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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-s2 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 heath 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 it 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 it 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 conjuntivits [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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Table 1
Summary of the anti-inflammatory effects of Ac2-26 peptide.

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	[17,20,25,27,29–35]
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]
NFkB	Reduce NFkB activation/translocation	[29,31]
ROS	Blocks NADPH oxidase activity induced by TNF-α	[41]

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

In this moment evidence suggests that host immune response contributes to the severity of COVID-19 as well the higher admissions at intensive care unit (ICU) and mortality [43–45]. In the severe cases of infected patients it was observed an increased plasma concentration of many pro-inflammatory cytokines as TNF-α IL-6, IL-8, G-CSF, MCP-1, IP-10, MIP-1α characterizing the CSS and the consequent hyperinflammation and MOF [45]. Recent works suggested that drugs as glucocorticoid, anti-IL-6 antibody (Tocilizumab), IL-1β antagonist (Anakinra) could modulate this extreme host reaction resulting in a better prognostic for severe COVID-19 patients [46]. Recently the RECOVERY trial from the Oxford University showed that treatment with 6 mg of dexamethasone for 10 days reduce the mortality of patients with the severe form of COVID-19 [8]. This result was highly associated the presence of lung inflammation. The use of glucocorticoids was previously suggested to others lung infections (e.g. MERS, SARS, severe influenza and community-acquired pneumonia) however the lack of randomized/controlled trials and the heterogeneity of doses or medical conditions discourage it use [47–50]. Moreover glucocorticoid is not indicated in patients with comorbidities like Cushing syndrome or noncompensate diabetes mellitus [51,52]. In this way a drug with similar anti-inflammatory profile but lacking the side effects could be a tool to treat these patients.

As mentioned above, the ANXA1 derived peptide Ac2-26 share many anti-inflammatory effects of the glucocorticoids including the inhibition of several cytokines production (see Table 1). These effects were observed in different pre-clinical models using *in vitro* and *in vivo* experiments. The potent inhibitory effect of Ac2-26 over inflammation indicates that the ANXA1-derived peptide could be relevant to reduce the COVID-19 severity and associated deaths. The increased levels of IL-6 and others mediators of inflammation like IL-1β, TNF-α triggers the so called cytokine storm syndrome which is closely related with the COVID-19 evolution and seems responsible for 28% of the deaths [3,6]. The cytokine storm promotes an uncontrolled inflammation with directly lung failure and it inflicts multi-organ damage failure, mostly in cardiac, hepatic and renal systems. *In vitro* and *in vivo* studies demonstrated that Ac2-26 peptide was able to reduce inflammation and enrolled mediators in many models where inflammation is relevant and then it was suggested to treat several diseases as allergy, cancer, stroke, sepsis or ischemia [11,24,53]. In lungs, Ac2-26 showed protective effects in by reducing inflammation in different conditions [24,25,29,42] suggesting it could have an important paper during COVID-19 treatment. The myocardium damage is also present in patients with severe COVID-19 [54]. In this tissue the Ac2-26 showed a protective effect after ischemia–reperfusion injury [55]. Acute kidney injury rate to 50% of patients in severe COVID-19 being a risk factor for mortality [56]. A work showed that annexin-A1 N-terminal derived-peptide can protect renal tissue against *Bothrops moojeni* Venom-induced inflammation in rats [32]. Complementary, Ac2-26 showed renal protection against drug-associated inflammation (e.g. tacrolimus or cyclopsporin) or in model of ischemia–reperfusion [57–59]. Taking together these findings suggest that Ac2-26 could have a relevant protective action on hyperinflammation-driven MOF during COVID-19 and probably reducing severity and death.

