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# Interleukin 6 is a two-edged sword: A centerpiece in the immune response against the SARS-CoV-2

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## Abstract

Both Innate and adaptive immune systems are essential for an individual's survival as they offer protection from invading pathogens. The Innate immune responses, by their non-specificity, protect from newly infecting viral strains, thereby maintaining body homeostasis by playing a significant role in inflammation and acute-phase protein production. IL-6 has a pleiotropic effect on inflammation, immune responses, and hematopoiesis and increases the production of acute-phase proteins upon inflammation that is responsible for the recruitment of neutrophils and macrophages at the site of inflammation. It further controls the T cell responses and activates the innate immune system's cells to counteract infections. However, whether IL-6 is pathogenic or protective is still a matter of debate. Various proteins like nuclear factor kappa beta, activator protein 1, and nuclear factor IL-6 increase the production of IL-6, whereas Regnase-1 and Roquin result in destabilization of the IL-6 mRNA, thereby decreasing the production of IL-6. IL-6 itself controls the production of interferon regulatory protein 1 and acute-phase proteins during inflammation. There is evidence to support the protective role of IL-6 in the genesis of immune responses during viral infections. However, more studies are required to delineate the exact role of IL-6 in innate immune responses to draw concrete conclusions.

## Introduction

Humans are exposed to millions of pathogens every day through contact, inhalation, or ingestion. An individual's ability to stay healthy and escape from infection depends upon the immune responses mounted against the offending agents. The Adaptive immune system, by virtue of its memory, recognizes specific pathogens and neutralizes them upon subsequent exposure. Initially, these responses are slow to develop as specific clones of B cells, and T cells need to be activated, which further proliferate and expand in number. Hence, there can be a considerable delay for the adaptive immune responses to come into effect [1]. Therefore, during the early stages of infection, the innate immune system acts as a barrier to protect us from viral and bacterial contamination. In contrast to the adaptive immune system, innate immunity is not specific to a particular pathogen as it recognizes the offenders by a group of proteins secreted by them which act at the site of infection and by structural proteins present on the pathogens themselves. Innate immunity plays a crucial role in activating the adaptive immune responses in their early stages, thus playing a crucial role at multiple levels [2].

Although the adaptive immune system is required for the production of neutralizing antibodies, it is not the primary line of defense against viral infections [3,4]. Innate immunity is responsible for the resolution of viral infections. According to several studies, macrophages and neutrophils can protect against major influenza infection caused by Orthomyxoviridae RNA viruses [5]. Fully differentiated macrophages were found to release inflammatory cytokines and interferons (IFN-α/β), leading to the resolution of H3N2 viral infection in mice [6]. Since more recent studies suggest that infection can lead to a more significant number of pathological changes in the lungs, as well as the case of specific lung injury, which in turn accelerates the clearance of the viral disease, protecting the neutrophils has been demonstrated to be a part of an infection's treatment strategy [7,8]. Higher pro-inflammatory cytokines, as Interleukin-6 (IL-6), IL-1b and tumor necrosis factor-alpha (TNF-α) have typically been linked to increased lung pathology during influenza infections [9].

IL-6 is produced mostly by macrophages, but also some other immune cell types such as Dendritic cells and mast cells. It has pleiotropic actions, meaning it has multiple medical effects on inflammation, the immune system, and hematopoiesis. Higher levels of IL-6 are usually found in many other inflammatory conditions because of the continuous activation by mediators. IL-6 can also be expressed by both endothelial cell, epithelial cells and some fibroblast cells when a specific stimulus is applied [10]. As originally described, different biological properties of IL-6 were tagged with distinct names. For instance, the term B-stimulating factor 2 (BSF-2) was given to IL-6 because it activates B cells to become plasma cells [11]. Similarly, IL-6 was also named hepatocyte-stimulating factor (HSF) because it controls the production rate of many acute phase reactants in liver cells [12].

