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DOI:
10.1016/j.autrev.2020.102572

Document Version
Peer reviewed version

Citation for published version (Harvard):
Raucci, F, Mansour, AA, Casillo, GM, Saviano, A, Caso, F, Scarpa, R, Mascolo, N, Iqbal, AJ & Maione, F 2020, 'Interleukin-17A (IL-17A), a key molecule of innate and adaptive immunity, and its potential involvement in COVID-19-related thrombotic and vascular mechanisms', *Autoimmunity Reviews*.
https://doi.org/10.1016/j.autrev.2020.102572

Interleukin-17A (IL-17A), a key molecule of innate and adaptive immunity, and its potential involvement in COVID-19-related thrombotic and vascular mechanisms.

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Keywords: COVID-19, IL-17A, platelet, thrombus, vascular diseases.

Abbreviations: COVID-19, Coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; EC, endothelial cells; ERK-2, extracellular signal regulated kinase-2; HUVECs, human umbilical vein endothelial cells; IL-, interleukin-; IVIG, intravenous immunoglobulin; LMWH, low molecular weight heparin; SARS, severe acute respiratory syndrome; SEPSIS-3, Third International Consensus Definitions for Sepsis; TF, tissue factor; Th-, T-helper; TNF-α, tumor necrosis factor-α; WHO, World Health Organization.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome (SARS) which first appeared in Wuhan, China, December 2019, and has since spread globally [1]. To date, official figures released by World Health Organization (WHO), indicate over 3 million cases worldwide with over 200,000 deaths. However, the number of newly diagnosed patients has started to decline, suggesting that the rate of transmission is beginning to be controlled by countries [2]. Although most patients have mild symptoms and good prognosis after infection, some develop severe symptoms and die due to multiple organ failure [3,4,5]. Based on the published literature and clinical observations, researchers and clinicians around the world have postulated about the pathogenesis of this viral infection in humans. We know that the virus has the capacity to cross mucous membranes (especially nasal and larynx mucosa), and in severe cases leads to multiple systemic manifestations and pneumonia requiring mechanical ventilation [6].

Interestingly, COVID-19 disease prognosis is strongly correlated to clinical characteristics of patients, with high risk associated to those with a concomitance of cardiovascular risk factors, primarily obesity, hypertension, and diabetes mellitus [4,7]. In the context of COVID-19-associated cardiovascular manifestations, more recent studies report that the disease is commonly complicated with coagulopathy linked to disseminated intravascular coagulation (DIC) and/or thrombotic and thromboembolic disease [4,8,9]. For these reasons, many patients with severe COVID-19 meet the Third International Consensus Definitions for Sepsis (SEPSIS-3) [10].

Moreover, we must consider that the development of thrombotic and thromboembolic disease could be a direct consequence of the systemic inflammatory process related to interleukin (IL)-6 and IL-17A up-regulation [11,12,13,14]. This clinical scenario has prompted the use of intravenous immunoglobulin (IVIG) and low molecular weight heparin (LMWH) anticoagulant therapy as early as possible, particularly when circulating T and B cells numbers decrease, and inflammatory

cytokines and D-Dimer (a non-specific parameter of thrombi formation) increase abnormally [15,16,17]. While IVIG has shown efficacy in the treatment of patients with influenza and SARS, more clinical data is required, for both IVIG and LMWH, to confirm significant efficacy in COVID-19 patients [18,19,20].

IL-17A and COVID-19-related thrombotic and vascular mechanisms

Viral infection and subsequent systemic and/or local inflammation is a common cause of DIC [21,22,23] due to increased synthesis of cytokines such as as tumor necrosis factor-α (TNF-α), IL-1β, IL-6, IL-17A and IL-18 [24].

IL-17A (commonly known as IL-17) is the most studied member of the IL-17 cytokine family. It is produced by T-helper (Th)-17 lymphocytes, and by innate cellular components [25,26]. This "unique" pro-inflammatory cytokine, highly produced and modulated in patients with chronic inflammatory-based diseases, also plays a role in the cardiovascular system, and more specifically, it is involved in the cardiovascular complications associated to autoimmune and inflammatory-based diseases [27].

Indeed, in the attempt to find a link between inflammatory markers and endothelial dysfunction, Marder *et al.,* [28] demonstrated that elevated IL-17A levels strongly correlated with vascular dysfunction in subjects affected by rheumatoid arthritis. Furthermore, it has been shown that, human umbilical vein endothelial cells (HUVECs), treated with IL-17A, synergistically with TNF-α, induces tissue factor (TF) expression and modulates thrombomodulin [29] and thrombosis formation [30, 31].

In addition to IL-17A role on the vascular endothelium, data, from our research group and others has also highlighted a role for this cytokine in platelet biology. We previously reported IL-17A ability to increase, in both mouse and human, platelet activation [32] and to modulate, *in vivo*,

arterial thrombus formation [33] through the extracellular signal-regulated kinase-2 (ERK-2) signaling pathway [34]. Moreover a study from Ding *et al.,* [35] investigated the role of IL-17A in mouse and human deep vein thrombosis (DVT) formation, and found that this cytokine promotes DVT pathogenesis by enhancing platelet activation/aggregation, neutrophil infiltration, and endothelial cell (EC) activation. Collectively, these data suggest that the use of an anti-IL-17A monoclonal antibody may be useful for DVT-related syndromes.

Discussion

Taken together all these various pieces of evidence (albeit minimal) we have, we would like to hypothesize that in COVID-19 patients, IL-17A could potentially promote a pro-thrombotic state in the vascular system. Indeed, the increasing level of this cytokine related to COVID-19 infection would not be, *per se*, a stimulus for thrombogenesis but, most likely, enhance platelet aggregates at sites of vascular injury (**Figure 1**). Based on these assumptions, it would be fascinating to characterize IL-17 levels in bronchoalveolar lavage fluid (BALF) and plasma/serum samples) of mild- and severe-infected COVID-19 patients, and potentially go on to test the efficacy of antibodies targeting IL-17A (alone or in a sequential therapy with anti-IL-6 agents) for the treatment of thrombotic, as well respiratory and systemic manifestations of severe COVID-19. These could be useful not only for new therapeutic strategies but also for improving our understanding of the etiopathogenesis and genetic susceptibility of COVID-19 infection.

Conflict of interest

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.

Author contributions

FR, AAM, GMC and AS drafted the manuscript. FC, RS, NM, AJI and FM wrote and revised the manuscript. All Authors gave final approval to the publication.

Acknowledgments

This work was in part supported by MIUR (PRIN 2017; 2017A95NCJ/2017A95NCJ_002, “Stolen molecules - Stealing natural products from the depot and reselling them as new drug candidates”). AJI is supported by Birmingham Fellowship and AAM by a Saudi Government/KKU scholarship.

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Figure 1: Schematic representation of inflammatory pathways (left part) involved in the COVID-19-related respiratory syndrome. The inflammatory scenario induced by COVID-19 has cardiovascular implications (right part, top panel) in terms of Th-1/Th-17/T-reg balance that favors the production of IL-17A. The overproduction of this cytokine (right part, bottom panel) amplifies platelet hyper-reactivity and thrombus formation.