Elevated Interleukin-10 Levels in COVID-19: Potentiation of Pro-Inflammatory Responses or Impaired Anti-Inflammatory Action?

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INTRODUCTION

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 (1, 2). 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. To accomplish this, IL-10 inhibits pro-inflammatory cytokine synthesis and antigen presentation in activated monocytes/macrophages and dendritic cells, while also limiting excessive T cell activation and proliferation (1, 2). 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 (1, 2). IL-10’s ability to inhibit pro-inflammatory cytokine expression also requires the inositol phosphatase SHIP1 (3) and the anti-inflammatory effects of IL-10 may specifically be mediated by its ability to induce SHIP1-STAT3 complex formation (4), thereby differentiating IL-10 signaling from other cytokines that activate STAT3 (e.g. IL-6).

POSSIBLE EXPLANATIONS FOR ELEVATED IL-10 LEVELS IN COVID-19

A common feature and presumable cause of death among patients with severe cases of the coronavirus disease 2019 (COVID-19; caused by the SARS-CoV-2 virus) is the overproduction of pro-inflammatory cytokines arising from excessive immune cell activation (i.e., cytokine release syndrome, often referred to as “cytokine storm”) (5). The dramatic early rise in IL-10 – canonicly classified as an anti-inflammatory cytokine – appears to be a distinguishing feature of hyperinflammation during severe SARS-CoV-2 infection (6) and several studies indicate that IL-10 levels predict poor outcomes in patients with COVID-19 (7, 8). Based on its well-established role as an anti-inflammatory and immunosuppressive cytokine (1, 2), the dramatic elevation in IL-10...
could be interpreted as an attempt to temper hyperinflammation and prevent tissue damage. However, the concurrent elevations in IL-10 and various pro-inflammatory cytokines, and the observed relationship between elevated IL-10 levels and disease severity, suggest that IL-10 is either failing to appropriately suppress inflammation (as observed in other inflammatory conditions (9–11) or acting in a manner that deviates from its traditional role as an anti-inflammatory molecule. Indeed, one explanation for the seemingly paradoxical observation of concurrently elevated IL-10 and pro-inflammatory cytokine levels is the ability of IL-10 to act as a pro-inflammatory and immunostimulatory molecule under certain contexts (6). Another compelling and previously unexplored explanation is the potential escape of activated immune cells from IL-10’s anti-inflammatory action (i.e., IL-10 “resistance”) leading to overexuberant pro-inflammatory cytokine responses. In support of this hypothesis, we have reported resistance to IL-10’s anti-inflammatory action under hyperglycemic conditions in vitro (12, 13) and in individuals with type 2 diabetes (T2D) (12). Importantly, because T2D is a risk factor for increased COVID-19 disease severity and mortality (which is markedly lower with well-controlled blood glucose levels) (14), IL-10 resistance may provide a mechanistic link between hyperglycemia/T2D and adverse COVID-19 outcomes.

In this article, we present evidence supporting the non-classical pro-inflammatory effects of IL-10 as a driver of cytokine storms during COVID-19 and consider resistance to IL-10’s classical anti-inflammatory action as an alternative novel mechanism underlying elevated IL-10 levels in patients with severe COVID-19 (summarized in Figure 1). We also highlight the potential utility of therapeutic avenues targeting components of the IL-10 signaling pathway as a viable strategy for restoring IL-10 action in COVID-19. Given that cytokine storms arising from hyperinflammation propagate tissue damage that can eventually cause multi-organ failure and death in severe COVID-19 cases (5), a greater understanding of IL-10’s role in COVID-19 pathogenesis is warranted for the development of effective strategies aimed at combatting the current pandemic.

EVIDENCE SUPPORTING THE ROLE OF IL-10 AS A PRO-INFLAMMATORY CYTOKINE

Although typically classified as anti-inflammatory and immunosuppressive cytokine, the effects of IL-10 are highly context-dependent and there are several scenarios where IL-10

![Figure 1](https://example.com/fig1.png)

