زانکۆی سەلاحەدین - هەولێر
Salahaddin University-Erbil

Interleukin 10 (IL-10)

Research Project

Submitted to the Department of (Biology) in partial fulfillment of the requirements for the degree of **BSc.** in **Biology**

Prepared by:

Abdulla Asrar Sheikh

Supervised by:

Mrs. Lawin A. Omar

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CERTIFICATE

This research project has been written under my supervision and has been submitted for the award of the **BSc**. degree in **Biology** with my approval as a supervisor.

Signature

Name: Mrs. Lawin A. Omar

Date: **8/4/2023**

DEDICATION

This effort I dedicate to **Allah** Almighty, my lord, my powerful foundation, my source of inspiration, wisdom, knowledge, and understanding. Throughout this project, he was the source of my energy.

Abdullah

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To begin with, I thank (**Allah**) for His blessing, which made me able to complete and perform this study with success, the lord of the universe, blessing, and peace be on **Muhammad** (Allah's peace and prayers be upon him).

Finally, I want to say thanks to all those I forgot here to mention his/her name, who assisted me even by one useful scientific word directly or indirectly.

ABSTRACT

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action).Interleukins are a class of cytokines that are secreted by different cells of the immune system and their main function is the regulation of immunity.Interleukin (IL)-10 is a pleiotropic cytokine known for its potent anti-inflammatory and immunosuppressive effects. Originally identified as a product of T helper 2 cells, IL-10 is now known to be produced by various myeloid- and lymphoid-derived immune cells participating in both innate and adaptive immunity,A primary function of IL-10 during infection is to inhibit the host immune response to pathogens and microbiota, thereby mitigating tissue damage and immunopathology,The anti-inflammatory effects of IL-10 are primarily mediated by its interaction with the IL-10 receptor (most highly expressed on monocytes/macrophages), which activates the JAK1-TYK2-STAT3 pathway leading to STAT3-mediated transcription of genes that limit the inflammatory response. The expression of IL-10 appears to be influenced by polymorphisms in its promoter, which may be associated with autoimmune disease. However, the definition of which of the many currently identified promoter polymorphisms are involved in disease pathogenesis.

Key words: Cytokines, IL -10, IL-10 polymorphism and Regulation of IL-10.

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1. Introduction

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). There are both pro-inflammatory cytokines and anti-inflammatory cytokines (Zhang and An, 2007). Interleukins are a class of cytokines that are secreted by different cells of the immune system and their main function is the regulation of immunity (Davids *et al*., 2016). IL-10 was initially named cytokine synthesis inhibitory factor (CSIF)(Howes *et al*., 2014) and is a potent anti-inflammatory cytokine that plays a crucial, and often essential, role in preventing inflammatory and autoimmune pathologies (Iyer and Cheng, 2012).IL-10 is a unique class 2 cytokine because it potently inhibits the production of pro-inflammatory cytokines such as IFNγ, tumor necrosis factor α (TNFα) (Walter, 2014). The involvement of IL-10 in many disease states has been demonstrated, both in animal models and in humans with mutations in the IL-10/IL-10R axis (Saraiva *et al*., 2020) . IL-10 is produced by almost all cell types within the innate (including macrophages, monocytes, dendritic cells (DCs), mast cells, neutrophils, eosinophils and natural killer cells) and adaptive (including CD4+ T cells, CD8+ T cells and B cells) immune systems (Gabryšová *et al*., 2014). Il-10 receptor 1 is specific for Il-10 binding, while Il-10 receptor 2 may be a signal transducing subunit of other representatives of Il-10 cytokine family. The binding of Il-10 to its receptor activates Janus kinase 1 (JAK1) and tyrosine kinase 2 (Tyk2). Both kinases phosphorylate Il-10R1 which subsequently phosphorylates and recruits signal transducer and activator of transcription 3 (STAT3)(Krawiec *et al.*, 2021). The aim of this study is to evaluate the mechanism, biological activity, source of IL -10, and IL-10 gene polymorphisms and their contribution to infections.