Although numerous investigations have demonstrated that human bronchial cells are capable of IL-6 response to various immunological and allergic stimuli, these findings have not all been reproduced, suggesting that one response may not be universal [13]. It has been demonstrated that the primary epithelial cells of the lungs, not the innate cells, demonstrate a long-constant expression of IL-6 before any environmentally-related activation [14]. Based on this study, it does not appear that IL-6 alone is related to other cytokines necessary for an inflammatory response. While in other research, it has been found that IL-6 can participate in the development as well as a marker of ongoing

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inflammation, it has now been found to be a player in the initiation of innate responses. Other studies have shown that IL-6 has a significant impact on innate responses [15]. Elevated levels of IL-6 have been found in the lungs and serum of patients infected with the influenza virus, including the 2009 H1N1 influenza pandemic [16]. However, whether IL-6 in these patients contributes to the lung pathology due to viral infection or whether IL-6 elevation is a protective mechanism that results in the elimination of viremia is still a matter of debate.

Studies have shown that IL-6 is important in maintaining effective control over T-cell reactions, migration of macrophages, as well as inhibiting cell death of epithelial cells, while at the same time encouraging phagocytosis of virally-infected cells. [17,18]. Thus, instead of being pathogenic in nature, IL-6 and IL-6-mediated downstream signals appear to be beneficial in promoting a quick recovery from RNA viral infections. Deficiency of IL6 or Interleukin – 6 receptors (IL-6R) has been correlated with reduced clearance of the H1N1 virus and is associated with neutropenia in the lung parenchyma infected mice [19]. Thus, it is vital to recognize the impact of Interleukin-6 and related proteins on innate immune responses' functioning. Also, research is required to delineate whether IL-6 is protective in viral infections or whether the increased levels of IL-6 have an opposite effect on the prognosis of viremia. This article describes the role of IL-6 in viral infections and its impact on the development and propagation of innate immune responses.

## Role of Innate immunity during viral infections

Pathogenic exposure stimulates the Innate immune system, which activates the macrophages and neutrophils along with the production of Interleukin-6. Granulocytes, upon activation, identify the exogenous pathogen-associated molecular patterns (PAMPs) in association with the pattern recognition receptors (PRRs), which for the majority of the RNA viruses are in the form of Toll-like receptors (TLRs) 3, 7, and 8, along with intracellular cytoplasmic PRRs such as MDA5 and RIG-I [20]. The receptors, as mentioned earlier, identify different forms of RNAs, namely 5′ triphosphate RNA and double-stranded RNA (dsRNA), which are produced by RNA virus themselves during the process of replication, that can be distinguished from those RNA species usually present in the human cells (such as capped mRNA in the cytoplasm). By this mechanism, innate immunity senses foreign material with pathogenic potential and triggers a cascade of downstream reactions, characterized by the production of type I and III interferons (IFNs) along with other pro-inflammatory cytokines. This leads to the induction of transcription factors in the nucleus, which is mainly in the form of Interferon stimulated genes (ISG) that not only possess antiviral activity but also increases the synthesis of acute-phase proteins, stimulates the B cells, helps in the differentiation of CD4 T cells into Th17 cells and amplifies the production of neutrophils [21]. Subsequently, this is followed by autocrine and paracrine signaling, which ensure that the infected and the surrounding uninfected cells express a multitude of Interferon stimulated genes (ISGs) which, along with the antiviral proteins so produced, work in synchrony to establish a so-called antiviral state that is capable enough to inhibit the further spread of the infection, with simultaneous activation of the adaptive immune responses. The regulation between activation and inhibition of signal transduction which acts to trigger the Innate immune responses is governed in a strict manner by phosphorylation and ubiquitination of the associated genes in the effector cells [22].