**Figure 1**: Potential explanations and consequences of elevated IL-10 levels in COVID-19. (A) Excessive stimulation of CD8+ T cells by IL-10 levels leads to T-cell overactivation and enhanced IFNγ levels, the latter of which further stimulates the production of pro-inflammatory factors by activated macrophages. The propagation of systemic inflammation is presumably bolstered by the IL-10 mediated activation of tissue-resident mast cells. (B) A hyporesponsiveness to IL-10 action (i.e., IL-10 “resistance”) impairs the ability of activated monocytes/macrophages to respond to circulating IL-10, thereby enhancing the release of pro-inflammatory cytokines such as TNFα into circulation. Mechanistically, this impairment in IL-10 action is associated with impaired STAT3 phosphorylation and appears to be driven by elevated blood glucose levels, providing a potential explanation for severe COVID-19 related outcomes in patients with diabetes. Treatment with the SHIP1 agonist ZPR-MN100 (previously known as AQX-MN100) overcomes high glucose-induced IL-10 resistance in macrophages and resolves colitis in IL-10 receptor knock-out mice, highlighting the potential of SHIP1 targeted therapeutics for combating severe COVID-19. [Created with Biorender.com].
enhances immune cell activation and proliferation causing the release of pro-inflammatory cytokines. For instance, Lauw et al. (15) were the first to demonstrate the pro-inflammatory effects of IL-10 in vivo during human endotoxemia. In this study, intravenous administration of recombinant IL-10 (25 µg/kg) potentiated the lipopolysaccharide (LPS)-induced increase in IFNγ and IFNγ-dependent chemokine production in healthy humans (15). These experiments were shortly followed by studies in patients with Crohn’s disease, where subcutaneous administration of high dose recombinant IL-10 (20 µL/kg) caused an increase in IFNγ production in phytohemagglutinin-stimulated whole-blood cultures (16).

Further support for the immunostimulatory role of IL-10 comes from studies in rodent tumour models where IL-10 administration promotes proliferation and expansion of tumour-resident cytotoxic CD8+ T cells as well as IFNγ production, thereby enhancing antitumor activity (17). In line with these rodent experiments, administration of pegylated recombinant IL-10 (20 µg/kg) to human cancer patients induces systemic immune activation as reflected by elevations in various pro-inflammatory cytokines and expansion of both systemic and tumour-resident CD8+ T cells (18, 19). Collectively, these findings indicate that high doses of IL-10 can induce pro-inflammatory responses in healthy participants as well as patients with autoimmune disease and cancer.

In light of the aforementioned findings, several lines of evidence support the potential pro-inflammatory actions of IL-10 in severe COVID-19 cases. First, many of the same cytokines that are elevated with high-dose IL-10 administration in the studies discussed above (e.g. IL-4, IL-7, IL-18, IFNγ, TNFα) are also elevated in severe COVID-19 cases in conjunction with elevated IL-10 levels (7, 8, 20, 21). Of note, the rise in IL-10 levels occurs during the early stages of SARS-CoV-2 infection, thus preceding elevations in pro-inflammatory cytokines that typify cytokine storms (8). Second, plasma levels of bacterial DNA and LPS – two known pathogen-associated molecular patterns (PAMPs) that activate inflammatory signaling in immune cells – are elevated in severe COVID-19 cases (22). Although IL-10 is a potent inhibitor of LPS-induced gene expression in macrophages (23), the ability of high concentrations of IL-10 to amplify pro-inflammatory responses to LPS (15) raises the possibility that the combination of elevated IL-10 and bacterial products drives inflammation in COVID-19. Moreover, because LPS is a known inducer of IL-10 production in macrophages (1), high levels of LPS may play a causal role in the observed elevations in IL-10 during COVID-19.

Given the ability of IL-10 to potently induce T cell activation in various cancer models (17), a final piece of evidence supporting the potential pro-inflammatory actions of IL-10 in COVID-19 is the observation of overactivated CD8+ T cells despite a reduction in overall CD8+ T cell count (24). IL-10-mediated hyperactivation of CD8+ T cells despite an overall reduced cell count may also explain why some studies report functional exhaustion of T cells in severe COVID-19 cases (25) and significant inverse associations between serum IL-10 levels and T cell count (26). The propagation of systemic of systemic inflammation by CD8+ T cell derived cytokines (e.g., IFNγ) would presumably be bolstered by IL-10 mediated activation of tissue-resident mast cells (27), which are abundant in lung epithelial membranes and have been implicated in COVID-19-related inflammation (28–30). Taken together, the aforementioned findings raise the intriguing possibility that the “non-classical” pro-inflammatory actions of IL-10 may contribute to the propagation of cytokine storms in COVID-19 (6), thus warranting further research into this avenue.