1. Literature Review

1.1. Cytokines

Cytokines, in the most general sense, are com- pounds produced by one type of cell that regulates the behavior of the same or other cells. They differ from hormones in that their effects are exerted locally within tissues, in a paracrine or autocrine fashion. They play essential roles in the activation and differentiation of immune cells, as well as proliferation, maturation, migration, and adhesion. They also have pro-inflammatory and anti-inflammatory properties. The primary function of interleukins is, therefore, to modulate growth, differentiation, and activation during inflammatory and immune responses. Interleukins consist of a large group of proteins that can elicit many reactions in cells and tissues by binding to high-affinity receptors in cell surfaces (Vaillant and Qurie, 2021). Cytokines are small proteins that bind to specific cell-surface receptors; as short-lived molecules. They have transient effects. Perhaps the best known sources of cytokines are leukocytes and also produced by monocytes, macrophages and lymphocytes, which explain the frequent description of these molecules as inflammatory mediators. Despite this distinction, cytokines are also produced by many other types of cells, including endothelial cells, fibroblasts and a variety of tissue epithelia (Zhang and An, 2007). Cytokines are molecular messengers of the innate and adaptive immunity that enable cells of the immune system to communicate over short distances in paracrine and autocrine manner (Conlon *et al.,* 2019). Cytokines play an important role in modulation of the immune response. They are produced by immune cells upon stimulation. By binding to specific receptors cytokines can up-regulate activation, proliferation and differentiation of target cells, mediate or regulate immune reactions, inhibit the growth of cells, act cytotoxic, induce or inhibit the production of other cytokines (Trifunović *et al.,* 2015). Immune response to pathogens involves the rapid activation of pro-inflammatory cytokines that serve to initiate host defense against microbial invasion. However, excess inflammation can give rise to systemic metabolic and hemodynamic disturbances harmful to the host. As a result, the immune system has evolved parallel anti-inflammatory mechanisms that serve to curb the production of pro-inflammatory molecules to limit tissue damage and to maintain or restore tissue homeostasis.1,2 Interleukin 10 (IL-10) is a potent anti-inflammatory cytokine that plays a crucial, and often essential, role in preventing inflammatory and autoimmune pathologies (Krawiec *et al.,* 2021).

1.2. Properties and biological activity of IL-10

IL-10 is the most important cytokine with anti-inflammatory properties besides TGF-β and IL-35. Structurally, IL-10 is a helical cytokine and exists in solution predominantly as a homodimer, composed of two polypeptide chains of 160 amino acids, each with a molecular weight of 20,6419 kD (Gonzalez-Garza *et al.,* 2020). It is produced by activated immune cells, in particular monocytes, macrophages and T cells. IL-10 acts through a transmembrane receptor complex, which is composed of IL-10R1 and IL-10R2, and regulates the functions of many different immune cells. IL-10 is considered a potent antiinflammatory cytokine that strongly inhibits the production of proinflammatory cytokines. Recent studies have suggested that IL-10 also has immune stimulatory properties on CD41, CD81 T cells, and/or NK cells, resulting in increased IFN-g production (fig. 1). Lauw et al., 2000 demonstrate that IL-10 stimulates the production of the pro inflammatory cytokine IFN-g during human endotoxemia. IFN-g is mainly produced by CD41 Th1 cells, CD81 T cells, and NK cells. IL-12 and IL-18 positively regulate IFN-g production (Lauw *et al.,* 2000). In monocytes/macrophages, IL-10 diminishes the production of inflammatory mediators and inhibits antigen presentation, although it enhances their uptake of antigens. Additionally, IL-10 plays an important role in the biology of B cells and T cells. The special physiological relevance of this cytokine lies in the prevention and limitation of over-whelming specific and unspecific immune reactions and, in consequence, of tissue damage. At the same time, IL-10 strengthens the "scavenger"-function and contributes to induced tolerance (Sabat *et al.,* 2010).

The dominant functions of IL-10 on target cells are:

1. Suppressive Effects of IL-10 on Macrophages, Dendritic Cells, and $CD4^+$ Helper T cells

Macrophages and dendritic cells become activated at the onset of infection. These cells mediate the initial inflammatory response and activate T and B cells (Howes *et al.,* 2014). Hence, macrophages and dendritic cells promote the immune response at several stages. IL-10 has strong suppressive activity on macrophages and dendritic cells. It can inhibit their cytokine (TNF, IL-12, etc.) and chemokine production, their maturation and migration to lymphoid organs, and their ability to present antigen to T cells. It can also inhibit the killing of an intracellular pathogen by macrophages. It is in this way that IL-10 can ‘shut down’ the immune response by dampening macrophage and dendritic cell activity directly (Moore *et al.,* 2001).

