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Review Article

The Role of Interleukin-10 in Leprosy: A Review

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Leprosy continues to be an important health issue in several endemic countries. The global incidence of this disease is greater than 200,000 new cases detected annually. This number has remained relatively stable during the past eight years, indicating ongoing transmission. The elimination of this disease, remains - a challenge for clinicians and scientists. Since leprosy is an infectious disease, the immune system plays an essential role in its development and progression. The unique immune response in each individual is due to the interaction of various cytokine products, both pro- and anti-inflammatory cytokines. Interleukin-10, an anti-inflammatory cytokine, plays a vital role in the immunity and pathogenesis of leprosy. Evidence suggests that interleukin-10 plays a cruicial roles in the clinical manifestation and progression of the disease in all subtypes of leprosy. An understanding of the biomolecular aspects of this disease is imperative and may lead to the discovery of new treatment-modalities and/or more effective prevention methods.

Keywords : Leprosy, Interleukin-10, Immune Response

Introduction

Interleukin-10 (IL-10), produced by immune cells upon certain types of stimulation, plays a significant role in regulating the immune response. This cytokine is secreted primarily by macrophages but also by T helper 1 (Th1) and T helper 2 (Th2) lymphocytes, cytotoxic T cells, B lymphocytes, mast cells, dendritic cells, and monocytes (Trifunovic et al 2015). Interleukin-10 mostly functions as an anti-inflammatory cytokine that can inhibit the activity of several immune cells, such as macrophages, natural killer cells, and Th1 cells, all of which are required for optimal pathogen clearance (Couper et al 2008). Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. It is considered a severe public health issue due to its severity. The evolution of this disease involves the complex immune mechanisms of the host. Macrophages play a central role in the interaction between the bacillus and the host (de Sousa et al 2017). Since *M leprae* is an obligate intracellular bacterium, inhibiting macrophage activity by IL-10 could disturb the clearance of the pathogen. The primary biological function of this anti-inflammatory cytokine appears in macrophages and dendritic

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cells (DCs). Interleukin-10 is a potent inhibitor of antigen presentation and down-regulates major histocompatibility complex (MHC) class II and co-stimulatory molecules on macrophages. It also inhibits DC maturation and differentiation from monocyte precursors. Another important effect is inhibiting the production of pro-inflammatory cytokines and mediators from macrophages and DCs. The central inflammatory cytokines, such as IL-1, IL-6, IL-12, and tumour necrosis factor (TNF), are significantly suppressed after exposure to IL-10. The inflammatory chemokines (both CC and CXC types) are also suppressed by IL-10, as is macrophage matrix metalloprotease production. Interleukin-10 can further inhibit inflammation by increasing the release of IL-1 receptor antagonists by macrophages and targeting naive CD4+ T cells, possibly inhibiting the CD28 signalling pathway (Mege et al 2006). These mechanisms could not only lead to susceptibility to leprosy but could also play a substantial role in determining the subtype of the disease. Several previous studies have been conducted regarding the role of IL-10 in the susceptibility of individuals to leprosy and the subtype of the disease, particularly in the field of genetics (Santos et al 2002, Malhotra et al 2005, Cardona-Castro et al 2012, Felix et al 2012, Oktariana et al. 2021).

Production, Structure, and Function of Interleukin-10

Production

Interleukin-10 is produced by macrophages, monocytes, T-cells, B-cells, dendritic cells, monocytes, and mast cells, and its primary function in vivo is to limit the inflammatory response. The gene encodes this protein on chromosome 1q31-32 and contains four introns and five exons (Opdal 2004). The variability of IL-10 secretion, which ranges from 50% to 75%, could be caused by genetic factors (Reuss et al 2002). The gene expression of this cytokine is regulated at translational and transcriptional levels (Moore et al 2001). The regulation of IL-10 production is triggered by microbial products, which are recognised through a Toll-like receptor (TLR). Then several signal transduction pathways are activated, including MAPK, PI3K/AKT, and NF-κB, resulting in the activation of several transcription factors. The binding of transcription factors occurs in the promoter region. Therefore, the promoter region plays an important role in regulating gene expression (Lis & Walther 2016). The promoter part of this gene consists of a region 5 kb upstream of the transcription start site, which may contain several polymorphisms along with the gene itself. These polymorphisms, together with the haplotype variants that can be formed, may play a role in the disruption of the binding affinity at the IL-10 transcription site, thereby potentially contributing to the amount of IL-10 produced (Kube et al 2001, Lazarus et al 2002, Malhotra et al 2005).

Structure and Function

Structurally, the IL-10 protein consists of 160 amino acids, which have a molecular mass of 37 kDa, and is biologically active as a non-covalent homodimer. Each dimer has a molecular mass of 18.5 kDa (Mege et al 2006, Walter 2014). Interleukin-10 is a class II cytokine family member, which involves several other cytokines such as Interleukin-19, Interleukin-20, Interleukin-22, Interleukin-24 (Mda-7), Interleukin-26, IFN-α, IFN-β, and IFN-γ (Ouyang & O'Garra 2019). From the quaternary structure point of view, the IL-10 family members can be found as monomers, consisting of six α-helices, A-F (Trivella et al 2010, Minshawi et al 2020). The main feature of each α-helical antiparallel cytokine structure is a left-handed four-helix bundle (Walter 2004). These α-helices function as intracellular messengers, while the receptors are composed of an intracellular domain, an extracellular binding

space, and a membrane-spanning helix. Two subunits generate a functional receptor complex; they are IL-10R1 and IL-10R2 (Pestka et al 2004). IL-10R1 and IL-10 show high affinity, and the recruitment of IL-10R2 marginally contributes to ligand binding (Mosser & Zhang 2013).

The interaction between L-10 and its receptor complex activates the Janus tyrosine kinases, Jak1 and Tyk2, which primarily phosphorylate tyrosine residues and recruit STAT3, the downstream common transcription factor interleukin-10–interleukin-10R (Mosser & Zhang 2013). STAT3 translocates to the nucleus, binding to STAT elements in the gene and mediating most of the inhibitory action of IL-10 on the innate and adaptive immune responses (Riley et al 1999, Minshawi et al 2020).

