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

Running title: IL-17A and COVID-19.

Francesco Maione[1], Gian Marco Casillo[1], Federica Raucci[1] and Mariarosaria Bucci[1,*].

[1]Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Via Domenico Montesano 49, 80131, Naples, Italy.

[*]**Author for correspondence:** Mariarosaria Bucci, Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Via Domenico Montesano 49, 80131, Naples, Italy. Phone: (+39)081678634. E-mail: mrbucci@unina.it

Word count: 1.930 (excluding abstract, references and figure legends)

Acknowledgements

This work was supported by MIUR (PRIN 2017; 2017A95NCJ/2017A95NCJ_002, "Stolen molecules - Stealing natural products from the depot and reselling them as new drug candidates").

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.

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 levels of interleukin-17A (IL-17A) 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, this cytokine can 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.

Keywords: Cytokine storm, COVID-19, IL-17A, Immunotherapy, Th17.

Abbreviations: AIFA, Italian Pharmaceutical Agency; 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; IFN-γ, Interferon-γ; IP-10, Interferon-inducible protein 10; MCP1, 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.

1. Introduction

Despite the huge effort of the scientific community to comprehend the molecular basis of COVID-19 signs and symptoms the physiopathology of COVID-19 is still not fully clarified (Rivellese, et al., 2020; Shoenfeld, 2020). 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 (Ye, et al., 2020; Hirano, et al., 2020; Quirch, et al., 2020; Honore, et al., 2020).

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 (Mahesh, et al., 2021). 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 (National Health Commission Office of State, 2020). Even if better outcomes in patients with severe COVID-19 pneumonia who received tocilizumab have been observed in case reports (Michot et al., 2020; Zhang et al., 2020), 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 (Rosas et al., 2021).

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 cyto-chemokines (Chen et al., 2020; Xu et al., 2020).

Indeed, among the variety of cytokines involved, several reports reveal elevated levels of T-helper-17 (Th)17 cells and circulating IL-17A in the peripheral blood of SARS-CoV-2 infected patients (Bulat, et al., 2020; Megna, et al., 2020). 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 (Hoffmann, et al., 2020). In line with this view, the hypothesis of a direct relationship between elevated levels of IL-17A and disease severity and progression are becoming more consistent (Leija-Martinez, et al., 2020; Pacha, et al., 2020).

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

In the nineties, the identification of two distinct subsets of helper T cells, IFN-γ-producing Th1 cells and IL-4-producing Th2 cells, enabled the scientific community to better understand the immunopathology of inflammatory diseases in humans (Yang, et al., 2008; Noack, et al., 2014). 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 additional, and distinct, subset in helper T cell population named Th17 (Miossec, et al., 2012). 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 (D’Acquisto, et al., 2010). The IL-17A peculiarity compared to the other cytokines relies on the presence of 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 (Maione, 2016). Chronologically, the discovery of IL-17A as a pro-inflammatory cytokine in arthritis preceded the description of the Th17 cells by many years. However, only in more recent years 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 (Maione, et al., 2009; Maione, et al., 2018). 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 (**Figure 1**).

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 (D'Acquisto, et al., 2010; Lubberts, 2015). Indeed, this cytokine is implicated in the mechanisms involved in cell activation, growth, and proliferation (Gaffen, 2004; Kehlen, et al., 2002). 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) (Pedraza-Zamora, et al., 2017; Wojkowska, et al., 2014). Indeed, both preclinical and clinical data have underlined the importance of IL-17A as a regulator of PMNs infiltration due to its chemotactic activity (Maione, et al., 2009; Witowski, et al., 2000). 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 (Ley, et al., 2006), thereby fostering the differentiation of the progenitors hematopoietic $CD34^{+}$ towards neutrophils (Fossiez, et al., 1996). Il-17 can also induce other granulopoiesis markers and chemokines, such as growth-regulated oncogene-α (GRO-α), that regulate neutrophil penetration into tissues (Schwarzenberger, et al., 1998; Witowski, et al., 2000). 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 (Albanesi, et al., 1999; von Vietinghoff, et al., 2008; Xu, et al., 2010).