2. Stimulatory Effects of IL-10 on B Cells and $CD8^+$ Killer T cells

IL-10 can stimulate proliferation, survival, and antibody production from B cells. IL-10 can also promote the proliferation and cytotoxic activity of $CD8^+$ killer T cells (Moore *et al.*, 2001). The stimulatory effects of IL-10 on the overall immune response are less clear; however, they may be important in the settings of cancer, mucosal immunity, and antiviral immune responses (Mocellin *et al.*, 2005).

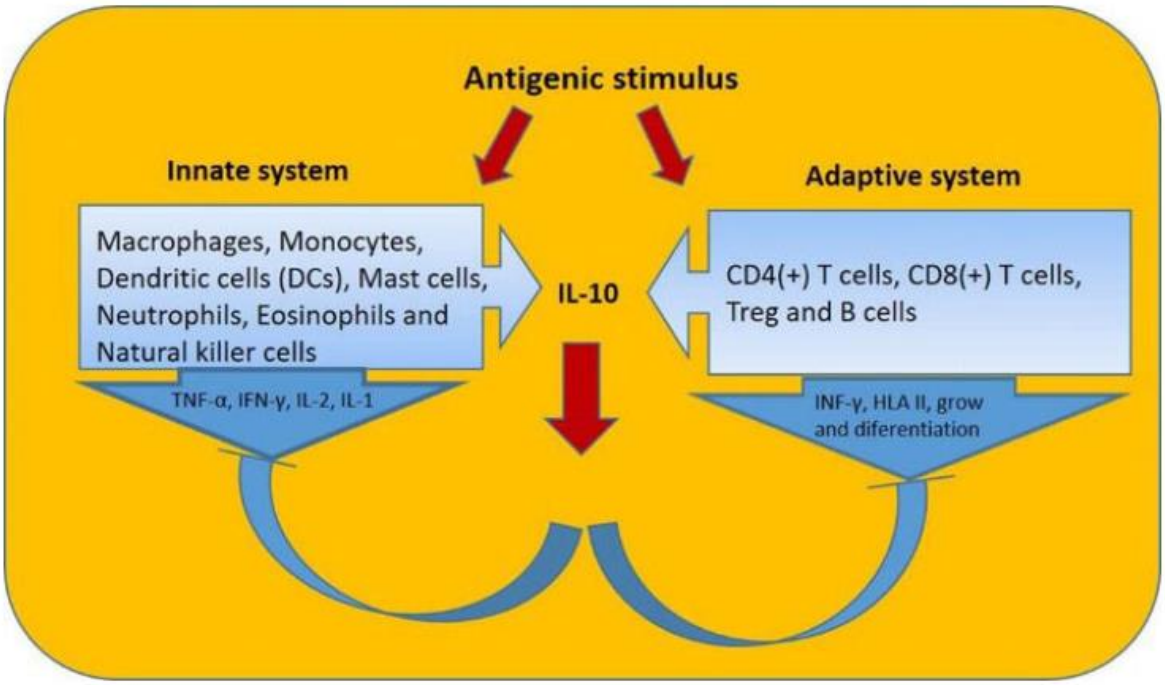

Figure (1): After antigenic stimulus on cells from innate and adaptive system, the IL-10 is expressed from these cells. To avoid severe danger from pro-inflammatory cytokines and reactive radicals, IL-10 acts as anti-inflammatory cytokine by blocking its expression (Gonzalez-Garza *et al.*, 2020).

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2.3. Cellular Sources of IL-10

IL-10 was initially described as a T helper 2 derived cytokine, however, it was widely accepted that IL-10 is not restricted to certain T cell subsets but instead of produced in almost all leukocytes (Ouyang *et al.*, 2011). IL-10 is produced by most cells of the innate and adaptive immune response. Of the innate cells, macrophages, dendritic cells, mast cells, neutrophils, eosinophils, and natural killer cells are all sources of IL-10. Of the adaptive cell types, B cells,