**IL-10 RESISTANCE AS A LINK BETWEEN HYPERGLYCEMIA/T2D AND SEVERE COVID-19 – RELATED OUTCOMES**

Another compelling and novel explanation for elevated IL-10 levels in the face of systemic hyperinflammation in severe COVID-19 cases is the potential inability of IL-10 to inhibit pro-inflammatory cytokine production and release from activated monocytes/macrophages (e.g. IL-10 “resistance”). This scenario may help explain why the existence of hyperglycemia and diabetes is linked to disease severity and mortality in patients with COVID-19 (31), and why improved glycemic control is associated with better outcomes (14). Studies from our lab were the first to demonstrate the concept of IL-10 “resistance” under hyperglycemia in vitro [recently replicated by an independent group (13)] and from immune cells isolated from patients with T2D (12). In our experiments, the ability of IL-10 (10 ng/mL) to inhibit TNFα production in response to LPS stimulation was reduced in whole-blood cultures from individuals with T2D as compared to healthy age and BMI-matched controls (12). A similar resistance to IL-10’s anti-inflammatory action was observed in macrophages cultured in high-glucose media suggesting that hyperglycemia was responsible for the reduced anti-inflammatory function of IL-10 in T2D (12). Mechanistically, the hyperresponsiveness to IL-10 action correlated with impaired STAT3 phosphorylation under hyperglycemia and responsiveness was restored with a small molecule activator of the inositol phosphatase SHIP1 (12), highlighting the STAT3/SHIP1 axis as a potential target for restoring IL-10 action (4). Although the concept of aberrant immune cell activation in response to high glucose is well-established, recent in vitro experiments indicate that exposure to high glucose also enhances SARS-CoV-2 replication in monocytes (32). This hyperglycemia-induced potentiation of SARS-CoV-2 replication in monocytes requires glycolytic flux (32), which is noteworthy (and perhaps further supportive of IL-10 resistance) because the anti-inflammatory effects of IL-10 in macrophages are typically mediated by oxidative metabolism (33).

As mentioned earlier, levels of bacterial DNA and LPS are elevated in patients suffering from severe cases of COVID-19 (22). Although one line of reasoning can interpret elevated LPS levels in COVID-19 as support for the pro-inflammatory effects of IL-10 (as above), these observations can alternatively also be interpreted as support for IL-10 resistance. Specifically, because the IL-10-STAT3 axis inhibits ~20% of LPS-induced genes (1),
failure of IL-10 to inhibit cytokine production from IL-10 resistant monocytes/macrophages during endotoxemia may explain why various pro-inflammatory cytokines are elevated despite high IL-10 levels in severe COVID-19 cases.

Based on these observations, it is tempting to speculate that a similar resistance to IL-10’s anti-inflammatory action may underpin hyperinflammation in COVID-19, particularly in individuals with diabetes. Moreover, since systemic inflammation and natural killer cell activation – both of which are present during respiratory viral infections (34, 35) – can drive insulin resistance in skeletal muscle (34) and adipose tissue (36), the ensuing hyperinsulinemia/hyperglycemia may further propagate IL-10 resistance in individuals with T2D infected with SARS-CoV2. These speculations warrant further investigation to determine the contribution of IL-10 resistance to severe COVID-19 outcomes in individuals with diabetes.

**POTENTIAL THERAPEUTIC AVENUES TARGETING IL-10 SIGNALLING**

If IL-10 resistance is involved in COVID-19 adverse outcomes, then recent insights into the molecular aspects of anti-inflammatory IL-10 signaling may provide clues for novel therapeutic options. Chamberlain and colleagues (4) recently reported that anti-inflammatory IL-10 signaling involves induction of a SHIP1-STAT3 complex, which translocates to the nucleus resulting in inhibition of macrophage activation and resolution of inflammatory colitis in mice. In this study, a small molecule SHIP1 agonist acted like an anti-inflammatory “IL-10 mimetic” to inhibit macrophage activation and resolve colitis in IL-10 receptor knock-out mice. In line with these observations, we previously demonstrated that small molecule SHIP1 agonists could overcome high glucose-induced IL-10 resistance in macrophages (2). Thus, it seems plausible that a loss of normal SHIP1-STAT3 complex formation might be a mechanism that contributes to IL-10 resistance and that SHIP1 agonists can circumvent this to reduce inflammation. In this manner, it is intriguing to speculate that drugs targeting SHIP1 signaling could play a role in mitigating negative consequences of cytokine storms as a therapeutic option in COVID-19.

**CONCLUSIONS**

The drastic early rise in IL-10 in severe cases of COVID-19 is a distinguishing and seemingly paradoxical observation in light of IL-10’s classical role as an anti-inflammatory cytokine. The non-classical pro-inflammatory effects of IL-10 provide a plausible explanation for elevated IL-10 levels in the face of systemic inflammation (Figure 1A). Another novel and intriguing possibility that we have presented here is a potential “resistance” to IL-10’s classical anti-inflammatory actions, which may provide a mechanistic link between hyperglycemia/diabetes and severe COVID-19-related outcomes (Figure 1B). Further investigation into potential strategies aimed at counteracting the pro-inflammatory effects of IL-10 on CD8+ cells or restoration of IL-10’s anti-inflammatory action on macrophage cells may be beneficial for combatting hyperinflammation during SARS-CoV-2 infection. In this regard, small molecule SHIP1 agonists provide a promising avenue for exploration to restore anti-inflammatory IL-10 signaling.

**AUTHOR CONTRIBUTIONS**

HI, AM, and JL contributed to the conception of the work. HI and JL wrote the initial draft of the manuscript. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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