The involvement of neutrophils and, more generally, of PMNs during the early phase of acute inflammation, involves cyto-chemokines released by macrophages/monocytes subset (Cray, et al., 2009). 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 (Jovanovic, et al., 1998). 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 cluster of differentiation 99 (CD99), representing one of the main stimuli for monocytes maturation and activation (Wang, et al., 2014).

The biological effects exerted by IL-17A also includes 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 (Hwang, et al., 2004; Moseley, et al., 2003). 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 (Blauvelt, et al., 2018; Kehlen, et al., 2003). As schematically reported in **Figure 1**, considering the variety of its actions, IL-17A can be considered a "*not canonical*" pro-inflammatory cytokine. 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. 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 (Beringer, et al., 2019). Moreover, IL-17A, in combination with TNF-α, is also responsible for a pro-coagulant and pro-thrombotic state (Hot, et al., 2012; Maione, et al., 2011) thus providing evidence for its implication in the cardiovascular events associated with autoimmune diseases (Casillo, et al., 2020; Raucci, et al., 2020).

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 (MCP1), 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. Whilst a decrease in B cells, T cells, and natural killer (NK) cells was also observed in all affected individuals (Huang, et al., 2020).

Elevated levels of Th17 cells in the peripheral blood of SARS-CoV-2 infected patients have been described (Xu, et al., 2020). 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 (Xu, et al., 2020). 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 (Hoffmann, et al., 2020). In line with this hypothesis, a recent report highlighted that in COVID-19 patients with pneumonia, there is an increased capability of $CD4^+$ or $CD8^+$ T cells to produce *in vitro* IL-17A, activating neutrophils to release higher IL-17A within peripheral blood (De Biasi, et al., 2020). Notably, recent studies have demonstrated that the excessive IL-17A production, observed in patients with acute lung injury, is correlated to maladaptive neutrophil recruitment, stimulation of pro-inflammatory mediators, and prevention of apoptosis due to induction of granulocyte colony-stimulating factor expression (Orlov, et al., 2020). 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 (Bulat et al., 2021; Pasrija, et al., 2021).

At the present stage, three are commercially available options to block this target (**Figure 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, (Pacha, et al., 2020; Raucci, et al., 2020). 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 (Coskun, et al., 2020) and preliminary reports on COVID−19 patients who underwent to secukinumab treatment, suggest a favourable outcome (Di Lernia et al., 2020; Galluzzo, et al., 2020) thereby modulation of IL-17A signalling through the JAK/STAT inhibitor fedratinib has been proposed (Wu et al., 2020). However, further studies are necessary to test the benefit/risk ratio of IL-17A inhibitors in SARS-CoV-2 infected individuals.

5. Conclusion and perspective

COVID-19 has become an indisputable 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 as well. Therefore, also considering that the timing of post-vaccination immune coverage is still unknown, the need of effective and focused therapy to control COVID-19 clinical outcomes is becoming a priority. 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.

Author contributions

FM, GMC and FR drafted the manuscript. MB and FM revised the manuscript. All Authors gave final approval to the publication.

Declaration of transparency and scientific rigour

This Declaration acknowledges that this paper adheres to the principles for transparent reporting and scientific rigour of preclinical research as stated in the BJP guidelines for Design & Analysis, Immunoblotting, and Animal Experimentation, and as recommended by funding agencies, publishers and other organisations engaged with supporting research.