CD4þ helper T cells (Th1, Th2, and Th17), and CD8þ killer T cells can produce IL-10. Treg cells can also be a source of IL-10, and indeed mediate some of their regulatory activity through IL-10. Hence, the production of IL-10 appears to be a widely used feedback regulatory mechanism by immune cells to regulate themselves or cells surrounding them (Saraiva and O'Garra, 2010). Antigen-presenting cells (APCs) are an important source of IL-10 that serves to provide autocrine feedback to limit or resolve pro-inflammatory molecule production, restrict antigen presentation itself, enhance scavenger and phagocytic capabilities, and influence the development of adaptive responses (Mosser and Zhang, 2008). Stimulation of B cells with autoantigens, TLR4, TLR9 ligands, or vitamin D3 can also lead to Il-10 production (Heine, 2008). Recently, studies of a B-cell Il-10-deficient reporter mouse indicated a role for B-cell-derived IL-10 in limiting virus-specific CD8+ T-cell responses (Madan *et al.,* 2009). Additionally, non-immune effector types such as epithelial cells and keratinocytes are also capable of producing IL-10 in response to infection or tissue damage as well as tumor cells (Jung et al., 2004). Gonzalez-Garza *et al.,* (2020) demonstrated that High concentrations of IL-10 in the serum of cancer patients seem to correspond not only to the expression of this protein by immune cells, they shows that the cancer cell is capable of synthesizing it, which would cause an imbalance in the homeostasis of the immune system.

2.4. Regulation of IL-10

To produce IL-10, cells require activation by an external stimulus. In the case of macrophages and dendritic cells, this stimulus can be a pathogen encountered in the tissues. In other immune cell types, the triggers for IL-10 production are incompletely understood. On external stimulation, signaling pathways within the cell are initiated, which transmit a message to the nucleus inside the cell (fig.2). After transcription and translation the protein can then carry out its specialized function within the cell, or be released from the cell as is the case with cytokines (Saraiva and O'Garra, 2010). An additional layer of complexity is added by the fact that the presence of other cytokines in the cellular environment can affect the level of IL-10 production. An important example of this is the Th1 cytokine IFN-g, which can inhibit IL-10 production from macrophages and dendritic cells. It follows that IL-10 production is submitted to a fine regulation by a number of signal molecules, including glutamate, prostaglandin E2, mycoepoxydiene; all these compounds are able to enhance IL-10 release by microglia cells via

TLR-4 activation (Porro *et al.,* 2020). Several transcription factors, including Blimp-1, c-Maf, and GATA3, serve as potential regulators of IL-10 expression. Blimp-1 mice have been shown to develop a lethal multiorgan inflammatory disease caused by an accumulation of effector and memory T cells .Inactivation of c-MAF in the Treg cells has been found to result in dysfunction of IL-10 production and such mice were prone to spontaneous colitis. The transcription factor GATA3 has been described as a master regulator of IL-10 expression (Wei *et al.,* 2020).

