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Inflammation and JAK/STAT Signaling: New Clues for the Treatment of COVID-19

Reza Shirazinia[1], Mahdi Afshari[2], Ali Akbar Golabchifar[1*], Hosein Ali Arab[1], Abolfazl Panahi Mishkar[3]

[1]Department of Comparative Bioscience, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran
[2]Department of Community Medicine, Faculty of Medicine, Zabol University of Medical Sciences, Zabol, Iran
[3]Human Ecology, Kerman University of Medical Sciences, Kerman, Iran

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***Correspondence to**
Ali Akbar Golabchifar,
Email: aliakbar.golabchifar@gmail.com

Abstract
The coronavirus disease 19 (COVID-19) outbreak in Wuhan, Hubei province, is a global health problem affecting about 212 countries around the world, highlighting the importance of the global recruitment of scientists to find a way for managing this burden. So far, many studies have been conducted to find a treatment for COVID-19, some of which indicated promising results. In this situation, gathering the previously published evidence may provide new hypotheses/solutions in this regard. Based on the role of inflammation in COVID-19-related deaths, we attempted to find a rational relationship between Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling and COVID-19 and inform JAK/STAT signaling inhibitors as candidates to manage or even prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Therefore, it is hoped that the present study provides new clues about the relationship between JAK/STAT signaling and the SARS-CoV-2 infection to highlight the role of JAK/STAT inhibitors as a possible treatment for managing inflammatory situations observed in the SARS-CoV-2 infection.
Keywords: Inflammation, JAK/STAT pathway, COVID-19

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Introduction

The novel coronavirus disease 2019 (COVID-19) outbreak started in Wuhan, Hubei province, China in late December 2019, which progressed to spread through all parts of China and about 212 countries around the world and is considered a global health emergency.[1,2] On 11 March 2020, the World Health Organization (WHO) announced that COVID-19 is spreading like a pandemic.[3] The new reports of the WHO updated on 24 January 2021 confirmed about 99 544 378 cases of infection and 2 134 526 deaths worldwide.[2] As it is known, the COVID-19 outbreak is characterized by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which is in common with some features and clinical manifestations observed in the other outbreaks of this family of viruses.[4] To this end, studies on SARS-CoV-2 revealed that this virus uses the angiotensin-converting enzyme II (ACE2) to enter the cells. This receptor is highly expressed on lung alveolar epithelial cells, describing why lungs are heavily susceptible to this virus.[5] The entry of SARS-CoV-2 to the cells down-regulates the ACE2 on lung alveolar epithelial cells.[6] ACE2 is a carboxypeptidase and a homologous of ACE. By the degradation of angiotensin II to the vasodilator angiotensin 1-7 (Ang 1-7) ACE2, it acts as a key regulator of the renin-angiotensin system.[7] Another option for the entrance of the SARS-CoV-2 to the permissive cells is serine protease TMPRSS2.[8] It has been observed that SARS-CoV-2 uses the TMPRSS2 for S glycoprotein priming needed for viral entry to the permissive cells.[8] Serine protease TMPRSS2 is present in the respiratory tracts. This enzyme is involved in the pathogenesis of various respiratory viruses, including the Middle East respiratory syndrome (MERS) coronavirus infection, SARS-CoV, influenza A virus (IAV), and the like. TMPRSS2 is shown to cleavage hemagglutinin, leading to the activation of diverse surface proteins of influenza A viruses in culture.[9-11] The downregulation of the ACE2 results in the uncontrolled effects of angiotensin II due to binding to the AT1 receptor, including vasoconstriction

