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Ac2-26 mimetic peptide of annexin A1 to treat severe COVID-19: A hypothesis

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ABSTRACT

The Coronavirus Diseases-2019 (COVID-19) pandemic leads many researchers around the world to study the SARS-CoV-2 infection and pathology to find a treatment for it. This generates a massive production of papers including pre-clinical, clinical and revisions but till now no specific treatment were identified. Meanwhile, like other coronavirus infections, COVID-19 leads to the cytokine storm syndrome resulting in hyperinflammation, exacerbated immune response and multiple organ dysfunctions indicating that drugs that modulate this response, as glucocorticoids could be a treatment option. However glucocorticoids have several side effects or usage limitations. In this sense a drug with anti-inflammatory effects and capable to reduce inflammation but with less after-effects could be a powerful tool to combat COVID-19. Thus the Ac2-26 Mimetic Peptide of Annexin A1 emerges as a possible therapy. The peptide has many anti-inflammatory effects described including the reduction of interleukin (IL)-6, one of the main mediators of cytokine storm syndrome. Therefore the hypothesis to use the Ac2-26 peptide to treat severe COVID-19 will be highlighted in this paper.

Introduction

The COVID-19 caused more than 1 million deaths worldwide being a important health problem [1]. This drove many research groups to better understand the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) biology and pathology to offer new insights for treatments and development of new therapies. Besides a lot of the patients have a good prognosis there are still some individuals that evolve to severe disease and even death [2]. Death seems to be related with the acute respiratory distress syndrome (ARDS) and multiple-organ failure (MOF) as a consequence of the cytokine storm syndrome (CSS) which was detected in several critical patients with COVID-19 [3,4]. Zhou and colleagues showed that IL-6 and inflammation are increased in critical patients with COVID-19 [5]. The higher levels of IL-6 seems fundamental to the disease aggravation and development of ARDS and MOF [6]. Hence, drugs that can control inflammation and IL-6 secretion could be a relevant tool to reduce COVID-19 severity and associated deaths [7,8]. It was observed that treatment for 10 days with the steroid anti-inflammatory dexamethasone was able to reduce death in patients with severe condition [8]. However it is well know that glucocorticoids have many side effects [9] including the immunosuppressive action that could potentially lead to increase of plasma viral load. It is well described that many anti-inflammatory effects of glucocorticoids are mediated by Annexin-A1 (ANXA1) protein witch act by activation of formyl peptide receptors (FPR) family [10]. The anti-inflammatory effects of ANXA1 can be mimic by its N-terminal domain with 26 amino acid termed Ac2-26 peptide [11]. Herein is presented the many effects of Ac2-26 peptide that support the use of it to treat severe COVID-19.

The hypothesis

During the acute inflammatory response several pro-inflammatory mediators are produced as well the endogenous anti-inflammatory and pro-resolving mediators [12,13]. These anti-inflammatory mediators act regulating the inflammation by reducing cell migration, edema, cytokine production as well promoting inflammatory cells apoptosis [14]. One of the anti-inflammatory mediators is a protein regulated by glucocorticoid named annexin-A1 (ANXA1), previously lipocortin-1 [15,16]. ANXA1 is a member a family of proteins that binds to membrane phospholipids resulting in inhibition of phospholipase A2 and eicosanoids production [11]. In many studies the anti-inflammatory effects of ANXA1 was reproduced by it N-terminal region of 26 amino acids termed Ac2-26 [10,17]. This peptide exerts its effects by activation of the formyl peptide receptor type 1 (FPR1) and type 2 (FPR2) [18,19]. The anti-inflammatory effects of Ac2-26 were observed in many experimental models where inflammation is an important component including allergic conjunctivitis [20], skin allograft survival [21], brain sepsis [22], experimental pneumococcal pneumonia [23], lung injury after ischemia–reperfusion [24], chronic obstructive pulmonary disease [25], allergic asthma and inflammation [26,27] and pain [28]. Table 1

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summarizes the anti-inflammatory effects described for the Ac2-26 peptide.

In vitro studies demonstrated that Ac2-26, a mimetic peptide of the full length ANXA1 protein, has anti-inflammatory effects described in several models of inflammation and disease. So it could reduce cytokine storm syndrome particularly in severe COVID-19. The peptide would be a promising treatment for patients with severe respiratory symptoms and multiple organ. Additional pre-clinical and initial clinical research must be conducted to define the efficacy and safety of the Ac2-26 peptide for the SARS-CoV-2 infection.