Role of IL-10 in Innate and Adaptive Immune Responses

In the regulation of innate immunity, IL-10 disrupts the secretion of several inflammatory mediators by macrophages, polymorphonuclear neutrophils, and monocytes as well as the increased production of molecules that corroborate the anti-inflammatory effect of IL-10 (Mege et al 2006, Commins et al 2008). A study of IL-10-deficient mice revealed that the animals showed a poor innate immune response to the antigens of intestinal bacteria and later developed chronic inflammatory bowel disease (Kube et al 2001).

In the regulation of adaptive immunity, IL-10 affects antigen-presenting cells and T cells by inhibiting the production of other cytokines, such as-12 and IL-18. It reduces the expression of MHC class II molecules and co-stimulates their molecules. Additionally, IL-10 inhibits DC differentiation from monocytes, alters dendritic cell migration by modulating the surface expression of chemokine receptors, and induces apoptosis in plasmacytoid dendritic cells (Moore et al. 2001, Mege et al. 2006). Interleukin-10 also inhibits the expression of CXC chemokine receptor-4 (CXCR4), interleukin-2, interleukin-5, tumour necrosis factor (TNF), and the response to stromal cell-derived factor-1, which can induce the energy or non-responsiveness of CD4+ T cells (Sundstedt et al 1997).

Role of IL-10 in Various Diseases

Several studies have been conducted regarding the role of IL-10 and immune-mediated diseases, such as autoimmune and infectious diseases (Iyer & Cheng 2012). Interleukin-10 plays an important role as an immunoregulator during several types of infection, including viral, bacterial, protozoan, fungal, and helminth infections (Couper et al 2008). Interleukin-10 can induce an anergic state and lead to the persistence of bacteria in hosts. This can cause the evolution of infectious diseases. Furthermore, numerous clinical reports revealed that IL-10 is associated with mycobacterium infection (Yamamura et al 1991, Murray & Young 1999, Higgins et al 2009).

Leprosy : Immunopathogenesis

Leprosy is a chronic infection in humans that affects the peripheral nerves, skin, and other organs. The cause of this disease is the bacterium. *M leprae* remains endemic in several countries, such as India, Brazil, Indonesia, China, and Nepal (Li et al 2021). *M leprae* enters the body through the nose and then spreads to the skin and nerves through the circulatory system (Walker & Lockwood 2006). These bacteria invade three main targets: the monocyte-macrophage system, the peripheral nervous system (Schwann cells), and the small blood vessels (endothelial cells and pericytes) (Abulafia & Vignale 1999). In the early stages of protection, the non-specific mechanism mainly involves the monocytes, which function as phagocytic cells. In addition to the monocytes, the response to infection also increases the production of neutrophils from the bone marrow.

The production of neutrophils is induced by CSF cytokines (Sari et al 2013).

Neutrophils phagocytise both circulating and extravascular microbes that only last for a few hours, resulting in partial lysis (Abbas et al 2019). The monocytes in circulation last up to five days; however, they can migrate to the connective tissue and survive for several months as histiocytes (Abulafia & Vignale 1999). Numerous bacilli that escape will be transported with the monocytes in the bloodstream. These microorganisms can even replicate inside the monocytes (Trojan horse phenomenon) and enter various organs (Sari et al 2013). These stimulated monocytes to differentiate into high-energetic activity macrophages that could form epithelioid cells in tuberculoid leprosy (TT) and leprosy cells or virchowcytes in lepromatous leprosy (LL). The activated macrophages in TT leprosy are also capable of the phagocytosis of intraneural bacilli. Macrophages also act as antigen-presenting cells (APCs) in cellular and humoral immune responses (Abulafia & Vignale 1999, Sari et al 2013).

The bacilli that emerge from dead and ruptured monocytes will invade Schwann cells and enter phagocytic vacuoles (phagosomes), so they can multiply and are protected from antibodies and macrophages. However, *M. leprae* can also leave its hiding place and enter the perineural tissue, eventually forming an epithelioid or lepromatous granuloma (Bokhary & Phung 2016). *M leprae* bacilli can survive for an extended period in Schwann cells because these cells do not have lysosomal enzymes to destroy bacteria (Nath 2016).

Phagocytic macrophages in TT type (Mitsuda-positive) leprosy can destroy all bacilli, thereby providing antigen information that is expressed on the surface of MHC class II molecules, presented by APCs, and inducing cellular immunity (involves Th-1 cells, which secrete interleukin-2 and IFN-gamma). Macrophages containing *M. lepra* bacilli induce the development of epithelioid cells. In LL (Mitsuda-negative) leprosy patients, phagocytic macrophages produce partial bacterial lysis. Ingested bacterial phospholipids enter the cytoplasmic vacuole, producing leprosy cells or virchowcytes. During the initial phase, immune stimulation does not play a role. It is believed that the mitochondrial dysfunction of the "Mitsuda-negative" state causes excessive free radical production and the depression of lysosomal phospholipase. In the advanced phase of LL, other macrophages can phagocytise virchowcytes, thereby providing neo-antigenic information expressed on MHC class II molecules, generating new APCs, secreting IL-4, and stimulating humoral immunity (Abulafia & Vignale 1999, Sari et al 2013).

Mycobacterium leprae phagocytosed by "Mitsuda-positive macrophages" is completely enhanced; Normal antigenic information can be retrieved and expressed by the cell surface. In the presence of MHC class II molecules, APCs can secrete interleukin-12 and stimulate Th-1 cells (CD4+), eventually producing interleukin-2 and IFN-gamma. The new macrophages are then activated and become epithelioid cells. However, when MHC class I is involved, cytotoxic T-lymphocytes (CD8+) cells can act on other macrophages to eliminate organisms by apoptosis (Abulafia & Vignale 1999, Sari et al 2013).

The immune response in leprosy is complex and involves both cellular and humoral immune responses. Most of the symptoms and complications of this disease are caused by an immunological reaction to the antigens possessed by *M. leprae*. If the immune response that occurs after infection is sufficient, then bacterial multiplication can be inhibited at an early stage to prevent the development of further clinical signs and symptoms (Goldsmith et al 2012).