Other point to mention is that during COVID-16 occurs coagulopathy with increased venous coagulation [60]. Besides there are no evidence of direct action of Ac2-26 on platelet aggregation there are two papers that presented effects of ANXA1 on coagulation. The first work of Kuster and colleagues observed an anti-plaque effect of human-recombinant ANXA1 in mice with atherosclerosis [61]. The second described a novel role for ANXA1, the ability to activate anti-thrombo-inflammatory circuits in cerebral during ischemia–reperfusion [62]. Since many the effects of ANXA1 are mediated by the interaction of it N-terminal domain with the FPR family, probably the Ac2-26 mimetic peptide would have similar effects on coagulation and a bonus effect in COVID-19 treatment.

Finally there are a few works with the actions of the full length ANXA1 protein in influenza infections. Schloer et al observed that ANXA1 was able to expand the number of alveolar macrophages by activating the FPR2 receptor resulting in a protective effect against influenza A infection. This protection was associated with significantly increased survival, impaired viral replication in the respiratory tract and finally a reduction of lungs damage [63]. However in a recent paper was suggested that annexin-A1 facilitate influenza infection [64]. More studies are needed to better understand the real participation of ANXA1 and it N-terminal-derived peptide on virus infection and the importance of it during the timeline of virus-based diseases especially in coronavirus diseases.

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.