6. References

AIFA GOV. (2020). TOCIVID-19_documenti.zip. https://www.aifa.gov.it/ricerca?q=tocilizumab

Albanesi, C., Cavani, A., Girolomoni, G. (1999). IL-17 is produced by nickelspecific T lymphocytes and regulates ICAM-1 expression and chemokine production in human keratinocytes: synergistic or antagonist effects with IFN-gamma and TNF-alpha. J. Immunol, 162(1), 494-502. PMID: 9886425

Beringer, A., Miossec, P. (2019). Systemic Effects of IL-17 in Inflammatory Arthritis. Review Nat Rev Rheumatol, 15(8), 491-501. DOI: 10.1038/s41584-019-0243-5

Blauvelt, A., Chiricozz, A. (2018). The Immunologic Role of IL-17 in Psoriasis and Psoriatic Arthritis Pathogenesis. Review Clin Rev Allergy Immunol, 55(3), 379-390. DOI: 10.1007/s12016-018-8702-3

Bulat, V., Situm, M., Azdajic, M. D., Likic, R. (2020). Potential role of IL-17 blocking agents in the treatment of severe COVID-19? Br J Clin Pharmacol, 87(3), 1578-1581. DOI: 10.1111/bcp.14437.

Casillo, G. M., Mansour A. A., Raucci, F., Saviano, A., Mascolo, N., Iqbal, A. J., Maione, F. (2020). Could IL-17 represent a new therapeutic target for the treatment and/or management of COVID-19-related respiratory syndrome? Pharmacol Res, 156, 104791. DOI: 10.1016/j.phrs.2020.104791

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., ... Zhang, L. (2020). Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study. Lancet, 395, 507-513. DOI: 10.1016/S0140-6736(20)30211-7

Coskun, B. I., Kurtaran, B., Tirasci, E., Guzel, R. (2020). Coronavirus disease 2019 (COVID-19) in a patient with ankylosing spondylitis treated with secukinumab: a case-based review. Rheumatol Int. 40(10), 1707-1716. DOI: 10.1007/s00296-020-04635-z.

Cray, C., Zaias, J., Altman, N. H. (2009). Acute phase response in animals: a review. Comp Med, 59(6), 517-526. PMID: 20034426

D'Acquisto, F., Maione, F., Pederzoli-Ribeil, M. (2010). From IL-15 to IL-33: the never-ending list of new players in inflammation. Is it time to forget the humble aspirin and move ahead? Biochemical Pharmacology, 79(4), 525-534. DOI: 10.1016/j.bcp.2009.09.015

244De Biasi, S., Meschiari, M., Gibellini, L., Bellinazzi, C., Borella, R., Fidanza, L., … Cossarizza, A. 245(2020). Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients 246with COVID-19 pneumonia. Nat Commun,11(1), 3434. DOI:10.1038/s41467-020-17292-4

247Di Lernia, V., Bombonato, C., Motolese, A. (2020). COVID−19 in an elderly patient treated with 248secukinumab. Dermatol Ther. 33(4), e13580. DOI: 10.1111/dth.13580.

249Fossiez, F., Djossou, O., Chomarat, P., Flores-Romo, L., Ait-Yahia, S., Maat, C., … Lebecque, S. 250(1996). T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic 251cytokines. J. Exp. Med, 183(6), 2593. DOI: 10.1084/jem.183.6.2593

252Gaffen, S. L. (2004). Biology of recently discovered cytokines: Interleukin-17 – a unique 253inflammatory cytokine with roles in bone biology and arthritis. Arthritis Res.Ther, 6, 240-247. DOI: 25410.1186/ar1444

255Galluzzo, M., Tofani, L., Bianchi, L., Talamonti, M. (2020). Status of a real−life cohort of patients 256with moderate−to−severe plaque psoriasis treated with secukinumab and considerations on the use 257of biological agents in the Covid−19 era. Expert Opin Biol Ther. 20(8), 829-830. DOI: 25810.1080/14712598.2020.1779217.

259Hirano, T., Murakami, M. (2020). COVID-19: A New Virus, but a Familiar Receptor and Cytokine 260Release Syndrome. Comment Immunity, 52(5), 731-733. DOI: 10.1016/j.immuni.2020.04.003

261Hoffmann, M.., Kleine-Weber, H., Schroeder, S., Kruger, N., Herrler, T., Erichsen, S., … 262Pohlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked 263by a Clinically Proven Protease Inhibitor. Cell, 181(2), 271-280. DOI: 10.1016/j.cell.2020.02.052

