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Interleukin-17A (IL-17A): A silent amplifier of COVID-19

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ABSTRACT

One of the hallmarks of COVID-19 is the cytokine storm that provokes primarily pneumonia followed by systemic inflammation. Emerging evidence has identified a potential link between elevated interleukin-17A (IL-17A) levels and disease severity and progression. Considering that per se, IL-17A can activate several inflammatory pathways, it is plausible to hypothesize an involvement of this cytokine in COVID-19 clinical outcomes. Thus, IL-17A could represent a marker of disease progression and/or a target to develop therapeutic strategies. This hypothesis paper aims to propose this "unique" cytokine as a silent amplifier of the COVID-19 immune response and (potentially) related therapy.

1. Introduction

Despite the considerable effort of the scientific community to comprehend the molecular basis of Coronavirus disease 2019 (COVID-19) signs and symptoms, the physiopathology of COVID-19 is still not fully clarified [1–3]. Nevertheless, what it is widely ascertained is that COVID-19-related pulmonary inflammation is associated with increased plasma levels of a pattern of pro-inflammatory cytokines that include interleukin (IL)−6, IL-17A, tumour necrosis factor-α (TNF-α) Interferon-γ (IFN-γ) and IL-12, defining a characteristic feature known as cytokine storm [4–8].

The cytokine storm, and related cytokine release syndrome (CRS), can be considered as "an inflammatory response flaring out of control", mostly responsible for the mortality in COVID-19 patients [9–11]. In this context, the potential role of IL-6 in COVID-19 pneumonia has provided a rationale for the investigation of IL-6 signalling inhibitor tocilizumab [12]. Even if better outcomes in patients with severe COVID-19 pneumonia who received tocilizumab have been observed in case reports [13, 14], in a recent randomized trial involving hospitalized patients with moderate to severe COVID-19 pneumonia, the use of tocilizumab did not result in significantly better clinical status or lower mortality [15].

On this basis, the need for effective treatments for patients with severe COVID-19 pneumonia, specifically targeting the cytokine storm, continues to be a major challenge. In particular, it is becoming apparent that in some patients, severe COVID-19 disease is accompanied by a fulminant immune reaction characterized by pronounced infiltration of macrophages and monocytes into the alveolae, a pro-inflammatory T-helper 17 (Th17) response, and elevated levels of inflammatory cytochemokines [16–18].

Indeed, among the variety of cytokines involved, several reports reveal elevated levels of Th17 cells and circulating IL-17A in the peripheral blood of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infected patients [19,20]. This clinical evidence is of particular importance since IL-17A induces the production of other pro-inflammatory mediators such as IL-1, IL-6, TNF-α that, together with matrix metalloproteinases, may play a pertinent role in tissue damage [21]. In line with this view, the hypothesis of a direct relationship between elevated levels of IL-17A and disease severity and progression are

Abbreviations: ARDS, acute respiratory distress syndrome; CD99, cluster of differentiation 99; COVID-19, Coronavirus disease 2019; CRS, cytokine release syndrome; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GRO-α, growth-regulated oncogene-α; ICAM-1, intercellular adhesion molecule-1; IL-, interleukin-; IL-R, Interleukin- Receptor; ILC3s, innate lymphoid cells (ILC3s); IFN-γ, Interferon-γ; IP-10, Interferon-inducible protein-10; MAIT, mucosal-associated invariant T; MCP-1, monocyte chemoattractant protein-1; MIP-2, macrophage inflammatory protein-2; MMP-, matrix metalloproteinase-; NK, natural killer; PDGF, platelet-derived growth factor; PECAM-1, platelet endothelial cell adhesion molecule-1; PMNs, polymorphonuclear cells; SARS-CoV-2, severe acute respiratory syndrome Coronavirus 2; Th, T-helper; TNF-α, tumour necrosis factor-α; VEGF, Vascular endothelial growth factor.

