

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

Raucci, Federica; Mansour, Adel Abo; Casillo, Gian Marco; Saviano, Anella; Caso, Francesco; Scarpa, Raffaele; Mascolo, Nicola; Iqbal, Asif Jilani; Maione, Francesco

DOI:

[10.1016/j.autrev.2020.102572](https://doi.org/10.1016/j.autrev.2020.102572)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

*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>

[Link to publication on Research at Birmingham portal](#)

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

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

3 Federica Raucci<sup>1,#</sup>, Adel Abo Mansour<sup>2,3,#</sup>, Gian Marco Casillo<sup>1</sup>, Anella Saviano<sup>1</sup>, Francesco Caso<sup>4</sup>,  
4 Raffaele Scarpa<sup>4</sup>, Nicola Mascolo<sup>1</sup>, Asif Jilani Iqbal<sup>2,1,\*</sup> and Francesco Maione<sup>1,\*</sup>.

5

6 <sup>1</sup>ImmunoPharmaLab, Department of Pharmacy, School of Medicine and Surgery, University of  
7 Naples Federico II, Via Domenico Montesano 49, 80131, Naples, Italy.

8 <sup>2</sup>Institute of Cardiovascular Sciences (ICVS), College of Medical and Dental Sciences, University  
9 of Birmingham, Birmingham, B15 2TT, UK.

10 <sup>3</sup>Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Khalid  
11 University, Guraiger, Abha 62529, Saudi Arabia.

12 <sup>4</sup>Rheumatology Research Unit, Department of Clinical Medicine and Surgery, University of Naples  
13 Federico II, via S. Pansini 5, 80131 Naples, Italy.

14

15 <sup>#</sup>These authors share first co-authorship

16

17 **\*Author for correspondence: Asif J Iqbal**, Institute of Cardiovascular Sciences (ICVS), College  
18 of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK. E-mail:  
19 A.J.Iqbal@bham.ac.uk; **Francesco Maione**, ImmunoPharmaLab, Department of Pharmacy, School  
20 of Medicine and Surgery, University of Naples Federico II, Via Domenico Montesano 49, 80131,  
21 Naples, Italy. Phone: (+39)081678429. E-mail: francesco.maione@unina.it

22

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

24

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

31

32

33

34

35

36

37

38

39

40

41

42

43

## 44 **Introduction**

45 Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory  
46 syndrome (SARS) which first appeared in Wuhan, China, December 2019, and has since spread  
47 globally [1]. To date, official figures released by World Health Organization (WHO), indicate over  
48 3 million cases worldwide with over 200,000 deaths. However, the number of newly diagnosed  
49 patients has started to decline, suggesting that the rate of transmission is beginning to be controlled  
50 by countries [2]. Although most patients have mild symptoms and good prognosis after infection,  
51 some develop severe symptoms and die due to multiple organ failure [3,4,5]. Based on the  
52 published literature and clinical observations, researchers and clinicians around the world have  
53 postulated about the pathogenesis of this viral infection in humans. We know that the virus has the  
54 capacity to cross mucous membranes (especially nasal and larynx mucosa), and in severe cases  
55 leads to multiple systemic manifestations and pneumonia requiring mechanical ventilation [6].

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

63 Moreover, we must consider that the development of thrombotic and thromboembolic disease could  
64 be a direct consequence of the systemic inflammatory process related to interleukin (IL)-6 and IL-  
65 17A up-regulation [11,12,13,14]. This clinical scenario has prompted the use of intravenous  
66 immunoglobulin (IVIG) and low molecular weight heparin (LMWH) anticoagulant therapy as early  
67 as possible, particularly when circulating T and B cells numbers decrease, and inflammatory

68 cytokines and D-Dimer (a non-specific parameter of thrombi formation) increase abnormally  
69 [15,16,17]. While IVIG has shown efficacy in the treatment of patients with influenza and SARS,  
70 more clinical data is required, for both IVIG and LMWH, to confirm significant efficacy in  
71 COVID-19 patients [18,19,20].

72

### 73 **IL-17A and COVID-19-related thrombotic and vascular mechanisms**

74 Viral infection and subsequent systemic and/or local inflammation is a common cause of DIC  
75 [21,22,23] due to increased synthesis of cytokines such as as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-  
76 1 $\beta$ , IL-6, IL-17A and IL-18 [24].

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

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

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

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

98

## 99 **Discussion**

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

111

112

113

114

115 **Conflict of interest**

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

118

119 **Author contributions**

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

122

123 **Acknowledgments**

124 This work was in part supported by MIUR (PRIN 2017; 2017A95NCJ/2017A95NCJ\_002, “Stolen  
125 molecules - Stealing natural products from the depot and reselling them as new drug candidates”).  
126 AJI is supported by Birmingham Fellowship and AAM by a Saudi Government/KKU scholarship.