264Honore, P. M., Barreto Gutierrez, L., Kugener, L., Redant, S., Attou, R., Gallerani, A., De Bels, D. 265(2020). Inhibiting IL-6 in COVID-19: we are not sure. Crit Care, 24(1), 463. DOI: 10.1186/s13054-266020-03177-x

267Hot, A., Lenief, V., Miossec, P. (2012). Combination of IL-17 and TNFalpha induces a pro-268inflammatory, pro-coagulant and pro-thrombotic phenotype in human endothelial cells. Ann Rheum 269Dis, 71(5), 768-776.DOI: 10.1136/annrheumdis-2011-200468

270Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., … Cao, B. (2020). Clinical features of 271patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 395(10223), 497-506. DOI: 27210.1016/S0140-6736(20)30183-5

273Hwang, S. Y., Kim, J. Y., Kim, K. W., Park, M. K., Moon, Y., Kim, W. U., Kim H. Y. (2004). IL-27417 induces production of IL-6 and IL-8 in rheumatoid arthritis synovial fibroblasts via NF- κ B- and 275PI3 kinase/Akt-dependent pathways. Arthritis Res. Ther, 6(2), R120–R128.DOI: 10.1186/ar1038

276Jovanovic, D. V., Di Battista, J. A., Martel-Pelletier, J., Jolicoeur, F. C., He, Y., Zhang, M., … 277Pelletier, J. P. (1998). IL-17 stimulates the production and expression of proinflammatory 278cytokines, IL-beta and TNF-alpha, by human macrophages. J. Immunol, 160(7), 3513-3521.PMID: 2799531313

280Kehlen, A., Pachnio, A., Thiele, K., Langner, J. (2003). Gene expression induced by interleukin-17 281in fibroblast-like synoviocytes of patients with rheumatoid arthritis:upregulation of hyaluronan-282binding protein TSG-6. Arthritis Res. Ther, 5(4), R186-R192. DOI: 10.1186/ar762

283Kehlen, A., Thiele, K., Riemann, D., Langner J. (2002). Expression, modulation and signaling of 284IL-17 receptor in fibroblast-like synoviocytes of patients with rheumatoid. Clin. Exp. Immunol, 285127, 539–546.DOI: 10.1046/j.1365-2249.2002.01782.x

286Leija-Martinez, J. J., Huang, F., Del-Rio-Navarro, B. E., Sanchez-Munoz, F., Munoz-Hernandez, 287O., Giacoman-Martinez, A., … Espinosa-Velazquez, D. (2020). IL-17A and TNF-alpha as potential 288biomarkers for acute respiratory distress syndrome and mortality in patients with obesity and 289COVID-19. Med Hypotheses, 144, 109935. DOI: 10.1016/j.mehy.2020.109935

290Ley, K., Smith, E., Stark, M. A. (2006). IL-17A-producing neutrophil-regulatory Tn lymphocytes. 291Immunol. Res, 34(3), 229-242. DOI: 10.1385/IR:34:3:229

292Lubberts, E. (2015). The IL-23-IL-17 axis in inflammatory arthritis. Nat. Rev. Rheumatol. 11, 415-293429. DOI: 10.1038/nrrheum.2015.53

294Mahesh, G., Anil Kumar, K., Reddanna, P. (2021). Overview on the Discovery and Development of 295Anti-Inflammatory Drugs: Should the Focus Be on Synthesis or Degradation of PGE(2)?. J. 296Inflamm. Res. 3(14), 253-263. DOI: 10.2147/JIR.S278514.