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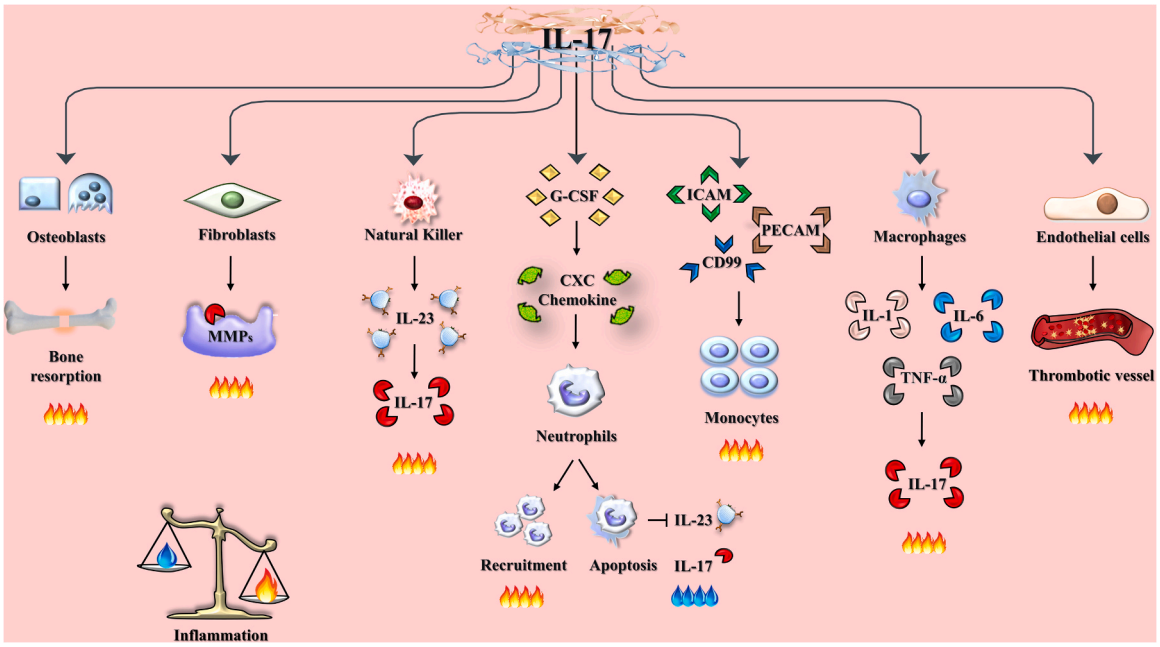

Fig. 1. Biological function of IL-17. Scheme of the main biological function of IL-17A on different cells and soluble factor. Taking into account the variety of its actions, IL-17A can be considered a "not canonical" pro-inflammatory cytokine since it plays a unique role in the context of ongoing inflammatory diseases by exacerbating cellular and biochemical events activated during the acute phase of the inflammatory response.

becoming more consistent [22,23].

2. IL-17A: from discovery to COVID-19

In the nineties, identifying two distinct subsets of helper T cells, IFN-γ-producing Th1 cells and IL-4-producing Th2 cells, enabled the scientific community to understand better the immunopathology of inflammatory diseases in humans [24,25]. However, the observation that T cell-mediated experimental autoimmune and auto-inflammatory diseases were independent by Th1 and Th2 subsets prompted the investigators to identify any distinct subset in the helper T cell population named Th17 [26].

Therefore, the discovery of Th17 cells and relative IL-17 cytokines family gave a new impulse to the immunology field, bridging the gap and giving not only “a wider vision" of both innate and adaptive immunity, but also to identify this ”unique” cytokine as a silent amplifier of the immunity process [27]. The IL-17A peculiarity relies on a specific subset of T helper cells that selectively produce this cytokine, namely Th17. The discovery of IL-17A and its biological function has revolutionized the field of immunology. and it has completely changed the way we look at many immune-related and inflammatory-based diseases [28]. Chronologically, the discovery of IL-17A as a pro-inflammatory cytokine in arthritis preceded the description of the Th17 cells by many years. However, following the identification of Th17 cells, a significant role for this cytokine in host defence, as well as in the context of acute and chronic inflammation, has been definitively assessed [29,30]. Data available from both basic research and clinical trials demonstrate that the IL-17A immune axis is undoubtedly characterized by distinct biological effects that vary among diseases.