increased inflammation and thrombosis.[6] It has been declared that the activity of angiotensin II through the AT1 receptor leads to the activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, precisely jak2 and tyrosine kinase 2, as well as the JAK family substrates STAT1 and STAT2 that may inform us about the role of the JAK/STAT signaling pathway and inflammation in the pathogenesis of the COVID-19.[12] The inflammation in COVID-19 patients is observed in various studies.[12-14] Higher levels of cytokines such as interleukin-7 (IL-7), tumor necrosis factor (TNF), IL-6, and IL-1β resemble what has been described as a cytokine storm and macrophage activation syndrome.[15] Higher levels of the other markers of inflammation (e.g., C-reactive protein, ferritin, D-dimers, CC-chemokine ligand 2, CCL3, CXC-chemokine ligand 10, and the soluble form of the α-chain of the IL-2 receptor) are also observed in COVID-19 patients; this indicates the fact that dysregulated mononuclear phagocyte compartment contributes to the COVID-19 hyperactivation of the immune system and inflammation.[16-18] An important pathway observed in the pathogenesis of inflammation is the JAK/STAT pathway, which contributes to the observed effects of cytokines.[19] The role of this pathway in inflammatory diseases (e.g., rheumatoid arthritis, psoriasis, and inflammatory bowel disease) has been evidenced in previous research.[20] Based on the role of inflammation and the JAK/STAT signaling in the pathogenesis of various diseases, it was hypothesized that these factors may be tied to COVID-19, and these would also inform scientists about new clues about the pathogenesis and the treatment of this disease.

Inflammation and COVID-19

Inflammation is a physiological process protecting our cells from infection and other noxious stimuli that spontaneously are terminated by endogenous or exogenous pathways, leading to physiological homeostasis.[21] The dysregulation of these pathways results in uncontrolled inflammation and various kinds of diseases.[22,23] As previously described, inflammation and cytokine storm are important characteristics of COVID-19 due to the exaggerated host immune response. High levels of cytokines, especially IL-6, usually are observed in patients who die in hospitals from COVID-19.[24] The immune system recognizes viruses by using pattern recognition receptors, especially Toll-like receptors (TLRs). When infection by COVID-19 occurs, the virus infects cells such as antigen-presenting cells, dendritic cells, and macrophages which present SARS-CoV-2 antigens to the other T cells, leading to T cell activation and differentiation, as well as huge cytokine release. Subsequently, this process activates transcription factors such as nuclear factor-kappa B (NF-κB), IRF3, and mitogen-activated protein kinase pathways, along with the expression of other inflammatory factors. The exposure of T cells to TLRs results in the production of pro-IL-1β, finally turning into active mature IL-1β that is a mediator of lung inflammation, fever, and fibrosis. Higher levels of cytokines present in COVID-19 patients describe an abnormal level of the immune response to the SARS-CoV-2 infection. Previous studies reported higher levels of IL-7, IL-1RA, IL-1B, IL-9, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF), fibroblast growth factor, interferon-γ (IFN-γ), IFN-γ-inducible protein (IP10) in critically COVID-19 patients. In addition, the other observed parameters were platelet-derived growth factor, macrophage inflammatory protein 1 alpha (MIP1A), monocyte chemoattractant protein (MCP1), TNF-α, and vascular endothelial growth factor in addition to significantly higher levels of IL-6, IL-2, IL-10, IL-7, IP10, G-CSF, MCP1, MIP1A, and TNF-α in critically COVID-19 patients in comparison to mild COVID-19 patients.[12,25,26] These findings describe the non-usual situation in the immune system of COVID-19 patients. Some studies revealed that SARS-CoV-2 infects immune cells such as macrophages and lymphocytes. Peripheral blood lymphopenia is also another consequence of SARS-CoV-2 infection that is found in the majority of patients (82.1%).[27] Growing attention to studies regarding the effectiveness of anti-inflammatory drugs for COVID-19 resulted in pieces of evidence describing that some kinds of anti-inflammation strategies may be useful for the management of cytokine storm observed in this pathologic condition.[27] In the search to find options for the treatment of COVID-19, Russell et al found that low-dose prednisolone and tacrolimus exhibit beneficial properties after SARS-CoV-2 infection basically in the early acute phases of infection. Further, high levels of IL-6 in this disease show that inflammation is directly related to this pathologic condition.[28,29] Wang et al also declared that SARS-CoV-2 enters T cells through the S protein-mediated membrane fusion. They also reported that SARS-CoV-2 cannot replicate in MT-2 cells. Additionally, they concluded that T cells are more susceptible to the infectivity by SARS-CoV-2 than SARS-CoV which is the reason for drastically COVID-19 pandemic spread and deaths in the world. Because of the low rate of the expression of hACE-2 on T cells, this theory raises that some kind of other receptors than hACE2 on T cells may mediate SARS-CoV-2 entry to immune cells.[30] Accordingly, in this regard, there is more need for investigations about the receptors that may mediate these processes. Our studies about this subject informed us about CCR5, which is a chemokine that may be involved in the entrance of SARS-CoV-2 to T cells. This chemokine mediates the entry of the HIV-1 virus into CD4 cells.[31] Patterson et al found that the disruption of the CCL5/RANTES-CCR5 pathway in COVID-19