References

[1] Who. No Title. Https://Covid19WhoInt/ 2020. https://covid19.who.int/.
[2] Chih Cheng L, Tzu Ping S, Wen Chien K, Hung Jen T, Po RH. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020.
[3] Mahmudpour M, Roozbeh J, Keshavarz M, Farrokhi S, Nabipour I. COVID-19 cytokine storm: the anger of inflammation. Cytokine 2020. https://doi.org/10.1016/j.cyto.2020.155151.
[4] Ruscitti P, Berardicurti O, Iagnocco A, Giacomelli R. Cytokine storm syndrome in severe COVID-19. Autoimmun Rev 2020. https://doi.org/10.1016/j.autrev.2020.102562.
[5] Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. Natl Sci Rev 2020. https://doi.org/10.1093/nsr/nwaa041.
[6] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020;20:363–74. https://doi.org/10.1038/s41577-020-0311-8.
[7] Strohbehn GW, Heiss BL, Rouhani SJ, Trujillo JA, Yu J, Kacew AJ, et al. COVIDOSE: Low-dose tocilizumab in the treatment of Covid-19. MedRxiv Prepr Serv Heal Sci 2020. https://doi.org/10.1101/2020.07.20.20157503.
[8] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19 – preliminary report. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2021436.
[9] Longui CA. Glucocorticoid therapy: minimizing side effects. J Pediatr (Rio J) 2007;83:S163–77. https://doi.org/10.2223/JPED.1713.
[10] Perretti M, Dalli J. Exploiting the Annexin A1 pathway for the development of novel anti-inflammatory therapeutics. Br J Pharmacol 2009. https://doi.org/10.1111/j.1476-5381.2009.00483.x.
[11] Sheikh MH, Solito E. Annexin A1: Uncovering the many talents of an old protein. Int J Mol Sci 2018. https://doi.org/10.3390/ijms19041045.
[12] Gilroy DW, Lawrence T, Perretti M, Rossi AG. Inflammatory resolution: new opportunities for drug discovery. Nat Rev Drug Discov 2004;3:401–16. https://doi.org/10.1038/nrd1383.
[13] Serhan CN. The resolution of inflammation: the devil in the flask and in the details. FASEB J Off Publ Fed Am Soc Exp Biol 2011;25:1441–8. https://doi.org/10.1096/fj.11-0502ufm.
[14] Sugimoto MA, Vago JP, Perretti M, Teixeira MM. Mediators of the resolution of the inflammatory response. Trends Immunol 2019;40:212–27. https://doi.org/10.1016/j.it.2019.01.007.
[15] Perretti M, Gavins FNE. Annexin 1: an endogenous anti-inflammatory protein. News Physiol Sci an Int J Physiol Prod Jointly by Int Union Physiol Sci Am Physiol Soc 2003;18:60–4. https://doi.org/10.1152/nips.01424.2002.
[16] Kamal AM, Flower RJ, Perretti M. An overview of the effects of annexin 1 on cells involved in the inflammatory process. Mem Inst Oswaldo Cruz 2005;100(Suppl):39–47. https://doi.org/10.1590/s0074-02762005000900008.
[17] Perretti M, Ahluwalia A, Harris JG, Goulding NJ, Flower RJ. Lipocortin-1 fragments inhibit neutrophil accumulation and neutrophil-dependent edema in the mouse. A qualitative comparison with an anti-CD11b monoclonal antibody. J Immunol 1993;151:4306–14.
[18] Walther A, Riehemann K, Gerke V. A novel ligand of the formyl peptide receptor: annexin I regulates neutrophil extravasation by interacting with the FPR. Mol Cell 2000;5:831–40. https://doi.org/10.1016/s1097-2765(00)80323-8.
[19] Ernst S, Lange C, Wilbers A, Goebeler V, Gerke V, Rescher U. An annexin 1 N-terminal peptide activates leukocytes by triggering different members of the formyl peptide receptor family. J Immunol 2004;172:7669–76. https://doi.org/10.4049/jimmunol.172.12.7669.
[20] Gimenes AD, Andrade TRM, Mello CB, Ramos L, Gil CD, Oliani SM. Beneficial effect of annexin A1 in a model of experimental allergic conjunctivitis. Exp Eye Res 2015;134:24–32. https://doi.org/10.1016/j.exer.2015.03.013.
[21] Teixeira RAP, Mimura KKO, Araujo LP, Greco KV, Oliani SM. The essential role of annexin A1 mimetic peptide in the skin allograft survival. J Tissue Eng Regen Med 2016;10:E44–53. https://doi.org/10.1002/term.1773.
[22] Gavins FNE, Hughes EL, Buss NAPS, Holloway PM, Getting SJ, Buckingham JC. Leukocyte recruitment in the brain in sepsis: involvement of the annexin 1-FPR2/ALX anti-inflammatory system. FASEB J Off Publ Fed Am Soc Exp Biol 2012;26:4977–89. https://doi.org/10.1096/fj.12-205971.