3. IL-17A in acute and chronic inflammation

In the last few years, the scientific community has focused attention on IL-17A due to its pivotal role in the ongoing events typical of some inflammatory-based chronic diseases [27,31]. Indeed, this cytokine is implicated in the mechanisms involved in cell activation, growth, and proliferation [32,33]. Specifically, current studies have shown a close correlation, in the early stages of the inflammatory response, between IL-17A and the recruitment of polymorphonuclear cells (PMNs) [34,35]. Indeed, both preclinical and clinical data have underlined the importance of IL-17A as a regulator of PMNs infiltration due to its chemotactic activity [29,36]. In this context, it has been shown that IL-17A plays a main role in neutrophils maturation and differentiation. This is due to its ability to increase granulocyte-colony stimulating factor (G-CSF) release [37], thereby fostering the differentiation of the progenitors hematopoietic $CD34^{+}$ towards neutrophils [38]. IL-17 can also induce other granulopoiesis markers and chemokines, such as growth-regulated oncogene-α (GRO-α), that regulate neutrophil penetration into tissues [36,39]. Furthermore, IL-17A promotes also cyto-chemokines release namely IL-1, IL-6, TNF-α, macrophage inflammatory protein-2 (MIP-2), IL-8, Interferon-inducible protein-10 (IP-10) all used by neutrophils in chemotaxis [40–42].

The involvement of neutrophils and, more generally, of PMNs during the early phase of acute inflammation, involves cyto-chemokines released by macrophages/monocytes subset [43]. It has been reported that the release of macrophage-related cytokines, including IL-1, TNF-α and IL-6, is prompted by IL-17A to propagate and amplify the inflammatory onset [44]. Indeed, IL-17A induces monocyte adhesion, increasing the release of intercellular adhesion molecule-1 (ICAM-1), integrin α4, platelet endothelial cell adhesion molecule-1 (PECAM-1), and the cluster of differentiation 99 (CD99), representing one of the main stimuli for monocytes maturation and activation [45].

The biological effects exerted by IL-17A also include its synergistic activity with other pro-inflammatory “inducers”. IL-17A, in combination with IL-1β and TNF-α, enhances the inflammatory reaction in cartilage, synovium and meniscus [46,47]. IL-17A is also associated with the degradation of articular cartilage and destruction of bone (due to the production of the matrix metalloproteinase-(MMP-) 1 and MMP-13 collagenases in chondrocytes), the degradation of proteoglycans, and the expression of IL-6 and leukaemia inhibitory factor in fibroblast-like cells of the synovium [48,49].

As schematically reported in Fig. 1, IL-17A can be defined as "not canonical" pro-inflammatory cytokine, considering the variety of its actions. Indeed, it plays a unique role in the context of ongoing inflammatory diseases by exacerbating cellular and biochemical events activated during the acute phase of the inflammatory response.

