the pathogen to survive but limits the full extent of immunopathology and is a possible therapeutic target in the future [40- 43].

4. Interleukin-10 in Autoimmune Disorders

Interleukin-10 is also involved in many autoimmune disorders. The immune response in individuals with autoimmune disorders is typically shifted towards a Th1 response; this is where IL-10 might have a regulatory role in the shift to a more dominant Th2 response. During organ transplantation, IL-10 may be induced in response to antigens and may play a role in the induction of tolerance to graft antigens. It is believed that IL-10 may have regulatory effects on different antigen-presenting cells to induce tolerance, such as B cells, downregulation of Integrated Nuclear Factor- κ B signaling, and shifts in chemokines that could recruit regulatory cells. It has been found that IL-10 plays a role in downregulating T cell responses through decreased activation of α 4 β 1 receptor; this is necessary for adhesion of cells to VCAM-1 on B cells [3, 13, 18]. IL-10 has also been found to have anti-proliferative effects on T cells. It has been suggested that IL-10 may play a role in the promotion of a regulatory phenotype. The mechanism behind this is associated with the induction of a suppressive phenotype: reduced CD25⁺ and CD39⁺ T cells, decreased Th17 development, and upregulated Tregs. The transforming growth factor- β /IL-10 producing Bregs have also been shown to induce expression of programmed cell death on Treg cells. Strategies towards the decommission of IL-10-producing

Bregs could be beneficial for lupus patients with depleted Treg cells alongside reduced phenotypes of IL-10⁺ Bregs [44- 46]. The therapeutic potential of IL-10 in autoimmune diseases suggests that IL-10 may have both inhibitory and stimulatory effects in B cells. It has been found that an abrogation of IL-10 enhanced lupus-induced autoimmunity. It was found that only when mice with transgenic IL-10 and autoantibodies for rheumatoid factor were injected into SCID mice that the transgenic IL-10 antibodies were raised, suggesting that IL-10 was likely to control autoreactive B cells. Reduced levels of IL-10 with higher levels of IL-12 have been measured in rheumatoid arthritis patients, contrary to healthy controls. IL-10 has also been engineered in animal models, which caused a reduced severity of collagen-induced arthritis in mice that took part in the administration and addition of plasmablasts and macrophages. In IL-10-deficient mice, the mice develop anorectal lesions not long after birth and usually die within weeks. Systemic autoinflammatory disease, enterocolitis, and organ infiltrates were present via histological examination. TGF- β levels are increased in response to increased levels of IL-10, resulting in the formation of mucosal Tregs. In humans, IL-10 is used as a treatment agent for psoriasis and IBD. However, targeting IL-10 in an autoimmune condition may present some challenges. Targeting the Th2 response to induce IL-10 production and the switch of IgE to IgG production to create a shift in the balance of inflammation may be useful. So far, some autoantibodies do produce sufficient isotype switching. Therefore, the development of therapies for the control and maintenance of the balance would need to be on an individual basis. Overall, the IL-10 and the production thereof play a major part in the pathogenesis of many autoimmune disorders, by

either down- or upregulating the response in the inflamed state [47- 51].

4.1. Regulation of Autoimmune Responses

IL-10 has an apparent role in the downregulation of autoimmune responses. It is not only produced by specific subsets of T and B cells but also by a number of non-lymphoid cell populations. It appears to be most relevant in controlling the extent of autoimmune reactions to antigens encountered in mucus, which include ambient allergens acquired through mucosal surfaces, surface epithelial antigens involved in a spectrum of autoimmune celiac diseases, and gut flora encountered following oral tolerance induction. Thus, IL-10-deficient mice rapidly develop chronic, infiltrative autoimmune diseases such as those in the central nervous system and pancreas, where the antigens are accessible to APC and T cell reactivation. In view of this, IL-10 is seen as important for the generation and maintenance of self-tolerance in the periphery [25,52,53].