## Role of IL-6 in innate immune responses

IL-6 binds to its receptor, the IL-6 receptor (IL-6R) that exists in two variants, namely, the 80-kDa transmembrane form and 50–55-kDa soluble form [23,24], the transmembrane variant of which is present in few selected cells of the body like the leukocytes and hepatocytes whereas, the soluble form is present in the human serum. The fusion of IL-6 to its transmembrane or soluble IL-6 results in homodimerization of the Glycoprotein-130 (GP-130) bound to the cytoplasmic region of the IL-6 receptor thereby signaling a downstream cascade of events [25-27]. The activated ligand-receptor complex is a hexamer consisting of two molecules, each of IL-6, IL-6R, and the GP-130 [28]. These proteins further help in the recruitment of more inflammatory cells and granulocytes at the site of injury that help to remove the focus of infection.

## Regulatory mechanism of IL-6 synthesis

Following infection or tissue injury, IL-6 is produced immediately by macrophages and monocytes that play a crucial role in the elimination of pathogens by activating downstream immune cells and acute-phase proteins. In addition to this, when the stressors have been removed from the body, such that the homeostasis has been fully recovered, the synthesis of IL-6is terminated. Therefore, IL-6 production is upregulated in response to environmental stress and upon pathogenic exposure, the coordination of which is tightly controlled through both the transcriptional and post-transcriptional mechanisms [12]. However, disturbances in its regulation lead to excessive or persistent production of IL-6 that culminates in the development of various diseases. It has been shown that the cis-regulatory elements in the 5' untranslated region (UTR) of the human IL-6 gene contain protein binding sites for NF-kB, specificity protein 1, nuclear factor IL-6 (NFIL-6) and interferon regulatory factor 1 (IRF-1) which modulates IL-6 mRNA production [29]. These substances regulate the secretion of IL-6 upon exposure to environmental stress and pathogens, including specific viral proteins which is necessary for the binding of NF-kB and NFIL-6 to their target DAN motifs leading to enhanced production of IL-6. The binding, from the human TLV-1 virus, with NF-kB promotes IL-6 production [30]. In contrast, the DNA-binding activity of both NF-kB and NFIL-6 is augmented by the activity of the TAT protein in HIV-1 viruses [31].

IL-6 expression is also controlled by post-transcriptional regulation (32). It has been found that RNA-binding proteins can recognize different UTRs and bind to them in order to regulate the transcription of IL-6. The nuclease regulatory RNase-1 (Regnase-1) acts on the deregulation and degradation of IL-6 mRNA in the cytoplasm, which in knockout mice was found to be responsible for the development of autoimmune diseases accompanied by splenomegaly and lymphadenopathy [32]. Another RNA-binding protein, Roquin, identifies the target mRNAs overlapping with Regnase-1 [33] which degrades mRNA in cytoplasm destined for transcription as well as in the endoplasmic reticulum.

AT-rich interactive domain-containing protein 5a (Arid5a) is another RNA binding protein having an affinity to bind and regulate IL-6 mRNA [34]. The macrophages enhance Arid5a expression in response to IL-6, IL-1b, and lipopolysaccharide (LPS) induced under the influence of Th17-polarizing conditions in T cells. LPS injected in Arid5a gene knockout mice is unable to produce IL-6 resulting in the development of experimental autoimmune encephalomyelitis. Therefore, Arid5a counteracts the degrading effect of Regnase-1 on IL-6 mRNA, thereby reflecting the balance between Arid5a and Regnase-1 in maintaining IL-6 mRNA stability [35] and tyrosine-phosphorylated GP-130, respectively, to stop IL-6 signaling by means of a negative feedback loop [36]. Details of the proteins regulating the production of IL-6 during inflammation have been summarized in Table 1.