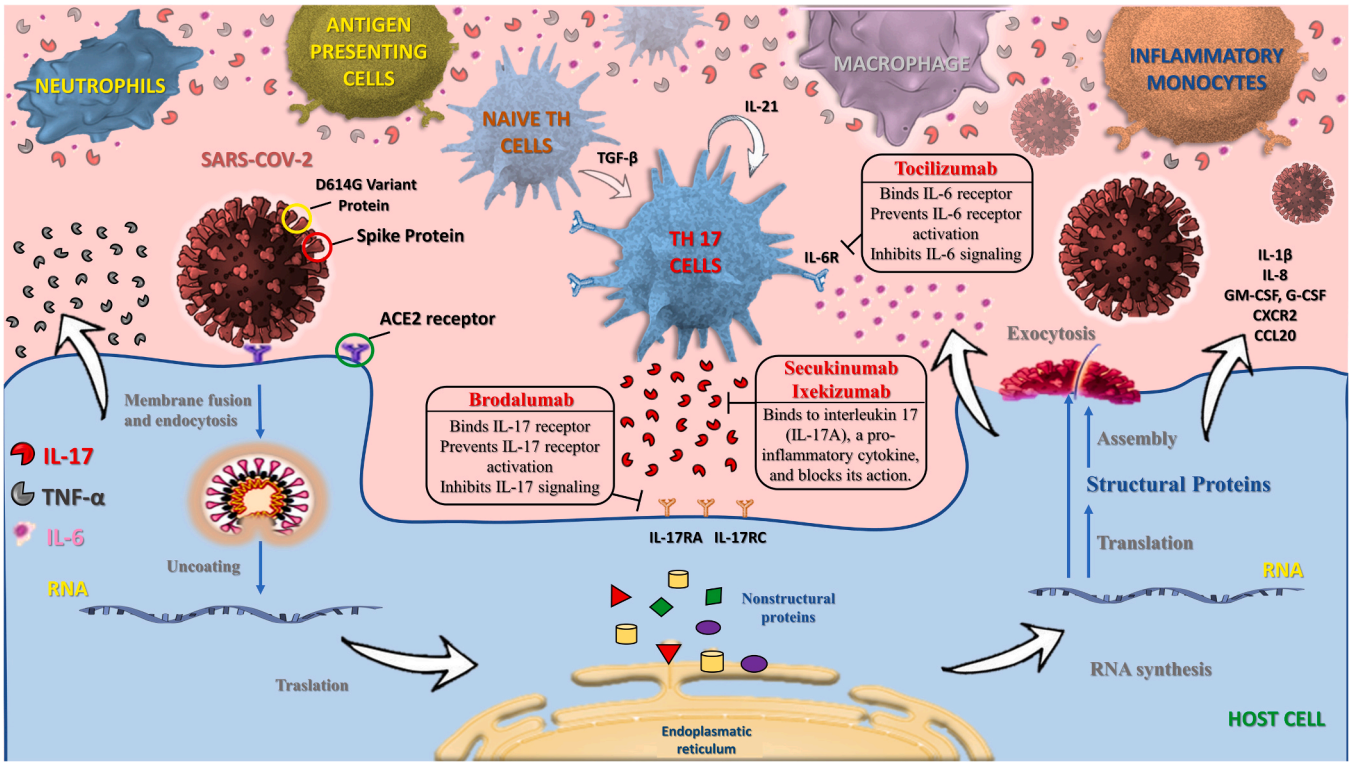

Fig. 2. Mechanism of COVID-19 replication and potential cytokines-related therapeutic targets. In the upper part of the figure is depicted the complex mechanism of COVID-19 infection followed by (bottom part) its replication. The cartoon also presents an overview of IL-6 and IL-17A (and cytokine-related available antibodies) signalling pathway. IL-17A binding a heterodimer receptor composed of IL-17RA and IL-17RC induces cytokines production. IL-17A signalling can.
be blocked by antibodies targeting IL-17A (Secukinumab or Ixekizumab) or the A chain of its receptor (Brodalumab).

Furthermore, although predominantly acting at the local site, IL-17A can also circulate in the bloodstream and thus may indirectly affect endothelial cells function, inducing vascular inflammation, increasing the risk of atherosclerosis, and/or cardiac and thrombotic events in patients with certain inflammatory-based diseases [50]. Moreover, IL-17A, in combination with TNF-α, is also responsible for a pro-coagulant and pro-thrombotic state [51,52], thus providing evidence for its implication in the cardiovascular events associated with autoimmune diseases [53,54].

4. IL-17A as a rheostat of COVID-19 immune response

To manage the severe pulmonary clinical manifestations coupled to tissues and organs dysfunctions generated by cytokine storm is one of the primary endpoints of therapeutic intervention against COVID-19. It has been reported increased levels of C-reactive protein, IL-1β, IL-1 Receptor (IL-1RA), IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-17A, G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ, IP-10, monocyte chemoattractant protein-1 (MCP-1), MIP-1α, MIP-1β, platelet-derived growth factor (PDGF), TNF-α, and vascular endothelial growth factor (VEGF) in patients experiencing CRS. Comparisons between severely affected individuals and non-severe cases showed higher leukocyte and neutrophil counts but lower lymphocyte levels. While a decrease in B cells, T cells, and natural killer (NK) cells was also observed in all affected individuals [55].

Elevated levels of Th17 cells in the peripheral blood of SARS-CoV-2 infected patients have been described [17]. This finding strongly suggests an amplifier role for IL-17A in the inflammatory response, since it triggers the production of other pro-inflammatory cytokines i.e. IL-1, IL-6, TNF-α [17]. Furthermore, the decrease in lymphocytic population subsets, coupled with the rise in Th17 cells and Th17-derived cytokines observed in these patients, consolidate the idea of an immune response that drives severe inflammation [21].