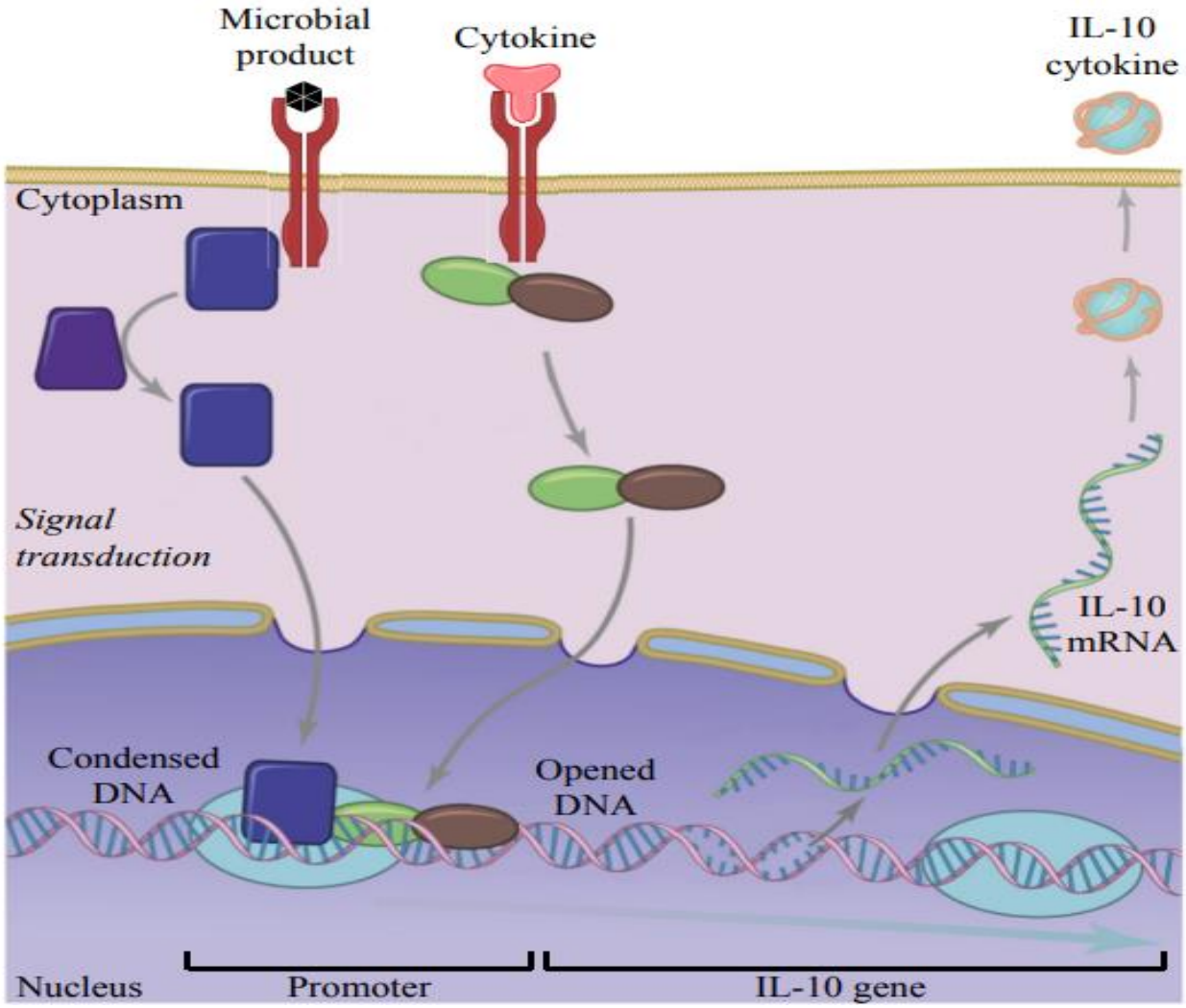

Figure (2): The regulation of IL-10 production in macrophages and dendritic cell. The detection of microbial products induces signaling cascades which ultimately lead to the binding of transcription factors to the il10 gene. Binding at the promoter of the gene or at enhancer sites induces the transcription of the il10 gene to produce il10 mRNA. Il10 mRNA is transcribed to make the IL-10 protein, which is released from the cell. The presence of other cytokines in the environment can also induce signals that modulate the level of IL-10 production (Howes *et al.,* 2014).

2.5. IL-10 and alpha-2-Macroglobulin (α2M)

Interleukin-10 has many functional partners including alpha-2-macroglobulin (α2M), with which it can form a complex. Alpha-2-macroglobulin, a large homotetrameric glycoprotein found in plasma and extracellular spaces, acts a protease inhibitor and can non-covalently bind and transport cytokines, including IL-10. The formation of these complexes increases the concentrations of these cytokines in the blood. Native α2M increases the half-life of bound cytokines in the plasma by protecting them from proteolysis and facilitates their recruitment to inflammation sites, where they induce anti-inflammatory responses. Disruption of these complexes promotes inflammation and favors cancer development (Sheikhpour *et al.,* 2018).

