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# Human Interleukin 2 (IL-2) Promotion of Immune Regulation and Clinical Outcomes: A Review

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**Abstract**

Interleukin 2 (IL-2) is a monomeric glycoprotein that is primarily produced by activated CD4+ T cells, CD8+ T cells and dendritic cells. It is characterized as a proinflammatory cytokine that is secreted by Th1 cells. IL-2 plays a central role in the activation of regulatory T cells to produce the cytokines tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ). IL-2 may also enhance the cytolytic activity of natural killer cells, thereby ensuring their significance in the control of the immune response, and effectively participate in the pathogenesis of several pathological conditions, such as cancer and metabolic, infectious, autoimmune and inflammatory diseases. We emphasize the importance of studies of IL-2 and discuss perspectives resulting from our increasing understanding of genetic diversity and its role in the immune response.

**Keywords:** IL-2; Immune response; Polymorphism; Parasitic infectious diseases

## Interleukin 2 and the Immune Response

Cytokines are produced by various immune system cells and perform several functions, including mediation of the immune and inflammatory responses. The effects of cytokines on the immune response depend on a number of factors, such as their local concentrations, receptor expression patterns and the integration of multiple signalling pathways in response to immune cells [1]. The immune system includes proinflammatory cytokines that can enhance the functions of other cytokines and the immune response and anti-inflammatory cytokines that suppress this response; various interleukins (ILs) stand out in these responses [2]. ILs are small protein molecules that signal specific cells to regulate the immune systems of organisms. They are primarily synthetized by T cells, monocytes, macrophages and endothelial cells. The functions of ILs include the facilitation of communication among immune system cells, regulation of transcription factors, and control of inflammation, cell differentiation, proliferation and antibody secretion [3]. The characterization of interleukin 2 (IL-2) as a T-cell growth factor was consolidated in 1975 at the Second International Lymphokine Workshop. The number of studies on this molecule increased quickly; by 1983, the IL-2 gene was cloned, and in 1992, the IL-2 crystal structure was described [1]. Analysis of the three-dimensional structure of the IL-2 molecule shows that it is composed of four "packed" α-helices. The first and fourth helices are connected by a long upper loop to form a typical structure known as "up-up-down-down". Within this configuration, the first two α-helices are turned upward, and the last two helices are turned downward. Importantly, the disulphide bond between the cysteines at positions 58 and 105 (Cys 58-105) of the second helix and the inter-helix region of the third and fourth α-helices are necessary to ensure the stability of the protein [3]. IL-2 is a monomeric glycoprotein with a molecular weight of approximately 15 kDa that is primarily produced by activated CD4+ T cells, CD8+ T cells and dendritic cells [4]. IL-2 is a proinflammatory cytokine that is secreted by Th-1 cells, and it effectively participates in the activation of T cells to produce the cytokines tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ); IL-2 can also enhance the 3 cytolytic activity of natural killer cells (NK) [5,6]. Therefore, IL-2 is used therapeutically to stimulate the immune system [7]. IL-2 also contributes to the development of regulatory T cells, which control the expansion and apoptosis of activated T cells [5,8]. Furthermore, IL-2 influences cell survival, differentiation [1] and the formation of immune memory cells [1,9] and acts as a negative regulator of immune activation [8]. Recent studies showed that IL-2 played a critical role in the differentiation and survival of regulatory T cells, thereby ensuring their significance in the control of the immune response [10]. Cytokines effectively participate in the pathogenesis of several pathological conditions, such as cancer and metabolic, infectious, autoimmune and inflammatory diseases [11,12]. Thus, IL-2 plays multiple roles in immune functions by contributing to the generation and propagation of antigen-specific immune responses [13]. Studies conducted with animals and humans showed that low doses of IL-2 induced expansion of regulatory T cells in vivo and suppressed autoimmune diseases; this phenomenon is representative of a novel therapeutic approach to modulate the immune response for the treatment of these types of illnesses [14]. Anti-humoral therapy associated with IL-2 administration led to the remission of metastatic

renal cell carcinoma in up to 30% of patients and increased the survival of patients with melanoma and acute myeloid leukemia [15]. In these situations, the administration of high doses of IL-2 was associated with improved survival, although the related adverse effects were considerably severe in most patients [16]. Cases of cellular and humoral immunodeficiency exhibited satisfactory outcomes following IL-2 administration [17].