patients demonstrated promising results, including a significant reduction in SARS-CoV-2 plasma viremia and IL-6 concentration, as well as the normalization of the CD4/CD8 ratio.[32] Hence, we advise exploration of this theory that CCR5 is probably associated with the entrance of the SARS-CoV-2 to T cells based on the present facilities, and the emergence of this topic should be considered specially.

JAK/STAT Signaling and Inflammation and COVID-19

The JAK/STAT signaling pathway is a cascade of reactions that perform the intracellular consequences of the attachment of cytokines and growth factors to their receptors. Briefly, after the attachment of a cytokine to its receptor, the receptor dimerizes, leading to the transphosphorylation of STATs following the transphosphorylation of JAKs that are attached to the internal part of the receptor by their SH2 domain. The activated STATs then dimerize and move to the nucleus, whereby they activate or suppress target gene promoters, leading to an effect.[33] The JAK/STAT signaling pathway mediates various cellular functions such as cell survival, proliferation, differentiation, migration, and apoptosis, as well as various developmental and homeostatic processes such as immune cell development, hematopoiesis, stem cell maintenance, mammary gland development, and organismal growth. In mammals, there are four Jaks and seven stats; The Jaks include Jak1, Jak2, Jak3, and tyrosine kinase 2, while the stats comprise STAT1, STAT2, STAT3, STAT4, STAT5 (STAT5A and STAT5B), and STAT6.[34,35] As mentioned earlier, the signaling pathways of about 60 cytokines, growth factors, and hormones such as IFN, IL, erythropoietin, and thrombopoietin that are involved in processes such as hematopoiesis and the regulation of the immune system are mediated through the JAK/STAT signaling.[36] Therefore, the regulation of the immune system and inflammation observed in the SARS-CoV-2 infection are partly accomplished by JAK/STAT signaling, and this may highlight a clue for the effectiveness of JAK/STAT inhibitors for the treatment and control of COVID-19.