2.6. IL-10 receptor and signaling pathway

IL-10 signaling occurs via a receptor consisting of two distinct polypeptide chains, subunits IL-10Rα (IL-10R1) and IL-10Rβ (IL-10R2). Accordingly, IL-10 initially binds to the extra-cytoplasmic domain (ECD) of IL-10R1 with high affinity, followed by low affinity interactions with the IL-10R2 subunit by both IL-10 and IL-10R1. IL-10R1 represents the ligand binding subunit of the receptor complex, whereas IL10R2 is the signaling subunit (Fig. 2) (Schönrich *et al.,* 2022). Next, JAK1 and TYK2 respectively interact with IL-10R1 and IL-10R2, become phosphorylated and mainly activate STAT3, leading to the implementation of gene transcription programs and consequent cellular responses (Santos *et al.,* 2021). The binding of Il-10 to its receptor activates Janus kinase 1 (JAK1) and tyrosine kinase 2 (Tyk2). Both kinases phosphorylate Il-10R1 which subsequently phosphorylates and recruits signal transducer and activator of transcription 3 (STAT3) (Krawiec *et al.,* 2021). These kinases further phosphorylate two functional tyrosine residues on the intracellular domain of the IL-10Rα, needed for the recruitment of STAT3. Activation of STAT3 by its phosphorylation allows its translocation to the nucleus, with the initiation of a specific transcriptional program that largely defines the IL-10–mediated anti-inflammatory response (fig. 3) (Saraiva *et al.,* 2019). IL-10 also affects the nuclear factor kappa B (NFκB) transcription factor pathway, a key signaling pathway with an established role in the mediation of inflammation and a response to tissue damage and/or infection. NFκB activation is also essential for maintenance of intestinal barrier integrity, through regulation of cellular proliferation, differentiation, and survival, and the mediation of

signaling and interaction between the mucosal immune system and the resident gut micro biota (Papoutsopoulou *et al.*, 2022).

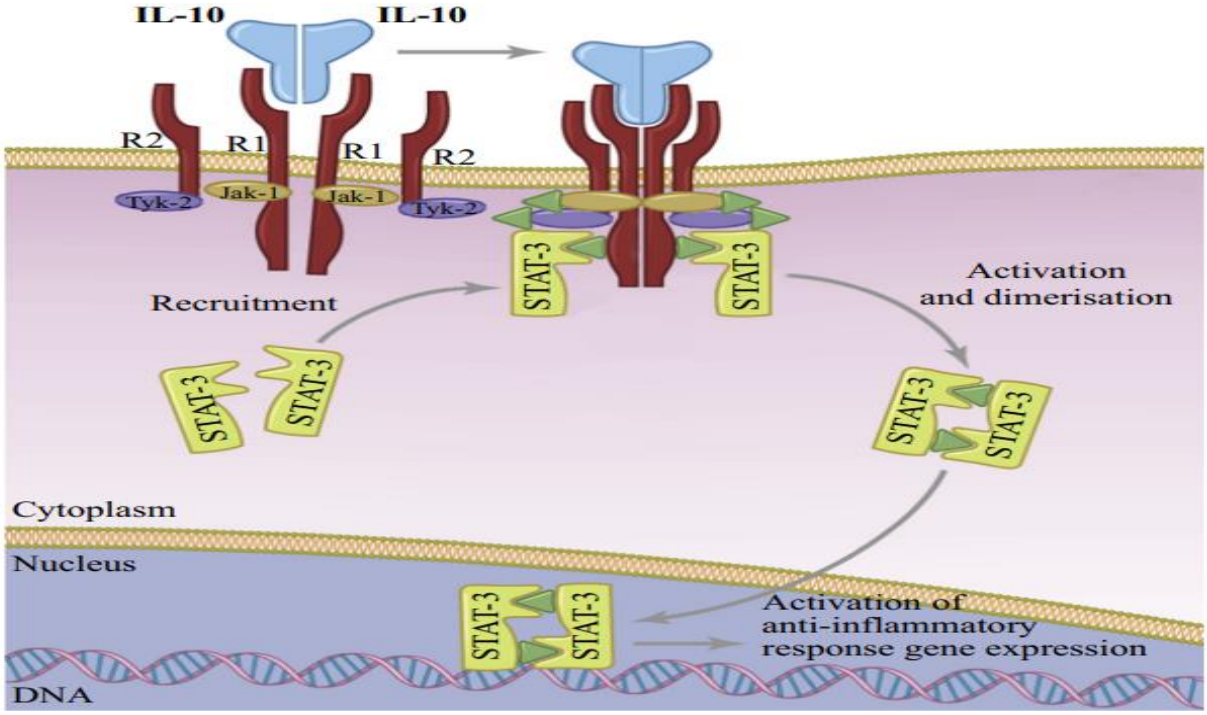

Figure (3): IL-10-induced signaling pathways. IL-10 binds the IL-10 receptor which is composed of IL-10R1 and IL-10R2 chains. The associated kinases, Jak1 and Tyk2, become activated and phosphorylate (green triangle) the IL-10R1 chain. STAT3 docks at the receptor and becomes activated by phosphorylation. Active STAT3 molecules dimerize and travel to the nucleus where they bind at specific genes to promote their transcription (Howes *et al.*, 2014).