## Genetic Variability of Il-2 and the Physiopathogenesis of Parasitic Infections and Autoimmune Diseases and Cancer

Individual genetic variability is an essential component of the immune response in general. This fact has become increasingly evident in recent years because genetic variability contributes to the susceptibility to, progression and outcomes of infectious and autoimmune diseases and cancer. While attempting to map its role in multifactorial and polygenic diseases, several studies revealed the true extension of human genetic variation [18]. Cytokines and their receptors emerged as intriguing targets of therapeutic intervention. Cytokine receptor subunit expression differs among various cell types. These subunits may be shared by different cytokines, which increases the complexity of these molecules [19]. The IL-2 receptor (IL-2R) is comprised of three subunits (α, β and γ) [20]. The The gene that encodes subunit α is located on chromosome 10; this subunit (also known as CD25 or Tac antigen) is the subunit to which IL-2 selectively binds. The main function of the IL-2R α chain is to mediate the receptor's affinity for its ligand. Different from the other two IL-2R subunits, subunit α is located in special regions of the plasma membrane [21]. Subunit α simply requires IL-2 binding to help subunits β and γ come closer and consequently, trigger the signaling cascade. The gene that encodes subunit β (p75 or CD122) is located on chromosome 22. The β and γ chains together constitute an intermediate affinity receptor that is sufficient to trigger the IL-2 signaling pathways. Subunits β and γ are located in regions close to subunit α, which is the subunit that selectively binds IL-2. The gene that encodes the γc chain of the IL-2R (common γ or p64) is located on chromosome X. Several cytokines share IL-2Rγ, such as IL-4, IL-7, IL-9, IL-15 and IL-21 [1]. When IL-2 receptor alpha (IL-2Ra) is activated, its soluble form is released into the serum. Thus, IL-2Ra protein concentration can be measured. In patients with colorectal and breast cancer, high serum IL-2Ra concentrations are indicative of disease progression and distant metastasis [22]. According to studies that analyzed genes encoding cytokines, several polymorphisms in the regulatory regions of these genes might be responsible for the changes in the production of the corresponding cytokines [23]. Several studies noted the importance of single-nucleotide polymorphisms (SNPs) in the occurrence of infectious and autoimmune diseases [24], the transplantation course [25] and the allele frequencies of populations [26]. The association of SNPs with human diseases has great potential for clinical applications because it provides new genetic markers for diagnosis and prognosis and possibly new therapeutic targets.

The IL-2 gene (3558) is located in chromosome 4, region q26-q27. It contains four exons separated by three introns, with a total extension of approximately 5 kb [27]. Several IL-2 gene polymorphisms are known, including those at positions -330 T/G and +114 T/G. Polymorphism -330 T/G (rs2069762) is located in the gene promoter region and is associated with increased susceptibility to inflammatory diseases and cancer, including rheumatoid arthritis and myeloid leukemia [28-30]. Additionally, studies show that changes in the serum IL-2 levels were found when this polymorphism was analyzed [29-31]. This finding was confirmed because the presence of allele G in gene position -330 was correlated with reduced IL-2 production *in vivo* [32]. Studies showed that the T lymphocytes of patients with SNP -330 G/G were able to produce larger amounts of IL-2 than the lymphocytes from patients with SNP -330 T/G or T/T, which suggests that the presence of -330T/G (rs2069762) in the aforementioned promoter region may influence IL-2 production in healthy individuals [33]. Studies on prostate cancer also found an association between genetic variants within IL-2 and the risk for this type of cancer, revealing a significant contribution of the IL-2 exon 1 variant rs2069763 G/T to disease susceptibility [34].

Several studies noted the possible association of asthma with genes that encoded components of the immune response, including cytokine genes, due to their roles in the pathophysiology of the disease [35]. One study investigated the association of the IL-2 gene polymorphism +114 T/G (rs2069763) and its genetic variants with asthma; however, no significant positive correlation was found [36]. IL2 +166 G/T is another polymorphism of the IL-2 gene that encodes a silent mutation that does not affect the amino acid sequence [37].

Studies on leishmaniasis showed that the presence of variants in the IL-2Rβ gene predisposed individuals infected with *Leishmania donovani* to the development of visceral leishmaniasis (VL), which indicated that the IL-2 signaling pathway participated in the occurrence of leishmaniasis [38]. Additionally, susceptibility to VL (caused by *L. donovani*) in Sudan (Aringa ethnic group) was controlled by locus 22q12 [39]. Another study showed that mutations in the IL-2Rβ gene located in locus 22q12 might be at least partially responsible for the genetic linkage with VL [38], thus demonstrating the importance of this IL-2 signaling pathway.