| Inflammatory component | Main result observed | References |
|------------------------|----------------------|------------|
| Neutrophil             | Inhibition of neutrophil migration and adhesion, increased L-selectin shedding, reduction of myeloperoxidase activity and induction of apoptosis | [17,20,25,27–35] |
| IL-6                   | Reduce production and signaling | [30,32,36,37] |
| IL-1β                  | Reduce production and effects on neutrophil migration | [28,32,36,38,39] |
| IL-8                   | Reduce production | [29,31] |
| Interferon-γ            | Reduce production | [36,40] |
| TNF-α                  | Reduce production and intracellular activated pathways | [28–30,36,41,42] |
| MCP-1 and MIP-1α        | Reduce production | [28,42] |
| Mast cell activation    | Reduce cell degranulation and release of histamine | [27] |
| Edema                  | Reduce exudate | [27,29] |
| Pain                   | Reduce pain response | [28,38] |
| NFκB                   | Reduce NFκB activation/translocation | [29,31] |
| ROS                    | Blocks NAPDH oxidase activity induced by TNF-α | [41] |

**Conclusion**

Ac2-26, a mimetic peptide of the full length ANXA1 protein, has anti-inflammatory effects described in several models of inflammation and disease. So it could reduce cytokine storm syndrome particularly in severe COVID-19. The peptide would be a promising treatment for patients with severe respiratory symptoms and multiple organ. Additional pre-clinical and initial clinical research must be conducted to define the efficacy and safety of the Ac2-26 peptide for the SARS-CoV-2 infection.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
[52] Pal R, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. Diabetes Metab Syndr Clin Res Rev 2020. https://doi.org/10.1016/j.dsx.2020.04.049.

[53] Zhang L, Zheng Y lei, Hu R hua, Zhu L, Hu C chen, Cheng F, et al. Annexin A1 Mimetic Peptide AC2-26 Inhibits Sepsis-induced Cardiomyocyte Apoptosis through LXA4/PI3K/akt Signaling Pathway. Curr Med Sci 2018. doi: 10.1007/s11596-018-1975-1.

[54] Babapoor-Farrokhran S, Gill D, Walker J, Rasekh R, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: Possible mechanisms. Life Sci 2020. https://doi.org/10.1016/j.lfs.2020.117723.

[55] Qin C, Yang YH, Wu L, Gao X, Stewart AG, Tu Y, et al. Cardioprotective potential of annexin-A1 mimetics in myocardial infarction. Pharmacol Ther 2015;148:47–65. https://doi.org/10.1016/j.pharmthera.2014.11.012.

[56] Adapa S, Aeddula NR, Konala VM, Chenna A, Narasala S, Madhira RR, et al. COVID-19 and renal failure: challenges in the delivery of renal replacement therapy. J Clin Med Res 2020.

[57] Araujo LP, Truzzi RR, Mendes GE, Burdmann EA, Oliani SM. Interaction of the anti-inflammatory annexin A1 protein and tacrolimus immunosuppressant in the renal function of rats. Am J Nephrol 2010. https://doi.org/10.1159/000339756.

[58] Araujo LP, Truzzi RR, Mendes GE, Burdmann EA, Oliani SM. Annexin A1 protein attenuates cyclosporine-induced renal hemodynamics changes and macrophage infiltration in rats. Inflamm Res 2012. https://doi.org/10.1007/s00011-011-0400-z.

[59] Facio FJ, Sena AA, Araújo IP, Mendes GE, Castro I, Luz MAM, et al. Annexin A1 mimetic peptide protects against renal ischemia/reperfusion injury in rats. J Mol Med (Berl) 2011;89:51–63. https://doi.org/10.1007/s00109-010-0666-6.

[60] Martín-Rojas RM, Pérez-Ruiz G, Delgado-Pinos VE, Domínguez-González A, Regalado-Artamendi I, Alba-Urdiales N, et al. COVID-19 coagulopathy: an in-depth analysis of the coagulation system. Eur J Haematol 2020. https://doi.org/10.1111/ejh.13501.

[61] Kusters DHM, Chatrou ML, Willems RAG, De Saint-Hubert M, Bawens M, van der Voet E, et al. Pharmacological treatment with annexin A1 reduces atherosclerotic plaque burden in LDLR-/− mice on western type diet. PLoS ONE 2015;10:e0130484 https://doi.org/10.1371/journal.pone.0130484.

[62] Senchenkova EY, Ansari J, Becker F, Vital SA, Al-Yafei Z, Sparkenbaugh EM, et al. Novel role for the AnxA1-Fpr2/ALX signaling axis as a key regulator of platelet function to promote resolution of inflammation. Circulation 2019;140:319–35. https://doi.org/10.1161/CIRCULATIONAHA.118.039455.

[63] Schlör S, Hübner N, Masemann D, Pajonczyk D, Brunotte L, Ehhardt C, et al. The annexin A1/FPR2 signaling axis expands alveolar macrophages, limits viral replication, and attenuates pathogenesis in the murine influenza A virus infection model. FASEB J Off Publ Fed Am Soc Exp Biol 2019;33:12188–99. https://doi.org/10.1096/fj.201901265R.

[64] Ampomah PB, Kong WT, Zharkova O, Chua SCJH, Samy RP, Lim LHK. Annexins in influenza virus replication and pathogenesis. Front Pharmacol 2018. https://doi.org/10.3389/fphar.2018.01282.