297Maione, F. (2016). Commentary: IL-17 in Chronic Inflammation: From Discovery to Targeting. 298Front Pharmacol, 7, 250. DOI: 10.3389/fphar.2016.00250

299Maione, F., Cicala, C., Liverani, E., Mascolo, N., Perretti, M., D'Acquisto, F. (2011). IL-17A 300Increases ADP-induced Platelet Aggregation. Biochem Biophys Res Commun, 408(4), 658-662. 301DOI: 10.1016/j.bbrc.2011.04.080

302Maione, F., Iqbal, A. J., Raucci, F., Letek, M., Bauer, M., D'Acquisto, F. (2018). Repetitive 303Exposure of IL-17 Into the Murine Air Pouch Favors the Recruitment of Inflammatory Monocytes 304and the Release of IL-16 and TREM-1 in the Inflammatory Fluids.Front. Immunol, 30. DOI: 30510.3389/fimmu.2018.02752

306Maione, F., Paschalidis, N., Mascolo, N., Dufton, N., Perretti, M., D'Acquisto, F. (2009). 307Interleukin 17 sustains rather than induces inflammation. Biochemical pharmacology, 77(5), 878-308887. DOI: 10.1016/j.bcp.2008.11.011

309Megna, M., Napolitano, M., Fabbrocini, G. (2020). May IL-17 have a role in COVID-19 infection? 310Med Hypotheses, 140, 109749. DOI: 10.1016/j.mehy.2020.109749

311Michot, J. M., Albiges, L., Chaput, N., Saada, V., Pommeret, F., Griscelli, F., … Stoclin, A. (2020). 312Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case 313report. Ann Oncol. 31(7), 961-964. DOI: 10.1016/j.annonc.2020.03.300

314Miossec, P., Kolls, J. K. (2012). Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev 315Drug Discov. 11(10),763-776. DOI: 10.1038/nrd3794.

316Moseley, T. A., Haudenschild, D. R., Rose, L., Reddi, A. H. (2003). Interleukin-17 family and IL-31717 receptors. Cytokine Growth Factor Rev, 14(2), 155-174.DOI: 10.1016/s1359-6101(03)00002-9

318Noack, M., Miossec P. (2014). Th17 and regulatory T cell balance in autoimmune and 319inflammatory diseases. Autoimmun Rev, 13(6), 668-677. DOI: 10.1016/j.autrev.2013.12.004.

320Orlov, M., Wander, P. L., Morrell, E. D., Mikacenic, C., Wurfel, M. M. (2020). A Case for 321Targeting Th17 Cells and IL-17A in SARS-CoV-2 Infections. Review J Immunol, 205(4), 892-898. 322DOI: 10.4049/jimmunol.2000554

323Pacha, O., Sallman, M. A., Evans, S. E. (2020). COVID-19: a case for inhibiting IL-17? Nat Rev 324Immunol, 20(6), 345-346. DOI: 10.1038/s41577-020-0328-z

325Pasrija, N., Naime, M. (2021). The deregulated immune reaction and cytokines release storm (CRS) 326in COVID-19 disease. Review Int Immunopharmacol, 90, 107225. DOI: 32710.1016/j.intimp.2020.107225

328Pedraza-Zamora, C. P., Delgado-Dominguez, J., Zamora-Chimal, J., Becker, I. (2017). Th17 cells 329and neutrophils: close collaborators in chronic Leishmania Mexicana infections leading to disease 330severity. Parasite Immunol, 39, e12420. DOI: 10.1111/pim.12420

331Quirch M., Lee, J., Rehman, S. (2020). Hazards of the Cytokine Storm and Cytokine-Targeted 332Therapy in Patients With COVID-19: Review. J Med Internet Res, 22(8), e20193. DOI: 33310.2196/20193

334Raucci, F., Mansour, A. A., Casillo, G. M., Saviano, A., Caso, F., Scarpa, R. … Maione, F. (2020). 335Interleukin-17A (IL-17A), a key molecule of innate and adaptive immunity, and its potential 336involvement in COVID-19-related thrombotic and vascular mechanisms. Review Autoimmun Rev, 33719(7), 102572. DOI: 10.1016/j.autrev.2020.102572

338Rivellese, F., Prediletto, E. (2020). ACE2 at the centre of COVID-19 from paucisymptomatic 339infections to severe pneumonia. Autoimmun Rev, 102536. DOI: 10.1016/j.autrev.2020.102536

340Rosas, O. I., Bräu, N., Waters, M., Go, C. R., Hunter, B. D., Bhagani, S., … Malhotra, A. (2021). 341Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 25, 3422028700. DOI: 10.1056/NEJMoa2028700.