IL-10 is crucial in maintaining self-tolerance. It inhibits the production of pro-inflammatory cytokines such as mononuclear phagocyte tumor necrosis factor- α and T-cell interferon- γ ; the latter reduces IL-12 and IL-10 receptor expression, preventing hyper-reactive immune responses. It has also been shown to have deleterious effects on the functional activity of autoimmune effector cells via the inhibition of MHC class II expression on B cells, monocyte mobilization, and secondary APC efficacy. The level of IL-10 production is also reported to decrease with the degree of autoimmune reactivity in some disorders, whereas it has been shown to rise in others, suggesting a regulatory role for this cytokine in the control of autoimmunity [1,54]. Genetically determined defects in IL-10 production may account for intraspecies susceptibility to various autoimmune

disorders, such as systemic lupus erythematosus, the vasculitides, and multiple sclerosis, where the presence of IL-10 polymorphisms is now established, whereas a number of investigations have commenced to search for such polymorphisms in type 1 diabetes and celiac diseases. Furthermore, raised IL-10 in vitro over time in subjects has been associated with a decreased odds ratio of developing multiple sclerosis. Besides its implications in genetic associations, IL-10 can be a compensatory cytokine in some types of destructive autoimmune processes, such as those seen in multiple sclerosis, because of its associated downregulation of IFN- γ , which itself is supportive of the disease process [55- 57].

4.2. Therapeutic Applications in Autoimmune Diseases

Interleukin-10 has been highlighted as a potential candidate for immunotherapy in a number of autoimmune diseases. Because many autoimmune conditions are mediated by T-helper type 1 or Th17 T cells, which secrete a range of proinflammatory cytokines and other factors, manipulation of the immune system to enhance IL-10 production or mimic its actions is seen as a promising approach. Interleukin-10 has an important immunosuppressive role in pregnancy and during infection with certain bacteria, and it might be possible to enhance the function of pre-existing regulatory T-cell populations in a similar way, rather than administering IL-10 directly. Interleukin-10 might provide an interesting target for development in conditions such as rheumatoid arthritis and multiple sclerosis, both of which have been clearly implicated as Th1- and Th17-mediated diseases. In fact, neutralization of endogenous IL-10 using monoclonal antibody reduces disease severity in mouse models of multiple sclerosis, although

whether this will be reflected in humans is unclear [25, 58- 60]. There have been a number of phase 1 and phase 2 clinical trials in patients with a range of conditions to assess the safety and efficacy of IL-10 treatment. In patients with Crohn's disease, a phase 2a clinical trial in patients with mild to moderate disease failed to show any effectiveness of prophylactic treatment with human recombinant IL-10-derived fusokine when compared with a placebo, although the study did not address whether the treatment had any therapeutic potential. It should be noted that the primary motivation behind this trial was to identify patients who might benefit from this treatment, rather than to directly assess the therapeutic potential of IL-10. More severe forms of disease might potentially be responsive to this type of treatment, and there is still considerable interest in the wider targeting of IL-10 and its regulatory actions more generally in Crohn's disease patients. Many enterprises are developing modified forms of IL-10 in order to optimize its potential as a therapeutic [61- 64]. In phase 1 trials in patients with moderate to severe rheumatoid arthritis, intravenous infusion of a polyethylene glycosylated human recombinant IL-10 was well tolerated and resulted in decreased disease activity. However, the evolution of erythema nodosum at the injection site around 3 weeks after treatment began required termination of further clinical studies. An injection of a solution containing IL-10 is painful, which must be taken into account when considering dosing. IL-10 given by intranasal administration in patients with allergic rhinitis increased IL-10 levels in lavage fluid and had a favorable safety profile, which supports the idea of mucosal delivery of the cytokine. A modified form of IL-10 with a small N-terminal fusion that confers greater stability was administered in a number of phase 1 trials, although the results have not been

disclosed. A conjugate of IL-10 with a tumor-specific antibody showed promise as a cancer therapeutic in mouse models and is now moving into early human clinical trials. Further clinical testing is required to determine whether IL-10 actually has therapeutic potential [65, 66].

5. Interleukin-10 in Cancer Immunotherapy

IL-10 is one of the fundamental immunoregulatory cytokines with far-reaching effects within the immunity network. Its influence is particularly well documented in the context of cancer. It has been demonstrated that IL-10 enhances immune evasion mechanisms, leading to the inability to reject tumors and correlating with poor prognosis in numerous cancer types. Nonetheless, a fair share of this association can be attributed to the different nature of IL-10's immunomodulation observed at steady state versus anti-tumor response. At the normal level of expression, IL-10 protects tissues from inflammation, preventing tissue damage and maximizing the effectiveness of the immune response. In the hypoxic, nutrient-deficient environment of solid tumors, the synthesis of IL-10 enhances the cancer cell-killing activities of immune cells while reducing the release of pro-inflammatory tissue-damaging molecules [67, 68]. There is a growing body of evidence indicating that local, short-term blockade of IL-10 in solid mouse tumors results in a failure to eradicate them as the mounted anti-tumor immune response becomes suppressed or off-target cytotoxicity diminishes, damaging healthy tissue. Relatively few studies directly evaluate the mechanisms of IL-10-driven immune activation in solid tumors. IL-10 can favor the immune-induced anti-tumor capacity of dendritic cells. It also has direct anti-tumor effects via downregulation of oncogenic pathways and cytotoxic action against