Mycobacterium leprae is an obligate intracellular bacterium, so the immune response that plays an important role in the body's resistance to infection is the cellular immune response. The cellular immune response results from macrophage activation by increasing its ability to suppress multiplication or destroy bacteria (Oktariana et al 2021).

The humoral immune response to *M. leprae* is the activity of B-lymphocyte cells located in the lymphocyte tissue and bloodstream. Stimulating the antigen components of these bacilli will convert B-lymphocyte cells into plasma cells, producing antibodies that will assist the opsonisation process. However, in leprosy, this humoral immune response function is ineffective. It can even cause certain leprosy reactions because it is produced in excess (as seen in LL) (Goulart & Goulart 2009).

According to the Ridley-Jopling system, leprosy is classified as an immune-mediated spectral disease, with TT at one end of the spectrum and LL at the other. The tuberculoid form is associated with a strong cell-mediated immunity (CMI) and a localised infection. In contrast, the lepromatous form is characterised by a deficient cell-mediated immune response with significant antibody production but an extremely weak CMI response. The tuberculoid form is associated with Th1 cytokines, such as interleukin-2, interleukin-12, TNF-alpha, and IFN-gamma. The lepromatous form is associated with T helper 2 and T helper 3 cytokines, such as interleukin-10, TGF-beta, and interleukin-4 (Tarique et al 2020).

The Role of Interleukin-10 in the innate Immune Response of leprosy

Interleukin-10 plays several roles in the development of leprosy, including the regulation of the innate immune response and the adaptive immune response and determining the subtypes of leprosy (Figure 1). In the innate immune regulation, IL-10 can inhibit the production of several pro-inflammatory interleukins that are important for the elimination of leprosy pathogens, such as IL-1, IL-6, IL-12, IL-18, IFN, TNF, CSF, LIF, PAF, and several other cytokines that are activated by monocytes or macrophages (Mege et al 2006).

The effect of IL-10 in inhibiting the production of IL-1 and TNF is extremely important for the enhancement of its anti-inflammatory activities because the synergistic activity of these cytokines plays a potential role in the inflammatory processes and pathways (Moore et al 2001). Interleukin-10 also inhibits the production of several chemokines by activated monocytes, such as CC and CXC. These chemokines are important for the recruitment of monocytes, dendritic cells, neutrophils, and T cells. Interleukin-10 can also inhibit the inflammatory response by inhibiting macrophage activities (O'Farrell et al 1998).

When *M leprae* enters the body, the first line of defense against the bacteria is the innate immune system, which consists of physical barrier components, solubilising factors, and phagocytic cells. The microbes that pass through the physical barrier will face the inflammation process, which consists of the recruitment of WBCs and plasma proteins. The two main phagocytic cells commonly recruited during the inflammation process are monocytes/macrophages and neutrophils (Putri et al 2021). Macrophages play an important role in the pathogenesis of leprosy due to their phagocytic effect. During the inflammatory response, bone marrow-derived monocytes enter tissues in large numbers as a defense mechanism against pathogens (Pinheiro et al 2018).

Phagocytosis is strongly influenced by opsonisation and adhesion molecules. Once pathogens are phagocytosed, their elimination occurs via oxidative pathways through reactive

oxygen intermediates and non-oxidative pathways through the degranulation of primary and secondary granules containing hydrolytic enzymes, proteolytic enzymes, lactoferrin, and defensins. This activity is strongly influenced by several host-derived cytokines, such as TNF, IFN, and CSF, which can increase macrophages' phagocytic and anti-bacterial activity. The CC and CXC chemokines can also increase anti-microbial activity in eliminating pathogens. Therefore, inhibiting several cytokines and chemokines by IL-10 may affect the activity of phagocytic cells in the innate immune response in leprosy (Laichalk et al 1996).

An in vitro study of IL-10 activity on the phagocytic effect of PMN on bacteria showed that IL-10 stimulation could inhibit PMN phagocytic activity by reducing the expression of opsonin molecules, such as the Fc and C3b receptors. Interleukin-10 can also inhibit CD11b cell surface expression, attenuate PMN bactericidal activity, and suppress superoxide production (Laichalk et al 1996). In a separate in vitro study, IL-10 was also shown to be a potent suppressor of macrophages (Kuhn et al 1993).

A previous study showed that IL-10 alters the metabolic program in macrophages, including inhibiting glycolytic flux, preventing dysfunctional