127

128

129

130

131

132

133

134

135

136 **References**

- 137 [1] Runfeng L, Yunlong H, Jicheng H, Weiqi P, Qin Hai M, Yongxia S, et al. Exerts Anti-Viral and  
138 Anti-Inflammatory Activity Against Novel Coronavirus (SARS-CoV-2). *Pharmacol Res* 2020;  
139 104761. <https://doi.org/10.1016/j.phrs.2020.104761>
- 140 [2] World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 73,  
141 [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-19.pdf?sfvrsn=5ae25bc7_4; 2020)  
142 [19.pdf?sfvrsn=5ae25bc7\\_4; 2020](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-19.pdf?sfvrsn=5ae25bc7_4; 2020) [Accessed 14 April 2020]
- 143 [3] Peng X, Xu X, Li Y, Cheng L, Zhou X, Ren B. Transmission Routes of 2019-nCoV and  
144 Controls in Dental Practice. *Int J Oral Sci* 2020; 12. [https://dx.doi.org/10.1038%2Fs41368-020-](https://dx.doi.org/10.1038%2Fs41368-020-0075-9)  
145 [0075-9](https://dx.doi.org/10.1038%2Fs41368-020-0075-9)
- 146 [4] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and Clinical  
147 Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive  
148 Study. *Lancet* 2020; 395:507-13. [https://doi.org/10.1016/s0140-6736\(20\)30211-7](https://doi.org/10.1016/s0140-6736(20)30211-7)
- 149 [5] Shoenfeld Y. Corona (COVID-19) time musings: Our involvement in COVID-19 pathogenesis,  
150 diagnosis, treatment and vaccine planning. *Autoimmun Rev* 2020; 102538.  
151 <https://doi.org/10.1016/j.autrev.2020.102538>
- 152 [6] Rivellesse F, Prediletto E. ACE2 at the centre of COVID-19 from paucisymptomatic infections to  
153 severe pneumonia. *Autoimmun Rev* 2020; 102536. <https://doi.org/10.1016/j.autrev.2020.102536>
- 154 [7] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of  
155 adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;  
156 395(10229):1054-62. [https://doi.org/10.1016/s0140-6736\(20\)30566-3](https://doi.org/10.1016/s0140-6736(20)30566-3) Epub 2020 Mar 11. Erratum  
157 in: *Lancet*. 2020 Mar 28;395(10229):1038. *Lancet*. 2020 Mar 28;395(10229):1038



- 158 [8] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with  
159 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395(10223):497-506.  
160 [https://doi.org/10.1016/s0140-6736\(20\)30183-5](https://doi.org/10.1016/s0140-6736(20)30183-5)
- 161 [9] Tang N, Li D, Wang X, Sun Z. Abnormal Coagulation parameters are associated with poor  
162 prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020; 18(4):844-47.  
163 <https://doi.org/10.1111/jth.14768>
- 164 [10] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The  
165 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;  
166 315(8):801–10. <https://doi.org/10.1001/jama.2016.0287>
- 167 [11] Caso F, Costa L, Ruscitti P, Navarini L, Del Puente A, Giacomelli R, et al. Could Sars-  
168 coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed  
169 subjects? *Autoimmun Rev* 2020; 19(5):102524. <https://doi.org/10.1016/j.autrev.2020.102524>
- 170 [12] McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including  
171 Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like  
172 Disease. *Autoimmun Rev* 2020; 102537. <https://doi.org/10.1016/j.autrev.2020.102537>
- 173 [13] Feng Y, Yu M, Zhu F, Zhang S, Ding P, Wang M. IL-9 Promotes the Development of Deep  
174 Venous Thrombosis by Facilitating Platelet Function. *Thromb Haemost* 2018; 118(11):1885-94.  
175 <https://doi.org/10.1055/s-0038-1673614>
- 176 [14] Casillo GM, Mansour AA, Raucci F, Saviano A, Mascolo N, Iqbal AJ, et al. Could IL-17  
177 represent a new therapeutic target for the treatment and/or management of COVID-19-related  
178 respiratory syndrome? This paper is dedicated to Sofia Maione born during COVID-19 outbreak.  
179 *Pharmacol Res* 2020; 104791. <https://doi.org/10.1016/j.phrs.2020.104791>

- 180 [15] Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, et al. The  
181 procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb*  
182 *Haemost* 2020. <https://doi.org/10.1111/jth.14854>
- 183 [16] Alger HM, Williams Iv JH, Walchok JG, Bolles MM, Fonarow GC, Rutan C. The Role of Data  
184 Registries in the Time of COVID-19. *Circ Cardiovasc Qual. Outcomes* 2020.  
185 <https://doi.org/10.1161/circoutcomes.120.006766>
- 186 [17] Atri D, Siddiqi HK, Lang J, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the  
187 Cardiologist: A Current Review of the Virology, Clinical Epidemiology, Cardiac and Other Clinical  
188 Manifestations and Potential Therapeutic Strategies. *JACC Basic Transl Sci* 2020.  
189 <https://doi.org/10.1016/j.jacbts.2020.04.002>
- 190 [18] Thachil J. The versatile heparin in COVID-19. *J Thromb Haemost* 2020.  
191 <https://doi.org/10.1111/jth.14821>
- 192 [19] Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al.  
193 Hematological findings and complications of COVID-19. *Am J Hematol* 2020.  
194 <https://doi.org/10.1002/ajh.25829>
- 195 [20] Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia  
196 induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis* 2020.  
197 <https://doi.org/10.1007/s11239-020-02105-8>
- 198 [21] Samad F, Ruf W. Inflammation, obesity, and thrombosis. *Blood* 2013; 122(20):3415-22.  
199 <https://doi.org/10.1182/blood-2013-05-427708>
- 200 [22] Morrell CN, Aggrey AA, Chapman LM, Modjeski KL. Emerging roles for platelets as immune  
201 and inflammatory cells. *Blood* 2014; 123(18):2759-67. <https://dx.doi.org/10.1182%2Fblood-2013->  
202 11-462432