malignant cells, mainly of blood and lymphoid origin. Antibody targeting of IL-10 is not underway, either as a single agent or in combination with other biologicals or chemotherapy, although results of such treatment are awaited from several clinical trials. It is conceptually difficult to use the IL-10 systemically to stimulate anti-tumor immunity without also suppressing it. Interleukin-10 does enhance the activity of therapeutic immune checkpoint inhibitors, potentially reducing the likelihood of adverse events seen with such biologicals due to the systemic addition of a pro-inflammatory cytokine [69- 71].

5.1. Immune Evasion Mechanisms in Cancer

Tumor cells are continually fighting a battle to survive in an environment with immune surveillance mechanisms that seek to eliminate abnormal cells expressing tumor antigens as part of the self-defense processes. Interleukin-10 (IL-10) can contribute to immune evasion of tumors in several different ways. It can not only act directly on diverse effector cell populations to impair tumor-specific immune responses and support neoplastic development, but also can induce changes in the immunological tumor microenvironment and might thereby actively contribute to tumor disease progression. Indirectly, the tumor can also exploit the systemic levels of IL-10 to improve its chances of escaping immune system attacks [6].

The key question is: How do neoplastic cells exploit IL-10 to suppress efficient anti-tumor immune responses? In principle, by acting on different cell populations, particularly in the tumor microenvironment, IL-10 plays a pivotal role in tumor immunological escape. IL-10 affects dendritic cells and is one of the most powerful anti-inflammatory cytokines, inducing differentiation of

regulatory T cells. Also, increased numbers of regulatory T cells in the peripheral blood and tumor tissue are associated with a higher risk of immune surveillance and, at the time of diagnosis, correlate with unfavorable clinical outcomes. IL-10 is acknowledged to potentiate the abilities of regulatory T cells to suppress the activity of antigen-presenting cells and activated effector T cells [6, 72]. Taking into account that only a careful, in-depth analysis of the IL-10-induced inflammatory and immunological conditions will lead to the exceptional potential of immunotherapeutic strategies using biological response modifiers, it is essential to support the targeting of IL-10 pathways in combination with additional immunotherapeutic approaches. Due to the existence of various biologically active IL-10 isoforms that exhibit multiple and sometimes conflicting biological activities, additional in-depth research is required to thoroughly examine the importance of the IL-10 isoforms in cancer biology and cancer therapy. Detecting raised intratumoral IL-10 levels represents a very critical and rapid approach to assess if alterations in the IL-10-dependent inflammatory and immunological microenvironment are linked to neoplastic development and/or neoplastic progression. Nevertheless, difficulties have been encountered when trying to detect IL-10 in tumor tissues, as IL-10 is a protein detectable both in soluble form and anchored on the cell membrane. In conclusion, IL-10 directly controls the molecular and cellular mechanisms that mediate tumor immune escape, wherein the net balance of its activities associated with the immune response determines the final control of the host anti-tumor capability of the immune system, going hand in hand with tumor progression [52,73].

5.2. Enhancing Anti-Tumor Immunity with

Interleukin-10

Interleukin-10 (IL-10) can also be applied to enhance anti-tumor immunity. Cultured dendritic cells transfected with IL-10 suppressed the progression of the autologous tumor in 3 out of 6 patients. A phase II clinical study is currently ongoing to evaluate the therapeutic effect of IL-10-secreting allogeneic L-cells and NK cells on recurrent or refractory cutaneous malignant melanoma. Gene preparations of IL-10 are expected to associate with PD-1 antibody synergistically. Similar to inhibitory receptor deletion therapy, the function of personnel (including T cells) can be restored using low-dose IL-10 gene therapy. IL-10 induced via an oncolytic virus vector is currently being evaluated in preclinical trials. These oncolytic hepatitis C virus preparations were effective in the treatment of eGFP and JFH-1 in NOD/SCID mice bearing human melanoma. After patients achieve a complete response with anti-cancer agents and/or CD8⁺ T-cell responses, IL-10 therapy may be feasible [52,74].