In line with this hypothesis, a recent report highlighted that in COVID-19 patients with pneumonia, CD4 + or CD8 + T cells are increased capability to produce in vitro IL-17A, activating neutrophils to release higher IL-17A within peripheral blood [56]. Recent studies have demonstrated that the excessive IL-17A production, observed in patients with acute lung injury, is correlated to maladaptive neutrophil recruitment, pro-inflammatory mediators' stimulation, and apoptosis prevention due to induction of granulocyte induction colony-stimulating factor expression [57]. Accordingly, a recent study has shown that in COVID-19 neutrophil/T cell cocultures, neutrophils can determine a substantial polarity shift toward Th17 coupled to a reduction of IFN-γ-producing Th1 cells [58]. Congruently, a retrospective analysis of IL-17 gene polymorphisms (that resulted in attenuated IL-17 production) in patients with acute respiratory distress syndrome (ARDS) revealed that these patients had an increased 30-day survival [59,60].

It should also be considered that group 3 innate lymphoid cells (ILC3s) and mucosal-associated invariant T (MAIT) cells are highly activated in patients with COVID-19, irrespective of the course of the disease, and express high levels of proinflammatory cytokines such as IL-17A, suggesting their possible involvement in COVID-19 immunopathogenesis [61,62]. Finally, bioinformatic analyses to delineate the potential genetic crosstalk between COVID-19 and Guillain-Barré syndrome have suggested that aberrant Th17 cell differentiation could represent a possible mechanism by which SARS-COV-2 can increase the risk of the autoimmune peripheral nervous disease [63]. Taken together, these findings underline a key role of IL-17A in COVID-19 and likely could pave the way to novel therapeutic approaches based upon IL-17A blockage by biological drugs that are already available [19,64].

At the present stage, three are commercially available options to block this target (Fig. 2): Secukinumab (human monoclonal antibody to IL-17A), Ixekizumab (humanized monoclonal antibody to IL-17A) and Brodalumab (human monoclonal antibody to the IL-17R). By targeting IL-17A, the monoclonal antibodies could operate upstream the cytokine

storm release, resulting in a reduction of neutrophil and inflammatory monocytes recruitment [54,59]. Consequently, IL-17A by inducing a pattern of pro-inflammatory cytokine, IL-6 included, could represent a convincing target for the treatment of severe and non-severe pulmonary inflammatory states in patients with COVID-19. In support of this hypothesis, a case-based review [65] and preliminary reports on COVID-19 patients who underwent secukinumab treatment suggest a favorable outcome [66,67], thereby modulation of IL-17A signalling through the JAK/STAT inhibitor fedratinib has been proposed [68]. However, further studies are necessary to test the benefit/risk ratio of IL-17A neutralizing antibodies in SARS-CoV-2 infected individuals or to test, preclinically and clinically, novel modulators/inhibitors of IL-17/IL-17R (unpublished data from our research group).

5. Conclusion and perspective

COVID-19 has become a real global burden. One of the main hallmarks is the cytokine storm that provokes primarily pneumonia followed by systemic inflammation. Currently, no treatment can act specifically against SARS-CoV-2 infection. Once administered to the global population, it will remain to see to what extent the vaccination program will be safe and effective and whether such vaccines act on the new variant/s. Therefore, also considering that the timing of post-vaccination immune coverage is still unknown, the need for effective and focused therapy to control COVID-19 clinical outcomes is becoming a priority. In addition, emerging investigations have identified a potential link between elevated levels of IL-17A and disease severity and progression. Since IL-17A per se can activate specific inflammatory pathways, it is plausible to hypothesize an involvement of this cytokine in COVID-19 infection, prompting suggestions of targeting this cytokine for therapeutic purposes and/or to use it as a marker of disease progression.

CRediT authorship contribution statement

FM, GMC and FR drafted the manuscript. CS, GA, LC, RS, FC, MB and FM revised the manuscript. All Authors gave final approval to the publication.

Conflict of interest statement

This article has been conducted and written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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