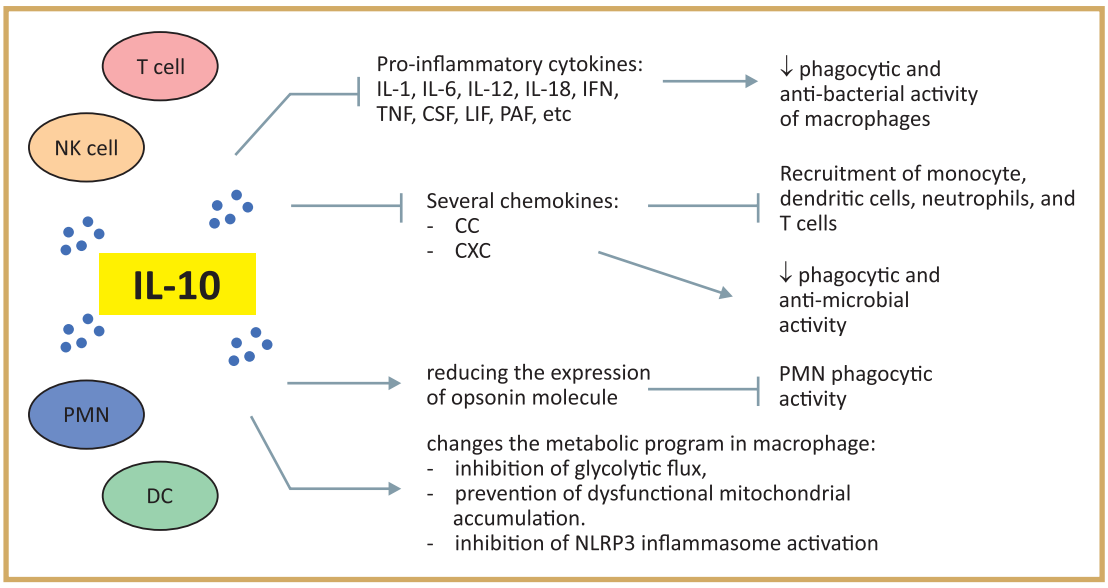

Figure 1 : The Role of Interleukin-10 in the innate immune response of leprosy. Interleukin-10 inhibits several pro-inflammatory cytokines that lead to a decrease in the phagocytic and anti-microbial activity of macrophages. It also inhibits the expression of several chemokines, which then inhibit the recruitment of monocytes, DC, neutrophils, and T cells. This condition also leads to a decrease in phagocytic and anti-microbial activity. A reduction in the expression of opsonin molecules attenuates PMN bactericidal activity and suppresses superoxide production. Interleukin-10 alters the metabolic program in macrophages, including inhibiting glycolytic flux, preventing dysfunctional mitochondrial accumulation, and inhibiting NLRP3 inflammasome activation, resulting in less potent macrophages.

mitochondrial accumulation, and inhibiting NLRP3 inflammasome activation (Ip et al 2017). The expression of the NLRP3 inflammasome influences the evasion mechanism of *M leprae* (Mendes et al 2020). A separate study revealed different results, i.e., IL-10 can induce the differentiation of monocytes in leprosy. Interleukin-10 induces phagocytosis, including the C-type lectin CD209 and the scavenger receptor, thereby phagocytosing the mycobacteria and oxidising low-density lipoproteins (Montoya et al 2009).

The Role of Interleukin-10 in the Adaptive Immune Response of leprosy

After *M. leprae* encounters the innate immune response as the first line of defense, the activation of the adaptive immune system is crucial in mitigating the intracellular bacteria that are not eliminated by the innate immune system. Furthermore, suppose the adaptive immune response does not destroy this pathogen. In that case, the development and subtype of leprosy will be determined by the type of adaptive immune response, which differs for each individual. Individuals with strong cell-mediated immune responses will develop paucibacillary (PB) leprosy. In contrast, individuals with poor cell-mediated or a predominant humoral response will develop multibacillary (MB) leprosy (Weiss et al 2020).

The T cell response will determine the outcome of leprosy development (Mi et al 2020). Many factors influence the polarisation of naive T cells to mature into T-helper 1 (Th1) or T-helper 2 (Th2) effector cells, such as the presence of immunologically active hormones, the local cytokine environment, the dose and route of antigen entry, the type of APCs that stimulate the T cells, and the signal strength of the T cell receptor for the MHC-antigens complex (Sadhu & Mitra 2018).

Interleukin-10 can affect APCs and T cells by inhibiting the production of several cytokines, downregulating MHC class II, suppressing TLR signalling, and interfering with co-stimulatory signal stimulation (Figure 2). Interleukin-10 plays a role in mycobacteria invasion and replication in early infection (Lima et al 2000). A study involving the incubation of APCs with IL-10 showed that the APCs inhibited the production of IFN-gamma by Th1 cells, as well as inhibited the production of IL2-induced IFN-gamma by Th1 cells. Conversely, IL-10 can also inhibit additional macrophage cell functions independent of MHC class II-TCR interactions (Fiorentino et al 1991). A separate study showed that IL-10 could also inhibit the production of IL4 and IL5 by Th2 cells. The pre-incubation of APCs with human IL-10 decreased the Th1 and Th2 cell function (Del Prete et al 1993).

Dendritic cells are particularly significant among the several types of APCs because they can induce the activation, differentiation, and proliferation of naive, antigen-specific T lymphocytes (Jonuleit et al 2000). The functional properties of DCs are strictly dependent on their maturational state. A previous study showed that, aside from its inhibitory effect on Tcell stimulatory potential, IL-10 prevents the maturation of human monocyte-derived DCs at an early stage (Morel et al 2002). IL-10 inhibits the differentiation of monocyte-derived DCs, resulting in immature DCs that express low levels of MHC class II and other surface molecules required for T cell activation (Koppelman et al 1997).

In contrast to DCs, monocytes and macrophages do not constitutively express MHC-II. These cells cannot function as APCs until IFNγ-induced activation occurs when MHC-II is produced, and sufficient co-stimulatory molecules are expressed. Like IL-10 affects TLR signalling, IL-10 signalling prevents IFNγ from activating

monocytes, which inhibits the generation of pro-inflammatory cytokines, MHC-II and co-stimulatory molecules, and monocyte APC activity. In addition to blocking the signalling pathways necessary for the activation of APCs, IL-10 can directly influence the molecular processes of antigenic peptide synthesis and MHC-II complex assembly (Mittal & Roche 2015).

Interleukin-10 reduces the expression of MHC class II molecules and co-stimulating molecules. A previous study showed that IL-10 affects the cell surface of MHC class II expression and reduces the accumulation of MHC class II molecules on the plasma membrane of monocytes. Interleukin-10 regulates MHC exocytosis and recycling, which leads to an accumulation of internalised MHC class II complexes in intracellular vesicles (Koppelman et al 1997).

Stimulation through the T-cell receptor (TCR) and a co-stimulatory signal is essential for activating T cells. Several cell surface receptors are activated due to ligands binding to them. The interaction of CD28 with molecules from the B7 family (CD80, CD86) presented by APCs provides the T cells with a significant co-stimulatory signal. Interleukin-10 inhibits the CD28 co-stimulatory pathway, which is associated with a key mechanism of peripheral Tcell tolerance. Interleukin-10 inhibits the T cell response, even when there is sufficient MHC-peptide complex to induce TCR but still in the requirement for co-stimulation. Interleukin-10 increases the threshold for T cell activation due to the interaction of the APCs and CD28 complex, thereby inducing an unresponsive condition of the immune system, i.e., T cell anergy (Akdis & Blaser 2001). T cell anergy is also associated with cytokine dysregulation, Th1 and Th2 cell paradigms, and regulatory T cells (Nath 2016). The differences in cell and antibody responses in leprosy are due to the variations in the subset of T cells and the cytokines released.