[23] Machado MG, Tavares LP, Souza GVS, Queiroz-Junior CM, Ascenção FR, Lopes ME, et al. The Annexin A1/FPR2 pathway controls the inflammatory response and bacterial dissemination in experimental pneumococcal pneumonia. FASEB J Off Publ Fed Am Soc Exp Biol 2020;34:2749–64. https://doi.org/10.1096/fj.201902172R.
[24] Gong J, Ju Y-N, Wang X-T, Zhu J-L, Jin Z-H, Gao W. Ac2-26 ameliorates lung ischemia-reperfusion injury via the eNOS pathway. Biomed Pharmacother 2019;117:109194https://doi.org/10.1016/j.biopha.2019.109194.
[25] Possebon L, Costa SS, Souza HR, Azevedo LR, Sant'Ana M, Iyomasa-Pilon MM, et al. Mimetic peptide AC2-26 of annexin A1 as a potential therapeutic agent to treat COPD. Int Immunopharmacol 2018;63:270–81. doi: 10.1016/j.intimp.2018.08.011.
[26] Wang L, Li W, Xu Y, Wei Q, Zhao H, Jiang X. Annexin 1-derived peptide Ac2-26 inhibits eosinophil recruitment in vivo via decreasing prostaglandin D_2. Int Arch Allergy Immunol 2011;154:137–48. https://doi.org/10.1159/000320228.
[27] Bandeira-Melo C, Bonavita AGC, Diaz BL, E Silva PMR, Carvalho VF, Jose PJ, et al. A novel effect for annexin 1-derived peptide Ac2-26: Reduction of allergic inflammation in the rat. J Pharmacol Exp Ther 2005;313. doi: 10.1124/jpet.104.080473.
[28] Luo Z, Wang H, Fang S, Li L, Li X, Shi J, et al. Annexin-1 mimetic peptide Ac2-26 suppresses inflammatory mediators in LPS-induced astrocytes and ameliorates pain hypersensitivity in a rat model of inflammatory pain. Cell Mol Neurobiol 2020;40:569–85. https://doi.org/10.1007/s10571-019-00755-8.
[29] Liao WI, Wu SY, Wu GC, Pao HP, Tang SE, Huang KL, et al. Ac2-26, an annexin A1 peptide, attenuates ischemia-reperfusion-induced acute lung injury. Int J Mol Sci 2017. https://doi.org/10.3390/ijms18081771.
[30] Pupjalis D, Goetsch J, Kottas DJ, Gerke V, Rescher U. Annexin A1 released from apoptotic cells acts through formyl peptide receptors to dampen inflammatory monocyte activation via JAK/STAT/SOCS signalling. EMBO Mol Med 2011;3:102–14. https://doi.org/10.1002/emmm.201000113.
[31] Girol AP, Mimura KKO, Drewes CC, Bolonheis SM, Solito E, Farsky SHP, et al. Anti-inflammatory mechanisms of the annexin A1 protein and its mimetic peptide Ac2-26 in models of ocular inflammation in vivo and in vitro. J Immunol 2013;190:5689–701. https://doi.org/10.4049/jimmunol.1202030.
[32] Stuqui B, de Paula-Silva M, Carlos CP, Ullah A, Arni RK, Gil CD, et al. Ac2-26 mimetic peptide of annexin A1 Inhibits local and systemic inflammatory processes induced by bothrops moojeni venom and the Lys-49 phospholipase A2 in a rat model. PLoS ONE 2015;10:e0130803https://doi.org/10.1371/journal.pone.0130803.
[33] Drechsler M, De Jong R, Rossaint J, Viola JR, Leoni G, Wang JM, et al. Annexin A1 counteracts chemokine-induced arterial myeloid cell recruitment. Circ Res 2015. https://doi.org/10.1161/CIRCRESAHA.116.305825.
[34] Lim LHK, Solito E, Russo-Marie F, Flower RJ, Perretti M. Promoting detachment of neutrophils adherent to murine postcapillary venules to control inflammation: Effect of lipocortin 1. Proc Natl Acad Sci USA 1998. https://doi.org/10.1073/pnas.95.24.14535.
[35] Hayhoe RPG, Kamal AM, Solito E, Flower RJ, Cooper D, Perretti M. Annexin 1 and its bioactive peptide inhibit neutrophil-endothelium interactions under flow: indication of distinct receptor involvement. Blood 2006;107:2123–30. https://doi.org/10.1182/blood-2005-08-3099.
[36] Lacerda JZ, Drewes CC, Mimura KKO, Zanon C de F, Ansari T, Gil CD, et al. Annexin A12-26 treatment improves skin heterologous transplantation by modulating inflammation and angiogenesis processes. Front Pharmacol 2018. doi: 10.3389/fphar.2018.01015.
[37] Gimenes AD, Andrade BFD, Pinotti JVP, Oliani SM, Galvis-Alonso OY, Gil CD. Annexin A1-derived peptide Ac2-26 in a pilocarpine-induced status epilepticus model: Anti-inflammatory and neuroprotective effects. J Neuroinflammation 2019. https://doi.org/10.1186/s12974-019-1414-7.
[38] Galvão I, Vago JP, Barroso LC, Tavares LP, Queiroz-Junior CM, Costa VV, et al. Annexin A1 promotes timely resolution of inflammation in murine gout. Eur J Immunol 2017. https://doi.org/10.1002/eji.201646551.