- 203 [23] Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of  
204 therapeutically targeting coagulation and other host defense mechanisms. *Blood* 2019; 133 (9), 906-  
205 918. <https://doi.org/10.1182/blood-2018-11-882993>
- 206 [24] Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular  
207 pathophysiology of autoinflammatory disease (\*). *Annu Rev Immunol* 2009; 27:621-68.  
208 <https://dx.doi.org/10.1146%2Fannurev.immunol.25.022106.141627>
- 209 [25] D'Acquisto F, Maione F, Pederzoli-Ribeil M. From IL-15 to IL-33: the never-ending list of  
210 new players in inflammation. Is it time to forget the humble aspirin and move ahead? *Biochemical*  
211 *Pharmacology* 2010; 79(4):525-34. <https://doi.org/10.1016/j.bcp.2009.09.015>
- 212 [26] Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family  
213 members. *Immunity* 2011; 34(2):149-62. <https://doi.org/10.1016/j.immuni.2011.02.012>
- 214 [27] Maione F. Commentary: IL-17 in Chronic Inflammation: From Discovery to Targeting. *Front*  
215 *Pharmacol* 2016; 7:250. <https://doi.org/10.3389/fphar.2016.00250>
- 216 [28] Marde W, Khalatbari S, Myles JD, Hench R, Yalavarthi S, Lustig S, et al. 17 as a novel  
217 predictor of vascular function in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 2011;  
218 70(9):1550-5. <https://dx.doi.org/10.1136%2Fard.2010.148031>
- 219 [29] Hot A, Lenief V, Miossec P. Combination of IL-17 and TNF $\alpha$  induces a pro-inflammatory,  
220 pro-coagulant and pro-thrombotic phenotype in human endothelial cells. *Annals of the Rheumatic*  
221 *Diseases* 2012; 71(5):768-76. <https://doi.org/10.1136/annrheumdis-2011-200468>
- 222 [30] Bouchnita A, Miossec P, Tosenberger A, Volpert V. Modeling of the effects of IL-17 and  
223 TNF- $\alpha$  on endothelial cells and thrombus growth. *C. R. Biol* 2017; 340(11-12):456-73.  
224 <https://doi.org/10.1016/j.crvi.2017.10.002>
- 225 [31] de Boer OJ, Li X, Teeling P, Mackaay C, Ploegmakers HJ, van der Loos CM, et al.  
226 Neutrophils, neutrophil extracellular traps and interleukin-17 associate with the organisation of

227 thrombi in acute myocardial infarction. *Thromb Haemost* 2013; 109(2):290-97.  
228 <https://doi.org/10.1160/th12-06-0425>

229 [32] Maione F, Cicala C, Liverani E, Mascolo N, Perretti M, D'Acquisto F. IL-17A increases ADP-  
230 induced platelet aggregation. *Biochem Biophys Res Commun* 2011; 408(4):658-62.  
231 <https://doi.org/10.1016/j.bbrc.2011.04.080>

232 [33] Maione F, Parisi A, Caiazzo E, Morello S, D'Acquisto F, Mascolo N, et al. Interleukin-17A  
233 Exacerbates Ferric Chloride-Induced Arterial Thrombosis in Rat Carotid Artery. *Int J Inflamm* 2014  
234 <https://doi.org/10.1155/2014/247503>

235 [34] Zhang S, Yuan J, Yu M, Fan H, Guo ZQ, Yang R, et al. IL-17A facilitates platelet function  
236 through the ERK2 signaling pathway in patients with acute coronary syndrome. *PLoS One* 2012;  
237 7(7):e40641. <https://doi.org/10.1371/journal.pone.0040641>

238 [35] Ding P, Zhang S, Yu M, Feng Y, Long Q, Yang H, et al. IL-17A promotes the formation of  
239 deep vein thrombosis in a mouse model. *Int Immunopharmacol* 2018; 57:132-38.  
240 <https://doi.org/10.1016/j.intimp.2018.02.006>

241

242

243

244

245

246

247

248 **Figure 1:** Schematic representation of inflammatory pathways (left part) involved in the COVID-  
249 19-related respiratory syndrome. The inflammatory scenario induced by COVID-19 has  
250 cardiovascular implications (right part, top panel) in terms of Th-1/Th-17/T-reg balance that favors  
251 the production of IL-17A. The overproduction of this cytokine (right part, bottom panel) amplifies  
252 platelet hyper-reactivity and thrombus formation.