Regulatory T cells also play an important role in T cell anergy. Interleukin-10 induces regulatory T cells, such as $FOXP3^{+}$, which have a suppressive function. Previous studies on FOXP3+ regulatory T (Treg) cells demonstrated elevated levels of these cells in LL patients, both in peripheral blood mononuclear cells (PBMC) and skin lesions (Kumar et al 2013). The results of a separate study demonstrated that an increase in CD163 expression was associated with the immunosuppressive effect of inflammation, which is commonly found in LL (Moura et al 2012).

In addition to suppressing antigen presentation and co-stimulating molecules, IL-10 can suppress the production of several inflammatory mediators. High levels of IL-10 are often found in MB leprosy compared to PB leprosy, and a low TNF/IL-10 ratio is associated with the development of leprosy (Cardoso et al 2011). Interleukin-10 can also inhibit the expression of IL2, IL5, TNF, CXCR4, and stromal cell-derived factor 1, disrupting CD4 cell function. In addition to disrupting CD4 function, IL-10 can decrease CD4 cell proliferation by inhibiting the production of several inflammatory cytokines, which leads to the immunological response towards antibody production (Garcia et al 2013).

At the humoral level, IL-10 can recruit and activate B cells and the signalling lymphocyte activation molecule (SLAM) (B cell activator), resulting in high levels of circulating antibodies (Mege et al 2006). Interleukin-10 is also a strong inducer of B-lymphocyte differentiation in vitro, which produces large numbers of antibodies (Llorente et al 1995).

Additionally, IL-10 inhibits the differentiation of monocyte-derived DCs, alters the migration of DCs, and induces apoptosis in plasmacytoid DCs. Interleukin-10 directly affects the function of CD4+ T cells by inhibiting the expression

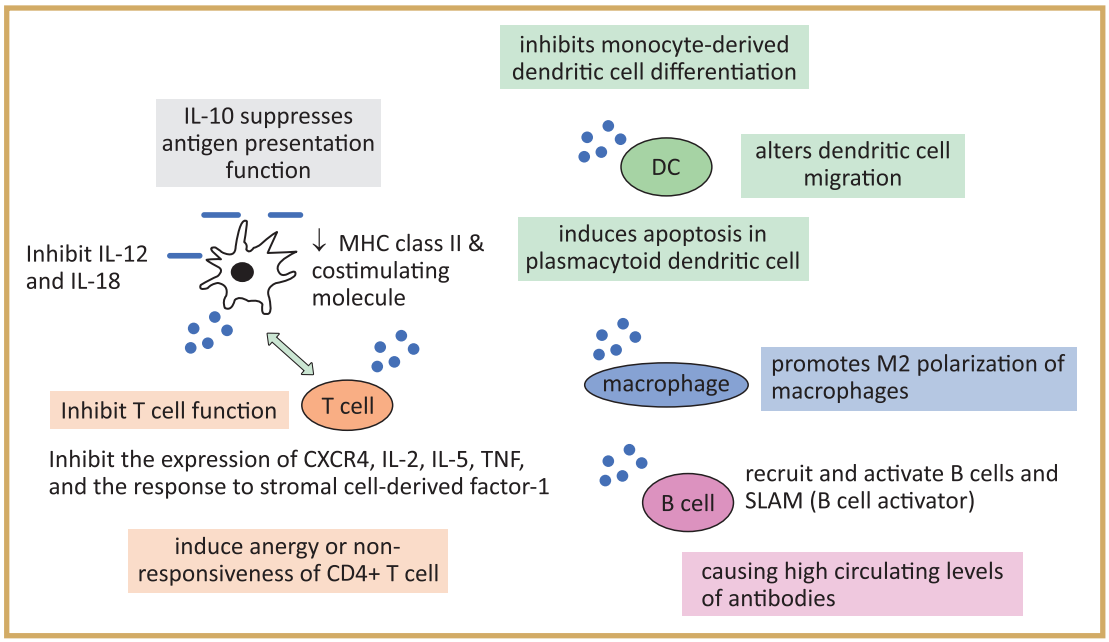

Figure 2 : The Role of IL-10 in the adaptive immune response of leprosy. The recognition of IL-10 by APCs suppresses their antigen presentation function. Interleukin-10 stimulates the production of its own mRNA in a positive feedback loop and is a major regulator of the strong APC-derived inflammatory cytokine IL-12. The major histocompatibility complex and co-stimulatory molecules of APCs are similarly downregulated by IL-10 exposure, which reduces the amount of antigen exposure T cells can receive. Interleukin-10 prevents the ability of naive T cells to differentiate into Th1 cells by limiting the generation of inflammatory cytokines and chemokines that allow APCs to go to the lymph nodes.

of CXCR4, IL-2, IL-5, TNF, and the response to stromal cell-derived factor-1, which can induce non-responsiveness or anergy. In B cells, via the expression of CXCL-13, IL-10 can recruit and activate B cells and the signalling lymphocyte activation molecule (SLAM) (B cell activator), resulting in high levels of circulating antibodies associated with the overproduction of IL-10 in clinical situations.

The Role of Interleukin-10 Gene Polymorphism in Leprosy

A previous hypothesis stated that the main factor that causes leprosy is the source of transmission. This theory is not entirely true because, in certain individuals, exposure to *M leprae* does not result in leprosy. This has aroused interest among several researchers who have begun investigating the role of the immune response in this disease. The immune response is believed to determine an individual's susceptibility to leprosy and the type of leprosy that will manifest. The unique immune response in each individual is the result of the interaction of various cytokine products in the body whose secretion is influenced by inflammation due to infection or stimulation of foreign antigens. The cytokine that is believed

to play an important role in the pathogenesis of leprosy is IL-10 (Li et al 2021).

Interleukin-10 elicits an anti-inflammatory effect by acting on activated macrophages to terminate the response to the microbe and return the system to a resting state after the microbe is destroyed. The upregulation of IL-10 can have an effect on decreasing macrophage activity in killing bacteria. Additionally, IL-10 can decrease the expression of MHC class II molecules and co-stimulation molecules, namely surface molecules that amplify or counteract the initial activating signal after interacting with the antigen/MHC molecules. Interleukin-10 is also involved in many other aspects of leprosy immunopathogenesis (Mege et al 2006).