JAK/STAT inhibitors are a class of drugs that block one or more molecules involved in the JAK/STAT pathway. JAK inhibitors are comprised of first-generation (tofacitinib, ruxolitinib, baricitinib, and oclacitinib) and second-generation (decernotinib, peficitinib, filgotinib, fedratinib, momelotinib, and lestaurtinib) types, all of which are used to treat various pathologic inflammatory conditions such as rheumatoid arthritis. First-generation JAK/inhibitors are also employed for the management and control of dermatological immune reactions.[37,38] Tofacitinib is a JAK1, JAK3, and JAK2 inhibitor approved for the treatment of rheumatoid arthritis. This drug blocks gp130 family cytokines, including IL-6 and IL-11, and type II cytokines such as IFN-α, IFN-β, and IL-10. Tofacitinib also inhibits the action of other ILs, including IL-2, IL-4, IL-6, IL-7, IL-9, IL-15, and IL-21.[39] Baricitinib is another drug from this class that blocks JAK1 and JAK2, leading to the inhibition of the effects of cytokines such as IFN-α, IFN-γ, IL-6, IL-12, IL-21, and IL-23.[5,40] Moreover, baricitinib inhibits the activity of AP2-associated kinase 1 (AAK1) and the cyclin G-associated kinase (GAK) that are the members of the numb-associated kinase family involved in the endocytosis mediated by clathrin.[5] Briefly, after the attachment of SARS-CoV-2 to the ACE2 receptor, the virus with the receptor undergoes clathrin-dependent endocytosis. Accordingly, the virus infection leads to the reduced number of ACE2 receptors and exaggerated effects of angiotensin II on the AT1R receptor, resulting in the inflammation, thrombosis, and vasoconstriction that are observed in the pathogenesis of SARS-CoV-2 as well.[6,41] The other drugs of this category (e.g., ruxolitinib and fedratinib) can also be used for the inhibition of the SARS-CoV-2 entry to the cells partly due to the inhibition of AAK1 and BMP-2-inducible protein kinase (BMP2K) (Bike) that are involved in the clathrin-mediated endocytosis.[42,43] Erlotinib is another drug from this category that also inhibits AAK1 and GAK that also mediate the clathrin-induced endocytosis.[44] Thus, the inhibition of the clathrin-mediated endocytosis by baricitinib and other JAK inhibitors such as ruxolitinib, fedratinib, and erlotinib may be a preventive strategy against SARS-CoV-2 infection, which needs more investigations. On the other hand, the exaggerated effect of angiotensin II on the AT1R receptor after ACE2 downregulation is partly accomplished by JAK2.[45] This also highlights the role of JAK/STAT inhibitors such as tofacitinib in the treatment and control of COVID-19. Another consequence of infection by SARS-CoV-2 is oxidative stress (OS).[46] Ntyonga-Pono found that antioxidant products against OS are important options for the treatment of COVID-19, highlighting that OS is involved in the pathogenesis of SARS-CoV-2 infection.[46] Previous studies revealed that reactive oxygen species (ROS) stimulate JAK2 by an indirect unknown molecular function. This indirect molecular function is partly due to the oxidative inhibition of the active site cysteine in protein tyrosine phosphatases, increasing the phosphotyrosine content of JAK2. Additionally, JAK2 activation causes ROS generation in atypical GPCR-mediated systems. Most of these studies are based on using AG490, which is a specific JAK2 inhibitor and a radical scavenger.[47,48] It has been indicated that the oxidation of proteins results in the release of inflammatory cytokines and peroxiredoxin 2 (PRDX2), which is a pro-inflammatory signal. After releasing, PRDX2 acts as a redox-dependent inflammatory mediator which activates macrophages, leading to the production and release of TNF-α.[22] Further, free radicals can increase the production of pro-inflammatory cytokines through

the activation of the transcription factor NF-κB.[49] Briefly, it may be hypothesized that the inhibition of JAK2 may alleviate the symptoms of COVID-19 by the inhibition of inflammation and OS.

JAK/STAT Signaling and Angiotensin II

There is a close relationship between JAK/STAT signaling and the activity of the renin-angiotensin system. Studies have expressed that JAK2 does not have an SH2 domain; therefore, another structure such as Src homology phosphatase 2 mediates the physical interaction between the AT1R receptor and JAK2. In this process, the C-terminus of AT1R is the docking site. Thus, JAK2 activation through the AT1R is mediated by a G protein-mediated pathway, and then further studies revealed that the G-protein independent pathway also mediates the activation of JAK2 by angiotensin II.[44,50] JAK2 activation through AT1R in the vascular smooth muscles leads to the rapid phosphorylation of STAT1 and STAT2, followed by the phosphorylation of STAT3.[44,51] The activation of STAT1α/β, STAT2, STAT3, STAT5a/b, and STAT6 in the heart myocytes also has been observed by the angiotensin II activity.[52] Hypertension is another complication observed with the pathogenesis of COVID-19. Hypertension is the most comorbidity detected in patients experiencing severe COVID-19 along with acute respiratory distress syndrome.[53,54] This may be partly due to the over-activation of angiotensin II on the AT1R in which JAK/ASTA is involved as well.[44,54] Therefore, the activation of the JAK/STAT pathway by AT1R is directly correlated with the physiopathology of the cardiovascular system in COVID-19, and the inhibition of the JAK/STAT pathway, precisely JAK2, by JAK/STAT inhibitors such as tofacitinib and baricitinib may reveal new alternatives for the treatment and management of COVID-19 (Figure 1).