2.7. IL-10 Gene Polymorphisms and Their Contribution to Infection

The expression of IL-10 appears to be influenced by polymorphisms in its promoter, which may be associated with autoimmune disease. However, the definition of which of the many currently identified promoter polymorphisms are involved in disease pathogenesis, and whether new, as yet unidentified polymorphisms might also play a role in IL-10 dysregulation, is still a subject of continued investigation (Gibson *et al.*, 2013). The gene encoded IL-10 is located on chromosome 1q31-q32. Polymorphisms in the promoter region of the IL-10 gene can affect the expression of IL-10 cytokine which leads to changes in inflammatory processes (Wiryani *et al.*, 2021). There are some single nucleotides polymorphisms (SNPs) have been identified in the IL10 promoter, containing five exons separated by four introns. Polymorphisms located in the 5′-

flanking region of the IL10 gene (Branga *et al.,* 2021). Three functional IL10 SNPs have been characterized; these are an adenine (A) to guanine (G) substitution at nucleotide -1082 (rs1800896), a thymine (T) to cytosine (C) substitution at nucleotide -819 (rs1800871), and an A to C substitution at nucleotide -592 (rs1800872). These polymorphisms led to different IL10 expression levels and determined inter-individual differences in IL-10 (Sheikhpour *et al.,* 2018). The evidence shows that alterations in the serum levels of IL-10 in cancer patients, the participation of the cancerous tumor in the synthesis of this cytokine, and its possible relationship with polymorphisms in the gene promoter, the gene of this protein (Gonzalez-Garza *et al.,* 2020). Much effort has gone into understanding which polymorphisms can predispose an individual to develop a condition, or make a person particularly susceptible to an infection. Polymorphisms have been identified in and near to the human IL-10 gene and some studies have linked these to disease susceptibility. Such as, certain variants of the IL-10 gene have been associated with enhanced susceptibility to Crohn's disease and ulcerative colitis. Polymorphisms in the IL-10 gene that resulted in low IL-10 production were associated with severe asthma (Maloy and Powrie, 2011). In viral infections, IL10-1082 promoter polymorphism has been associated with susceptibility to chronic hepatitis C infection and resistance to antiviral therapy (50). Another publication suggests that high IL-10 secretion indicated by the –1082 polymorphism or the promoter haplotype defined by single nucleotide polymorphisms at positions –1082, –819, and –592 protects against Epstein–Barr virus infection (Vidigal *et al.,* 2002).

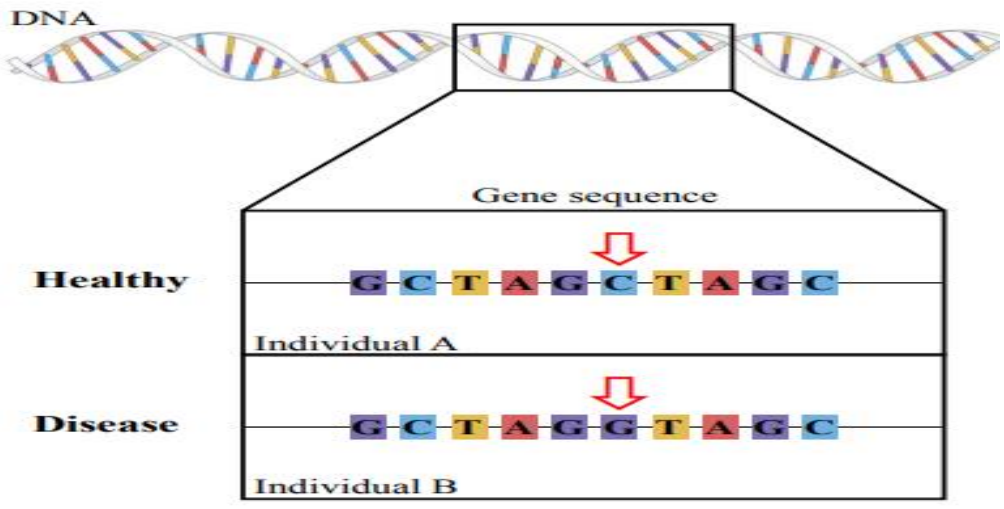

Figure (4): The principle of genetic polymorphism.