Polymorphism is a change or mutation at a specific point on a particular nucleotide site, causing differences in DNA sequences that occur in 1% of the population. A polymorphism that occurs at one point does not necessarily cause disease but can be a risk factor for the occurrence of a disease (Trent 2012). The production of IL-10 is regulated by the gene that codes for this cytokine. The IL-10 gene, located on chromosome 1 at 1q31-32, is approximately 4.7 kb in length and contains four introns and five exons. The 5' flanking region is the region of DNA attached to the 5' end of a gene, which contains promoters and may contain enhancers or other protein binding sites. This region mainly functions in the regulation of gene transcription. This region's polymorphisms can trigger transcriptional regulation changes (Trifunovic et al 2015).

Different polymorphisms in the IL-10 gene promoter influence disease prevalence and severity. Furthermore, several studies have shown that genetic factors can explain 50% to 70% of the variability in IL-10 secretion. Polymorphisms in the IL-10 gene promoter have been associated with the susceptibility, resistance, immune response, and clinical manifestations of leprosy (Cardona-Castro et al 2012). Mutations in these genes are believed to cause changes in the expression of the IL-10 gene (Alvarado-Arnez et al 2015). Polymorphisms in the promoter of this gene are believed to cause changes in the amount of IL-10 produced, which can affect the process of microbial elimination in the development of leprosy in individuals (Cardoso et al 2011).

Various studies have been conducted regarding the association of IL-10 gene promoter polymorphisms in leprosy patients in various populations. Research has been conducted on populations in Brazil, India, Colombia, Malawi, Mexico, China, and Indonesia, among others (Santos et al 2002, Félix et al 2012, Tarique et al 2020, Oktariana et al 2021). Several studies have shown that the IL-10 gene promoter polymorphism forms a certain haplotype pattern that is associated with an increased or decreased risk of developing leprosy (Chen et al 2013, Malhotra et al 2005, Cardona-Castro et al 2012, Franceschi et al 2009, Pereira et al 2009, Moraes et al 2004).

There are several genetic variants of the IL-10 gene. However, the most frequently studied variants are the three single nucleotide polymorphisms (SNPs) -1082 (G/A), -819 (C/T), and -592 (C/A), which form the three dominant haplotypes (GCC, ACC, and ATA). The -819 polymorphism is in linkage disequilibrium with the -592 polymorphism; -819C and -592C are inherited together, as are -819T and -592A. In addition to the SNPs, the promoter also contains two dinucleotide repeats (microsatellites), namely IL-10R and IL-10G, located at 1.2 kb and 4 kb upstream from the transcriptional start site. Five IL-10R alleles extending from 12 to 16 repeat CAs and 13 IL-10G alleles extending from 16 to 28 repeating CAs have been described. The IL-10R and IL-10G alleles are not randomly distributed

among the SNPs but combine to form haplotype families. Although endogenous and exogenous factors stimulate the cells to produce IL-10, their secretion is also dependent on IL-10R, IL-10G, and the SNP polymorphisms in the promoter region (Opdal et al 2004).

Conclusion

In the development of leprosy, IL-10 has several effects on the immune response. In the regulation of innate immunity, IL-10 inhibits the production of several inflammatory cytokines and chemokines that are important in the recruitment of T cells, DCs, monocytes, and neutrophils. Interleukin-10 also inhibits the inflammatory response by inhibiting macrophage and anti-microbial activities. In the regulation of adaptive immunity, IL-10 affects APCs and T cells by inhibiting the production of several cytokines. It reduces the expression of MHC class II molecules and co-stimulating molecules.

Additionally, IL-10 alleviates the differentiation of monocyte-derived DCs, alters DC migration by modulating the surface expression of chemokine receptors, and induces apoptosis in plasmacytoid DCs. Interleukin-10 also inhibits the expression of several cytokines and chemokines that can induce anergy or the non-responsiveness of CD4+ T cells. IL-10 can recruit and activate B cells and the SLAM (B cell activator) at the humoral level, resulting in high circulating antibodies.Interleukin-10 plays an essential and highly complex role in modulating innate and adaptive immune responses. Therefore, immunomodulatory therapy targeted IL-10 expression may help develop therapeutic strategies to combat leprosy.

References

1. Abbas AK, Lichtman AH, Pillai S (2019). Basic Immunology: Functions and Disorders of the Immune System, 6th edn, Sae-E-Book, Elsevier, India.
2. Abulafia J, Vignale RA (1999). Leprosy: Pathogenesis updated. *Int J Dermatol.* **38(5):** 321–334.
3. Akdis CA, Blaser K (2001). Mechanisms of interleukin-10-mediated immune suppression. *Immuno.* **103(2):** 131–136.
4. Alvarado-Arnez LE, Amaral EP, Sales-Marques C et al (2015). Association of IL10 polymorphisms and leprosy: A meta-analysis. *PLoS One*. **10(9):** 1–13.
5. Bokhary M, Phung TL (2016). Molecular Pathogenesis of Leprosy. *Curr Tropi Medi Rep.* **3(4):** 127–130.
6. Cardona-Castro N, Sánchez-Jiménez M, Rojas W et al (2012). IL-10 gene promoter polymorphisms and leprosy in a Colombian population sample. *Biomedi*. **32(1):** 71–76.
7. Cardoso CC, Pereira AC, Marques CS et al (2011). Leprosy Susceptibility: Genetic Variations Regulate Innate and Adaptive Immunity, and Disease Outcome. *Fut Microbiol*. **6(5):** 533–549.
8. Chen XH, Xiong JH, Ning Y et al (2013). IL-10 promoter SNPs and susceptibility to leprosy in ethnic groups from southwest China. *Gen Molec Res.* **12(3):** 2876–2885.
9. Commins S, Steinke JW, Borish L (2008). The extended IL-10 superfamily: IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29. *J Alle Clini Immun*. **121(5):** 1108–1111.
10. Couper KN, Blount DG, Riley EM (2008). IL-10: The Master Regulator of Immunity to Infection. *J Immunol.* **180(9):** 5771–5777.
11. de Sousa JR, Sotto MN, Quaresma JAS (2017). Leprosy as a complex infection: Breakdown of the Th1 and Th2 immune paradigm in the immunopathogenesis of the disease. *Fronti Immunol.* **8:** 18–21.
12. Del Prete G, De Carli M, Almerigogna F et al (1993). Human IL-10 is produced by both type 1 helper (Th1) and type 2 helper (Th2) T cell clones and inhibits their antigen-specific proliferation and cytokine production. *J Immunol*. **150(2):** 353–360.
13. Félix JSV, Cázarez-Salazar S, Ríos-Tostado JJ et al (2012). Lack of effects of the TNF-α and

IL-10 gene polymorphisms in Mexican patients with lepromatous leprosy. *Lepr Rev*. **83(1):** 34–39.