Conclusion

Tofacitinib is a JAK/STAT signaling pathway inhibitor that, due to the inhibition of the JAK/STAT pathway, prevents the activity of various kinds of cytokines that are involved in the pathogenesis of COVID-19. On the other hand, other drugs in this category such as Ruxolitinib, Fedratinib, Baricitinib, and Erlotinib inhibit AAK1, GAK, and BMP2K that mediate clathrin-dependent endocytosis; therefore, these drugs may be preventive options against SARS-CoV-2 entry to cells. Additionally, the over-activation of angiotensin II through the JAK2 signaling pathway is another confirmation of the efficacy of JAK/STAT inhibitors for SARS-CoV-2 infection. Moreover, evidence demonstrates that the inhibition of jak2 prevents inflammation and OS both of which mediate the injuries following SARS-CoV-2 infection. We also hypothesized that SARS-CoV-2 may be related to the CCR5 Chemokine to enter the immune cells, highlighting the way for further investigations about SARS-CoV-2 infection. Finally, JAK/STAT inhibitors such as Ruxolitinib, Fedratinib, baricitinib, Erlotinib, and tofacitinib may be suitable options for the prevention and management of SARS-CoV-2 infection due to inhibitory effects against SARS-CoV-2 endocytosis and inflammation.

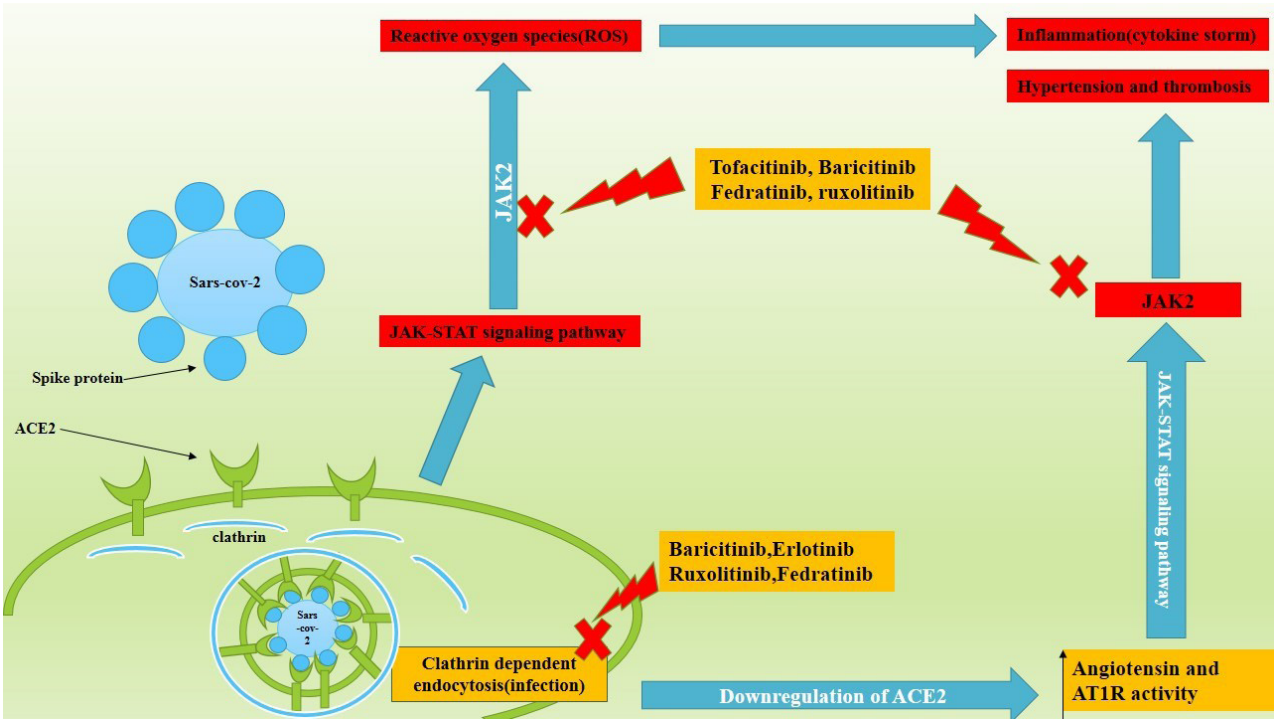

Figure 1. A Brief Description on the Correlation of the JAK/STAT Signaling Pathway and COVID-19. *Note*. JAK/STAT: Janus kinase (JAK)/signal transducer and activator of transcription; COVID-19: Coronavirus disease 19

Competing Interests
The authors have no conflict of interest to declare.

Ethical Approval
Not applicable.

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