Several methods are known for improving the delivery of IL-10. Particle delivery systems, including synthetic water-insoluble agents, FCA/IFA, and aluminum-treated emulsion, have recently been regarded as effective in clinical studies. The anti-tumor effects of IL-10 include the promotion of differentiation of effector T cells and augmentation of NK cells. The role of IL-10 in the development of acquired anti-cancer immunity has yet to be clarified. Early studies, including animal models, have proven that endogenous IL-10 suppresses anti-cancer immunity through an effect on the environment surrounding the cancer and/or immunity. In a B16 syngeneic transplant melanoma model, the metastasis rate and mortality were reduced in IL-10-deficient mice relative to normal

mice, and IL-10-deficient mice receiving intraperitoneal IL-10 injection had metastasis rates and mortalities comparable to those of normal mice [16].

6. Clinical Trials and Future Directions

Ongoing Clinical Trials

A listing of currently active clinical trials involving IL-10 as a treatment for a variety of different diseases is shown. These trials include a multitude of clinical and preclinical investigations into the potential of IL-10 as a therapeutic for cancer, inflammatory bowel disease, sepsis, atopic dermatitis, and allergies. IL-10 has potential use for the treatment of a broad range of other diseases, including autoimmune diseases, acute myocardial infarction, and solid organ transplantation [52]. The methodology of the two largest phase II clinical trials of IL-10 for cancer, key inclusion/exclusion criteria, and estimated end dates for follow-up are shown. The different methods employed in these clinical trials, including route of administration and concomitant chemotherapy, provide important information on patient welfare and potential efficacy. The results will either support further exploration of IL-10 as a therapy for cancer or lead researchers to investigate other delivery techniques, timing, or dosages for subsequent clinical trials [52].

Future Directions

Despite relevant studies in the present and past, the potential of IL-10 in cancer immunotherapy is still being defined. As shown by the listing of currently running clinical trials, the recruitment of relevant patient groups and ongoing funding and resources remain some of the main challenges in the development of IL-10 as a viable therapy. Fortunately, previous research has highlighted

potentially safer and more effective ways to utilize IL-10 in a clinical setting. The monotherapies and combination therapies, utilizing studied techniques of IL-10 delivery as well as more expensive alternatives, have the potential to provide profoundly effective results in clinical trials. Indeed, IL-10's ability to transform the tumor microenvironment represents a compelling reason to continue investigation in the strategic use of this cytokine. The purpose of the use of IL-10 is to condition immune populations by altering the balance of inflammatory and suppressive mechanisms to enable a successful attack to be mounted against the tumor in combination with other treatments. Preclinical research has exhibited the utility of specific genetically engineered cell delivery methods that could allow for safer and more effective usage of IL-10, possibly providing a promising alternative in the treatment of cancer. Further, international research on the frequency and optimal dose regimen of genetically engineered cells expressing IL-10 will allow the pursuit of cancer immunotherapy [13,52, 76].

6.1. Current Clinical Trials Involving Interleukin-10

Given the diverse range of conditions and diseases in which such a diverse array of participants' demographics and study endpoints are typically involved, many clinical trials are generally being undertaken across various nations, aiming to determine the safety or efficacy of administering IL-10 compared to placebo or control. Ensuring research and clinicians are aware of and can keep up to date on the current status and outcome of IL-10 therapy in the clinic is critical for the development and evolution of IL-10 as a licensed therapeutic globally. Below are a number of the publications that

have been released up to the point of submission, assessing the usage of IL-10 in certain diseases, and only a few of these are currently completed and submitted. Many of IL-10's trials have different complexities and subject requirements, such as various patient numbers, methods of administration, dosages, and outcomes [77].

In developing new therapies for disease prevention and treatment, immunomodulation has shown potential benefit for use in the form of IL-10, albeit with some caveats associated with patient variability and participant recruitment and sourcing. In several inflammatory diseases, IL-10 has been or is in the process of being assessed in a number of clinical trials. These diseases include, but are not limited to, non-alcoholic steatohepatitis, inflammatory bowel disease, psoriasis, ulcerative colitis, Crohn's disease, and colorectal cancer, as well as advanced tumors. It is hoped that with improved knowledge of patient demographics and dosing with IL-10, further studies may be able to help progress the development of IL-10 for the treatment of the varying range of diseases detailed [78].