14. Fiorentino DF, Zlotnik A, Vieira P et al (1991). IL-10 acts on the antigen-presenting cell to inhibit cytokine production by Th1 cells. *J Immunol.* **146(10):** 3444–3451.
15. Franceschi, DSA, Mazini PS, Rudnick CCC et al (2009). Influence of TNF and IL10 gene polymorphisms in the immunopathogenesis of leprosy in the south of Brazil. *Int J Infect Dis*. **13(4):** 493–498.
16. Garcia P, Alencar D, Pinto P et al (2013). Haplotypes of the IL10 gene as potential protection factors in leprosy patients. *Clini Vacce Immun*. **20(10):** 1599–1603.
17. Goldsmith LA, Katz SI, Gilchrest BA et al (2012). Fitzpatrick's Dermatology in General Medicine, 8th edn, *McGrawHill Medical*. pp. 2421–2429.
18. Goulart LR, Goulart IMB (2009). Leprosy pathogenetic background: A review and lessons from other mycobacterial diseases. *Archi Dermatol Res.* **301(2):** 123–137.
19. Higgins DM, Sanchez-Campillo J, Rosas-Taraco AG et al (2009). Lack of IL-10 alters inflammatory and immune responses during pulmonary *Mycobacterium tuberculosis* infection. *Tubercu*. **89(2):** 149–157.
20. Ip WKE, Hoshi N, Shouval DS et al (2017). Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. *Sci*. **356(6337):** 513–519.
21. Iyer SS, Cheng G (2012). Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. *Criti Rev Immuno*. **32(1):** 23–63.
22. Jonuleit, H., Schmitt, E., Schuler, G., Knop, J., & Enk, A. H. (2000). Induction of interleukin 10-producing, nonproliferating CD4+ T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells. *J Exp Med.* **192(9):** 1213–1222.
23. Koppelman B, Neefjes JJ, De Vries JE, et al (1997). Interleukin-10 down-regulates MHC class II αβ peptide complexes at the plasma membrane of monocytes by affecting arrival and recycling. *Immun.* **7(6):** 861–871.
24. Kube D, Rieth H, Eskdale J et al (2001). Structural characterisation of the distal 5′ flanking region of the human interleukin-10 gene. *Gen Immun.* ***2*****(4):** 181–190.
25. Kühn R, Löhler J, Rennick D et al (1993). Interleukin-10-deficient mice develop chronic enterocolitis. *Cell.* **75(2):** 263–274.
26. Kumar S, Naqvi RA, Ali R et al (2013). CD4+CD25+ T regs with acetylated FoxP3 are associated with immune suppression in human leprosy. *Molecul Immun*. **56(4):** 513–520.
27. Laichalk LL, Danforth JM, Standiford TJ (1996). Interleukin-10 inhibits neutrophil phagocytic and bactericidal activity. *FEMS Immuno Medic Microbi*. **15(4):** 181–187.
28. Lazarus R, Klimecki WT, Palmer LJ et al (2002). Single-nucleotide polymorphisms in the interleukin-10 gene: Differences in frequencies, linkage disequilibrium patterns, and haplotypes in three United States ethnic groups. *Genomi.* **80(2):** 223–228.
29. Li YY, Shakya S, Long H, Shen LF et al (2021). Factors Influencing Leprosy Incidence: A Comprehensive Analysis of Observations in Wenshan of China, Nepal, and Other Global Epidemic Areas. *Fronti Pub Heal.* **9**: 1–11.
30. Lima MCBS, Pereira GMB, Rumjanek FD et al (2000). Immunological cytokine correlates of protective immunity and pathogenesis in leprosy. *Scandi J Immunol*. **51(4):** 419–428.
31. Lis M, Walther D (2016). The orientation of transcription factor binding site motifs in gene promoter regions: Does it matter?. *BMC Genomi*. **17(1):** 1–21.
32. Llorente BL, Zou W, Levy Y et al (1995). Role of Interleukin 10 in The B Lymphocyte Hyperactivity and Autoantibody Production of Human Systemic Erythematosus. *J Exp Med.* **181:** 839-844.
33. Malhotra D, Darvishi K, Sood S et al (2005). IL-10 promoter single nucleotide polymorphisms are significantly associated with resistance to leprosy. *Hum Genet.* **118(2):** 295–300.