The immune response to malaria involves innate and adaptive mechanisms, including the participation of several cell types and soluble components that lead to the elimination of the etiologic agent or to immunopathology [40-42]. *Plasmodium vivax* elicits a specific immune response in the host that is mediated by humoral (Th2 lymphocytes) and cellular (Th1 lymphocytes) mechanisms. The humoral mechanisms are characterized by the involvement of antibodies that confer protection through the opsonization of merozoites, thereby blocking the invasion of erythrocytes. This response is characterized by the participation of T lymphocytes, which, after recognizing agents processed by antigen-processing cells (APCs), release interleukins that regulate macrophages, dendritic cells and even B lymphocytes to activate the immune response against the etiological agent.

B lymphocytes are activated by released IL-2, IL-4 and IL-5, which determine the type of antibodies that will be produced, as well as the immunoglobulin isotype switch. Regarding the cell-mediated response, ILs released by T lymphocytes increase the phagocytic activity of macrophages, neutrophils, dendritic cells, monocytes and NK lymphocytes to combat infections [40,42-44].

T lymphocytes are activated when the T-cell receptor (TCR) and CD4 or CD8 co-receptors recognize the major histocompatibility complex (MHC) expressed on APCs and bind to peptide antigens processed by lysosomal or proteasomal mechanisms [40,45]. However, binding alone does not suffice to trigger clonal expansion, which needs a second co-stimulatory signal provided by the APCs themselves through glycoproteins known as B7.1 (or CD80) and B7.2 (or CD86).

These glycoproteins bind to the corresponding receptor on T cells (the CD28 molecule) [45].

Several studies revealed an association between polymorphisms of human genes involved in the invasion of erythrocytes by parasites and the susceptibility to vivax malaria. Additionally, the variability in genes that encode molecules involved in the immune response is associated with changes in the pattern of parasitemia, clinical aspects and susceptibility to disease [18,46].

Concerning *P. vivax* erythrocyte invasion receptors and ligands, individuals heterozygous for the Duffy blood group antigens (FyA/FyB) were found to be more susceptible to malaria in Brazil [47]. However, Duffy-negative individuals may become infected with *P. vivax* via other receptors involved in erythrocyte recognition [47,48].

The role of the human leukocyte antigen (HLA) system in the immune response to Plasmodium antigens has been widely investigated. Allelic differences in these genes exhibited contradictory results among the various investigated endemic areas, including Brazil; therefore, it seems unlikely that they are the only mechanism responsible for deviations of the immune response [49-51].

The current knowledge about the genes involved in the immune response and the implications of their variability for the causes of disease has been greatly advanced by data from human genome sequencing. In addition to the genes and alleles involved in the pathogenesis of several diseases, association studies have allowed the frequencies of these alleles to be determined in these populations. Because genetic polymorphisms vary among different population groups, the heterogeneity of the Brazilian populations will contribute relevant information to the understanding of the causes of complex diseases, such as malaria. These studies also contribute knowledge on the evolution a functional implications of genetic polymorphisms.

## Concluding Remarks

The development of the immune response depends on a cellular and molecular complex that is essential for the protection of humans against infectious agents, autoimmune diseases and tumors. For the immune response to adequately occur, a balance is needed in the ability of the cells to respond to infectious agents and to suppress autoimmunity [52]. Thus, polymorphisms associated with modulation of the expression of genes that encode immune response co-stimulatory molecules might influence the occurrence of various diseases; indeed, several recent studies demonstrated this association [53].

Variability in genes that encode molecules involved in the immune response is associated with changes in the pattern of parasitemia, clinical aspects and susceptibility to disease. The current knowledge about the genes involved in the immune response and the implications of their variability for the cause of disease has been greatly advanced by data resulting from human genome sequencing. IL-2 is a cytokine that contributes to the differentiation and survival of regulatory T cells, thereby ensuring their significance in the control of the immune response and their effective participation in the pathogenesis of several pathological conditions, such as cancer and metabolic, infectious, autoimmune and inflammatory diseases [11,12]. Therefore, IL-2 plays multiple roles in immune functions by contributing to the generation and propagation of antigen-specific immune responses [13]. Although the relevant role of this molecule in the immune response is known, more studies on its function are needed, especially concerning parasitic infectious diseases.

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