343Schwarzenberger, P., La Russa, V., Miller, A., Ye, P., Huang, W., Zieske, A., … Kolls, J. K. 344(1998). IL-17 stimulates granulopoiesis in mice: use of an alternate, novel gene therapy-derived 345method for in vivo evaluation of cytokines. J. Immunol, 161(11), 6383-6389.PMID: 9834129

346Shoenfeld, Y. (2020). Corona (COVID-19) time musings: Our involvement in COVID-19 347pathogenesis, diagnosis, treatment and vaccine planning. Autoimmun Rev, 102538. DOI: 34810.1016/j.autrev.2020.102538

349The General Office of National Health Commission Office of State. (2020). TCM Administration. 350Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 6, Revised). 351http://www.kankyokansen.org/uploads/uploads/files/jsipc/protocol_V6.pdf.

352von Vietinghoff, S., Ley, K. (2008). Homeostatic regulation of blood neutrophil counts. J Immunol, 353181(8), 5183–5188. DOI: 10.4049/jimmunol.181.8.5183

354Wang, C. Q., Suarez-Farinas, M., Nograles, K. E., Mimoso, C. A., Shrom, D., Dow, E. R., … 355Krueger, J. G. (2014). IL-17 induces inflammation-associated gene products in blood monocytes, 356and treatment with ixekizumab reduces their expression in psoriasis patient blood. J Invest 357Dermatol, 134(12), 2990-2993. DOI: 10.1038/jid.2014.268

358Witowski, J., Pawlaczyk, K., Breborowicz, A., Scheuren, A., Kuzlan-Pawlaczyk, M., Wisniewska, 359J., ... Jörres, A. (2000). IL-17 stimulates intraperitoneal neutrophil infiltration through the release of 360GRO alpha chemokine from mesothelial cells. J Immunol, 165(10), 5814-5821. DOI: 36110.4049/jimmunol.165.10.5814

362Wojkowska, D. W., Szpakowski, P., Ksiazek-Winiarek D., Leszczynski, M., Glabinski, A. (2014). 363Interactions between neutrophils, Th17 cells, and chemokines during the initiation of experimental 364model of multiple sclerosis. Mediators Inflamm, 2014, 590409. DOI: 10.1155/2014/590409

365World Health Organization. (2021). WHO Coronavirus Disease (COVID-19) Dashboard. 366https://covid19.who.int/?
367gclid=Cj0KCQiA0MD_BRCTARIsADXoopaf2pY_Ar33GfkpEGYKvsFaiD2eYKVV4z1z6NVGA
368kcVfP8cpcXECCQaAhayEALw_wcB

369Wu D , Yang XO . Th17 responses in cytokine storm of COVID-19: an emerging target of JAK2 370inhibitor fedratinib. J Microbiol Immunol Infect 2020.doi:10.1016/j.jmii.2020.03.005

371Xu, S., Cao, X. (2010). Interleukin-17 and its expanding biological functions. Cell Mol Immunol, 3727(3), 164-174. DOI: 10.1038/cmi.2010.21

373Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., … Wang, F.S. (2020) Pathological 374findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med, 3758(4), 420-422. DOI: 10.1016/S2213-2600(20)30076-X.

376Yang, L., Anderson, D. E., Baecher-Allan, C., Hastings, W. D., Bettelli, E., Oukka, M., … Hafler, 377D. A. (2008). IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature, 378454(7202), 350-352. DOI: 10.1038/nature07021.

379Ye, Q., Wang, B., Mao, J. (2020). The pathogenesis and treatment of the `Cytokine Storm' in 380COVID-19. Review J Infect, 80(6), 607-613. DOI: 10.1016/j.jinf.2020.03.037

381Zhang, X., Song, K., Tong, F., Fei, M., Guo, H., Lu, Z., … Zheng. C. (2020). First case of COVID-38219 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv. 14(7), 3831307-1310. DOI: 10.1182/bloodadvances.2020001907.

384

385

386

387

388

389

Figure legends

Figure 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.

Figure 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).