34. Mege JL, Meghari S, Honstettre A et al (2006). The two faces of interleukin 10 in human infectious diseases. *Lancet Inf Dis.* **6(9):** 557–569.
35. Mendes ALG, Joaquim HDM, Zamae MIS et al (2020). Expression of nlrp3 inflammasome in leprosy indicates immune evasion of *Mycobacterium leprae*. *Memorias Do Instituto Oswaldo Cruz*. **115(16):** 1–7.
36. Mi Z, Liu H, Zhang F (2020). Advances in the Immunology and Genetics of Leprosy. *Fronti Immunol*. **11:** 1–15.
37. Minshawi F, Lanvermann S, McKenzie E et al (2020). The Generation of an Engineered Interleukin-10 Protein with Improved Stability and Biological Function. *Fronti Immunol*. **11:** 1–18.
38. Mittal, S. K., & Roche, P. A. (2015). Suppression of antigen presentation by IL-10. *Cur Opin Immunol.* **34**: 22–27.
39. Montoya D, Cruz D, Teles RMB et al (2009). Divergence of Macrophage Phagocytic and Antimicrobial Programs in Leprosy. *Cell Host Microbiol.* **6(4):** 343–353.
40. Moore KW, Malefyt RD, Robert L et al (2001). Interleukin -10 and the Interleukin -10 Receptor. *Molecu Cellu Bio*. **1(1):** 683–765.
41. Moraes MO, Pacheco AG, Schonkeren JJM et al (2004). Interleukin-10 promoter single-nucleotide polymorphisms as markers for disease susceptibility and disease severity in leprosy. *Gen Immunol.* **5(7):** 592–595.
42. Morel, A. S., Coulton, G., & Londei, M. (2002). Regulation of major histocompatibility complex class II synthesis by interleukin-10. *Immunol.* **106(2):** 229–236.
43. Mosser DM, Zhang Xi (2013). Interleukin-10: New perspectives of an old cytokine. *Immunol Rev.* **19(3):** 205–18.
44. Moura DF, de Mattos KA, Amadeu TP et al (2012). CD163 favors Mycobacterium leprae survival and persistence by promoting anti-inflammatory pathways in lepromatous macrophages. *European J Immunol*. **42(11):** 2925–2936.
45. Murray PJ, Young RA (1999). Increased antimycobacterial immunity in interleukin-10-deficient mice. *Infect Immunol*. **67(6):** 3087–3095.
46. Nath I (2016). Immunopathogenesis of Leprosy: A Model for T Cell Anergy. *EMJ Dermatol*. **4:** 95–101.
47. O'Farrell A, Liu Y, Moore KW et al (1998). IL-10 inhibits macrophage activation and proliferation by distinct signaling mechanisms. *The EMBO J*. **17(4):** 1006–1018.
48. Oktariana D, Argentina F, Hafy Z et al (2021). Association of −819 T/C IL-10 Gene Promoter Polymorphisms with Susceptibility to Leprosy in South Sumatera Indonesia. *Lepr Rev.* **92(2):** 162–169.
49. Opdal SH (2004). IL-10 gene polymorphisms in infectious disease and SIDS. *FEMS Immuno Medi Microbiol*. **42(1):** 48–52.
50. Ouyang W, O'Garra A (2019). IL-10 Family Cytokines IL-10 and IL-22: from Basic Science to Clinical Translation. *Immunol*. **50(4):** 871–891.
51. Pereira AC, Brito-de-Souza VN, Cardoso CC et al (2009). Genetic, epidemiological and biological analysis of interleukin-10 promoter single-nucleotide polymorphisms suggests a definitive role for -819C/T in leprosy susceptibility. *Gen Immunol.* **10(2):** 174–180.
52. Pestka S, Krause CD, Sarkar D et al (2004). Interleukin-10 and related cytokines and receptors. *Annual Rev Immunol*. **22:** 929–979.
53. Pinheiro RO, Schmitz V, de Andrade Silva BJ et al (2018). Innate immune responses in leprosy. *Fronti Immunol*. **9:** 1–15.
54. Putri WE, Budiamal S, Christopher PM (2021). Leprosy and Immune System : An Insight into the Innate Immune System. *Indian J Lepr*. **93:** 391–403.
55. Reuss E, Fimmers R, Kruger A et al (2002). Differential regulation of interleukin-10 production by genetic and environmental factors - A twin study. *Gen Immunol*. **3(7):** 407–413.
56. Riley JK, Takeda K, Akira S et al (1999). Interleukin-10 receptor signaling through the JAK-STAT pathway. Requirement for two distinct receptor-derived signals for anti-inflammatory action. *J Biologi Chemist*. **274(23):** 16513–16521.
57. Sadhu S, Mitra DK (2018). Emerging concepts of adaptive immunity in leprosy. *Fronti Immunol.* **9**: 1–7.

58. Santos AR, Suffys PN, Vanderborght PR et al (2002). Role of tumor necrosis factor-α and interleukin-10 promoter gene polymorphisms in leprosy. *J Infecti Dis*. **186(11):** 1687–1691.
59. Sari N, Amiruddin MD, Amin S et al (2013). Peran Interleukin-2 (IL-2), Interleukin-10 (IL-10), dan Tumor Necrosis Factor- α (TNF- α) pada penyakit kusta. *MDVI*. **40(1):** 35–40.
60. Sundstedt A, Höiden I, Rosendahl A et al (1997). Immunoregulatory role of IL-10 during superantigen-induced hyporesponsiveness in vivo. *J Immunol.* **158(1):** 180–186.
61. Tarique M, Naz H, Saini C et al (2020). Association of IL-10 Gene Polymorphism With IL-10 Secretion by CD4 and T Regulatory Cells in Human Leprosy. *Fronti Immunol.* **11**: 1–8.
62. Trent RJ (2012). DNA Genetic Testing. Molecular Medicine. Elsevier Inc. pp. 81–115
63. Trifunović J, Miller L, Debeljak Ž et al (2015). Pathologic patterns of interleukin 10 expression–a review. *Bioche Medic*. **25(1):** 36–48.
64. Trivella DBB, Ferreira-Júnior JR, Dumoutier L et al (2010). Structure and function of interleukin-22 and other members of the interleukin-10 family. *Cellu Molec Life Sci.* **67(17):** 2909–2935.
65. Walker SL, Lockwood DNJ (2006). The clinical and immunological features of leprosy. *British Medic Bull.* **77–78(1):** 103–121.
66. Walter MR (2004). Structural analysis of IL-10 and type I interferon family members and their complexes with receptor. *Adv Prote Chemis*. **68:** 171–223.
67. Walter MR (2014). The molecular basis of IL-10 functions: From receptor structure to the onset of signaling. *Curr Topi Microbio Immnol*. **380:** 191–212.
68. Weiss DI, Do TH, de Andrade Silva BJ (2022). Adaptive immune response in leprosy, Chapter 6.2. In Scollard DM, Gillis TP (ed), International textbook of leprosy. www.internationaltextbookofleprosy.org.
69. Yamamura M, Uyemura K, Deans RJ et al (1991). Defining protective responses to pathogens: Cytokine profiles in leprosy lesions. *Sci*. **254:** 277–279.

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