2.8. Role of IL-10 in Immune Responses

L-10 has an assortment of functions acting at the vascular and endothelial level, such as modulating vascular remodeling, reducing leukocyte adhesion and extravasation, mitigating leukocyte–endothelial interactions that facilitate coagulation, promoting vasodilatation via increased production of nitric oxide, and direct protection of the endothelium from oxidative stress via the down regulation of harmful reactive oxygen species (ROS)-producing enzymes, and/or the up regulation of antioxidant pathways (Garcia *et al.,* 2017). Given the connection between inflammation and fibro genesis, IL-10 has been a focus of potential ant fibrotic therapies because of its well-known role as an anti-inflammatory mediator. Despite the apparent dissimilarity of diseases associated with fibrotic progression, pathways involving IL-10 appear to be a conserved molecular theme. More recently, many groups have worked to develop novel delivery tools for recombinant IL-10, such as hydrogels, and cell-based therapies, such as in vitro activated macrophages, to directly or indirectly modulate IL-10 signaling (Steen *et al.*, 2020). IL-10 production also induces extensive changes in gene expression and cytokine release, which also lead to endotoxin tolerance and deviations in cellular function, maintenance, growth, and proliferation, as well as coagulation and fibrinolysis, cell–cell signaling or interaction, and cellular movement (Bakiri and Mingomataj, 2019). IL-10 can also dampen the harmful immune responses elicited in autoimmunity and allergy.

2.9. The Functions of IL-10 in Microbial Host Defense

Although IL-10 target vastly diverse cell types and induce different downstream biological effects, a common function for this cytokine during infection is to reduce damage and protect tissue integrity. IL-10 represses the inflammatory responses and minimizes tissue damage caused by excess inflammation. As extensively reported, IL-10 plays a major role in protecting the host from collateral damage; however, in certain viral, fungal, protozoan, and helminth, or bacterial infections, IL-10 may alternately impede pathogen clearance and contribute to chronic disease (Redford *et al.,* 2011). Of note, recent findings in both bacterial and viral infections have demonstrated that type I IFNs may promote chronic infections, in part by the induction of IL-10 (Howes *et al.,* 2014). Because inflammatory molecules can often be potent activators of cell death, increasing levels of IL-10 can moderate the extent of apoptosis that is induced in response to infection. For instance, in a *Chlamydia pneumonia* model, where bacterial clearance is

enhanced in the absence of IL-10, mice also develop severe inflammation and experience elevated levels of apoptosis. Notably, blocking the action of the CD8+ T cell–derived IL-10 results in enhanced pulmonary inflammation and lethal injury (Sun *et al.,* 2011). Increasing evidence indicates that IL-10 plays an important role in both the onset and development of auto-immune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SS), multiple sclerosis (MS), Crohn's disease (CD), and psoriasis (Wei *et al.,* 2020). However, the exact mechanisms of IL-10 in auto-immune diseases remain unclear (Tian et al., 2014). Mutations in the IL-10 or IL10R genes have also been associated with severe colitis in early childhood (Liu *et al.,* 2022). IL-10 appears to have considerable importance in the development of human cancer and its immune escape. These have suggested that it could serve as a biomarker for prognostic diseases or as a target for treatment. Two factors should be considered: high levels of this cytokine in the system, and genetic polymorphisms. Considering their possible role in the development and establishment of malignant cells, the first studies conducted to detect serum IL-10 levels in cancer patients, reported a higher concentration than in healthy subjects (Gonzalez-Garza *et al.,* 2020).

3. CONCLUSION

In conclusion, IL-10 is produced by various cell types, has multiple functions, and plays a critical role in regulating homeostasis at a global level. L-10 is an anti-inflammatory cytokine that maintains the balance of the immune response, allowing the clearance of infection while minimizing damage to the host and during infection it inhibits the activity of Th1 cells, NK cells, and macrophages, all of which are required for optimal pathogen clearance but also contribute to tissue damage. In consequence, IL-10 can both impede pathogen clearance and ameliorate immunopathology. Consequently, dysregulation of IL-10 can lead to more severe forms of immunopathology or development of autoimmune disease through enhanced or sustained inflammatory response.

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