6.2. Potential Future Applications and Research Directions

Given the increasing number of studies that demonstrate IL-10's immunomodulatory effects, the logical next step is to clinically test whether IL-10-targeting strategies aimed at overcoming the disadvantages of the cytokine can be beneficial in diseases. An ever-growing interest lies in developing novel therapies that not only inhibit target disease pathways but also have the potential to limit excessive immune damage to the patient's own tissues with the help of immunosuppressive mediators. IL-10 is thought to be an especially promising target, predominantly because of its

crucial role in immune homeostasis and the long-standing links with immunopathology. Tremendous progress is being made in advancing preclinical research on genetically engineered IL-10 and targeting the IL-10 pathways, particularly in inflammatory diseases and cancers. Such advanced research is addressing a number of key areas [1,52].

The identification of potential patient progression biomarkers or predictive response biomarkers of IL-10 therapies is considered crucial in utilizing IL-10-targeted drugs to their full potential. Once identified, patients might benefit from personalized medicine in a variety of ways. A deeper understanding of the cellular mechanisms by which IL-10 performs its beneficial effects, which is being addressed in clinical settings with therapeutic cytokines, is needed so that this can be further applied for improved novel therapeutic developments. Multiple approaches, including combination therapies, are emerging to selectively utilize IL-10's properties to their full potential and encourage further developments in targeting the IL-10 pathway in oncology and within the clinical areas of autoinflammatory and autoimmune disorders. A counterbalancing approach is also being undertaken by striving to develop other methods to modulate the IL-10 pathway. It takes a combined and personalized approach; thus, collaborative discussion and development of therapies are ongoing. It is still unclear who will turn their energy and resources toward the clinical development of IL-10. To date, all the advanced therapies planned for clinical trials appear to be strong. A first and novel approach in the field of systemic delivery of IL-10 is on the horizon with the instigation of a Phase I trial for the delivery of IL-10 by a proprietary tablet technology. Now that patterns are emerging, it will be interesting to see how the two distinct broad approaches to the clinical

development of IL-10 advance [52, 76].

7. Conclusion and Implications

In this article, we review the function and receptors of interleukin-10 (IL-10), its autocrine and paracrine mechanisms, and its roles in regulating both innate and adaptive immunity. Moreover, we discuss the major role of IL-10 in immunological, inflammatory, and autoimmune diseases, as well as its protective role against infections and radiation damage. We also explain the application of IL-10 in the clinical setting and its use as a precision therapy for lesions or diseases characterized by a better prognosis in IL-10-positive patients compared to IL-10-negative patients. We also discuss patents directed to those diseases characterized by a worse prognosis in IL-10-positive individuals or patents that focus on the use of human anti-IL-10 monoclonal antibodies, which will suppress the IL-10/IL-10R autocrine loop [3, 35]. Finally, we consider the limitations of IL-10 use and suggest that research should continue in order to fully understand the complete mechanisms of IL-10 in various tissues and diseases and to develop new strategies for the use of IL-10 or new therapeutic tools that modulate IL-10 receptors. In conclusion, IL-10 plays an important role in the pathogenesis of many diseases by regulating immune responses in different ways; however, its role and potential as a therapeutic, as well as the receptor-mediated signaling pathways, have not been fully discovered or utilized. A number of recent studies suggest that as a therapy, IL-10 is useful for the treatment of diseases with negative pathological effects compared to those with a better prognosis, especially for those that are characterized by autoreactive B cells and/or intralesional IL-10, which could potentially be combined to form the basis of a "precision medicine" that targets patients

who are expected to derive the most benefit from IL-10 treatment. In the future, IL-10 synthesis could be a new addition to an integrated approach in the treatment of some diseases, such as metastatic cancer following radiotherapy; the use of IL-10 may represent a promising option because it has been shown to have potential beneficial effects, ameliorating the adverse effects of radiotherapy, and may improve survival. Finally, IL-10 could be used at low concentrations for short periods of time or in combination with other therapeutic drugs, and its use in different disorders is foreseen [35, 52].

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