**Table 1.** Proteins regulating the production of IL-6 during inflammation

| **Proteins that upregulate IL-6 expression** | | |
|---|---|---|
| **Protein** | **Function** | **Ref** |
| Nuclear factor kB (NF-kB) | Increases the production of IL-6 by increasing the expression of IL-6 mRNA upon exposure to environmental stress, pathogens, and viral products | [44] |
| Specificity protein 1 | Increases the production of IL-6 via increased gene expression and mRNA production | [12] |
| Nuclear factor IL-6 (NFIL-6), also known as C/EBP-b | Regulation of IL-6 gene expression by increasing mRNA production. Also crucial for macrophage functioning and production of acute-phase reactants | [45] |
| Activator protein 1 | Increases the DNA binding capacity of NF-kB with the NF-kB binding domain on the IL-6 gene and increases its production. | [45] |
| AT-rich interactive domain-containing protein 5a (Arid5a) | Results in selective stabilization of the IL-6 gene and results in the production of IL-6 upon lipopolysaccharide exposure | [34] |
| **Proteins that downregulate IL-6 expression** | | |
| **Protein** | **Function** | **Ref** |
| Nuclease regulatory RNase-1 (Regnase-1) | Results into the destabilization of the IL-6 mRNA destined for transcription, therefore, reducing the IL-6 levels | [46] |
| Roquin | Degrades the transcriptionally inactive IL-6 mRNA in the stress granules | [33] |
| **IL-6 mediated protein synthesis** | | |
| **Protein** | **Function** | **Ref** |
| Interferon regulatory protein-1 (IRF-1) | IL-6 mediated production is associated with immune response, DNA damage, and apoptosis | [47] |
| Acute-phase proteins | IL-6 increases the production of serum amyloid A, fibrinogen, C-reactive protein, albumin during inflammation | [48] |

## Discussion

There is enough evidence to back up the fact that IL-6 plays a crucial role in viral infections. Some studies have shown that concerning IL-6 production, certain conditions appear to be a barrier to the innate immune responses during viral infections. The release of IL-6 can be compared to the hypotheses mentioned earlier to explain potential changes that might occur for IL-6 production during viral infections. Some viral strains can cross the barrier of the immune response and induce the production of IL-6 on the other. It is a link to the advancement of viral activity [37], which is consequently followed by an up-regulation in the production of IL-6, while on the other hand, polymorphisms in the promoter region of the IL-6 gene stimulate the overexpression of IL-6 during an immune response. This fact has been shown to correlate with viral progression [38]. The latter concept might be a better way to understand a set of clinical symptoms seen in one group during an outbreak that have the same trigger. It appears to increase the virulence of viruses in the host body by damaging Th1 cell polarization and functionality. This allows the virus to persist through viremia and causes CD8 T-cells to cease to develop into memory cells, thus reducing the capacity to fight viral load. Constant replication of the virus fails to grow into long-out plasma cells, limiting their ability to clear the virus [39,40]. Chronic infections increase levels of IL-6, which raises the issue of further accumulation of pathologies (inflammation plus cytokines and cellular presence) to this infection produces, which is an intense inflammation after an immune system is trained to look for foreign bodies [41]. It may be advantageous for several viruses, mainly because it offers new opportunities for future infections because it is new to the target cells to choose from [42]. What makes this possible is fascinating because it begs the question as to whether or not some viruses might have evolved to increase IL-6 selectively as a strategy for evading Innate immunity.

There is no sufficient research to support the relationship between IL-6 overexpression and pathogenicity, which may result in inhibition of autophagy in infected cells [43]. Additional research is also necessary to identify and understand the role of the inflammatory cytokine, IL-6, in viral infections and establish its usefulness as a biomarker for prognosis. An exploration of the IL-6 function as well as that of IL-6 inhibition in treating persistent infections might aid in developing its therapeutic benefit may reveal information about its utility in doing so. However, due consideration must be given to the conflicting results arising out of such studies carried out on the role of IL-6 in the progression of various viral infections. The possibility of the dual function of IL-6 depending upon diverse triggering events seen in various conditions depending upon individual virus characteristics needs to be explored, which will uncover the unseen role played by IL-6 in various infections both positively and in a negative way.

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