[39] La M, D'Amico M, Bandiera S, Di Filippo C, Oliani SM, Gavins FN, et al. Annexin 1 peptides protect against experimental myocardial ischemia-reperfusion: analysis of their mechanism of action. FASEB J Off Publ Fed Am Soc Exp Biol 2001;15:2247–56. https://doi.org/10.1096/fj.01-0196com.
[40] Kamal AM, Smith SF, De Silva Wijayasinghe M, Solito E, Corrigan CJ. An annexin 1 (ANXA1)-derived peptide inhibits prototype antigen-driven human T cell Th1 and Th2 responses in vitro. Clin Exp Allergy J Br Soc Allergy Clin Immunol 2001;31:1116–25. https://doi.org/10.1046/j.1365-2222.2001.01137.x.
[41] Peshavariya HM, Taylor CJ, Goh C, Liu GS, Jiang F, Chan EC, et al. Annexin peptide Ac2-26 suppresses TNFα-induced inflammatory responses via inhibition of Rac1-dependent NADPH oxidase in human endothelial cells. PLoS ONE 2013. https://doi.org/10.1371/journal.pone.0060790.
[42] Trentin PG, Ferreira TPT, Arantes ACS, Ciambarella BT, Cordeiro RSB, Flower RJ, et al. Annexin A1 mimetic peptide controls the inflammatory and fibrotic effects of silica particles in mice. Br J Pharmacol 2015. https://doi.org/10.1111/bph.13109.
[43] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. novel coronavirus in Wuhan, China. Lancet 2019;2020. https://doi.org/10.1016/S0140-6736(20)30183-5.
[44] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Novel Coronavirus-infected pneumonia in Wuhan, China. JAMA – J Am Med Assoc 2019;2020. https://doi.org/10.1001/jama.2020.1585.
[45] Machhi J, Herskovitz J, Senan AM, Dutta D, Nath B, Oleynikov MD, et al. The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections. J Neuroimmune Pharmacol 2020. https://doi.org/10.1007/s11481-020-09944-5.
[46] Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. (COVID-19): the experience of clinical immunologists from China. Clin Immunol 2019;2020. https://doi.org/10.1016/j.clim.2020.108393.
[47] Stockman LJ, Bellamy R, Garner P. SARS: Systematic review of treatment effects. PLoS Med 2006. https://doi.org/10.1371/journal.pmed.0030343.
[48] Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. Am J Respir Crit Care Med 2018. https://doi.org/10.1164/rccm.201706-1172OC.
[49] Lansbury LE, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza: An updated cochrane systematic review and meta-analysis. Crit Care Med 2020. https://doi.org/10.1097/CCM.0000000000004093.
[50] Siemieniuk RAC, Meade MO, Alonso-Coello P, Briel M, Evaniew N, Prasad M, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. Ann Intern Med 2015;163:519–28. https://doi.org/10.7326/M15-0715.
[51] Pivonello R, Ferrigno R, Isidori AM, Biller BMK, Grossman AB, Colao A. COVID-19 and Cushing's syndrome: recommendations for a special population with endogenous glucocorticoid excess. Lancet Diabetes Endocrinol 2020;8:654–6. https://doi.org/10.1016/S2213-8587(20)30215-1.

[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, Rasekhi RT, 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, May 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, Naramala S, Madhira BR, 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, Luz MAM, 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/10.1159/000309756.
[58] Araujo LP, Truzzi RR, Mendes GEF, Luz MAM, 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 FNJ, Sena AA, Araújo LP, Mendes GE, Castro I, Luz MAM, et al. Annexin 1 mimetic peptide protects against renal ischemia/reperfusion injury in rats. J Mol Med (Berl) 2011;89:51–63. https://doi.org/10.1007/s00109-010-0684-4.
[60] Martín-Rojas RM, Pérez-Rus G, Delgado-Pinos VE, Domingo-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 BAG, De Saint-Hubert M, Bauwens M, van der Vorst E, et al. Pharmacological treatment with annexin A1 reduces atherosclerotic plaque burden in LDLR-/- mice on western type diet. PLoS ONE 2015;10:e0130484https://doi.org/10.1371/journal.pone.0130484.
[62] Senchenkova EY, Ansari J, Becker F, Vital SA, Al-Yafeai 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.118.039345.
[63] Schloer S, Hübel N, Masemann D, Pajonczyk D, Brunotte L, Ehrhardt 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.