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Commentary

BAY 11-7082: An Anti-inflammatory Drug for COVID-19

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new coronavirus named by the International Committee on Taxonomy of Viruses. COVID-19 patients have high mortality due to respiratory failure from acute respiratory distress syndrome (ARDS) induced by SARS-CoV-2. The abnormal activation of P21-activated kinase (PAK1, RAC/CDC42-activated kinase 1) is reported in COVID-19. The PAK1 induces nuclear factor kappa B (NF-κB) activation as well as inflammatory pathways through its stimulation. BAY 11-7082 {(E) 3-[(4-methylphenyl)-sulfonyl]-2-propenenitrile is one of the therapies that inhibit inflammation via mentioned signaling pathway, therefore, we suggest that this drug can potentially be effective in treating COVID-19.

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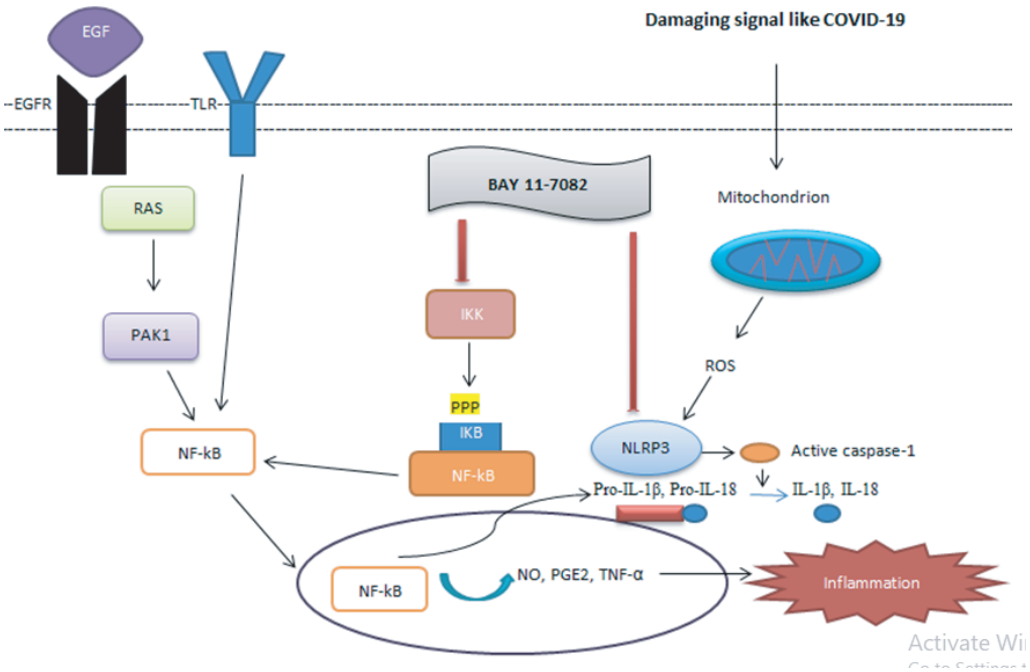
In late December 2019, a case of unknown pneumonia was described in Wuhan, People's Republic of China (PRC) [1]. The "COVID-19" and "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) are the names of the disease induced by novel coronavirus and the virus that suggested by the World Health Organization (WHO) and the International Committee on Taxonomy of Viruses, respectively [2] Respiratory failure from acute respiratory distress syndrome (ARDS) initiated by SARS-CoV-2 is the leading cause of mortality [3]. P21-activated kinase (PAK1, RAC/CDC42-activated kinase 1) is the key "pathogenic" kinase. The unusual stimulation of PAK1 induces several disorders/diseases including viral infections such as COVID-19 and influenza, and inflammation [4, 5]. In the PAK1 signaling pathway, first, epidermal growth factor (EGF) stimulates the epidermal growth factor receptor (EGFR) and then activates the downstream factor, RAS (guanosine-nucleotide-binding protein). This factor is upstream of PAK1. In the end, PAK1 may activate inflammatory pathways by nuclear factor kappa B (NF-κB) activation [6]. The NF-κB in most cells' cytoplasm is bound to an inhibitory protein, IkB (inhibitory protein of NF-κB complex). It has been revealed that cytokines and



EGF, Epidermal growth factor; EGFR, Epidermal growth factor receptor; RAS, Guanosine-nucleotide-binding protein; PAK1, P21 activated kinase 1; NF-KB, Nuclear factor kappa B; NO, Nitric oxide; PGE2, Prostaglandin E2; TNF-α, Tumor necrosis factor-alpha; IL-1β, Interleukin-1β; IL-18, Interleukin-18; TLR, Toll-like receptor; ROS, Reactive oxygen species; IKK, IKB kinase; IKB, Inhibitory protein of NF-KB complex; NLRP3, NLR family pyrin domain containing 3.

Figure 1: Anti-inflammatory effect of BAY 11-7082 on COVID-19.

oxidative stress stimulation lead to the activation of NF-κB. In this stimulation process, IκB kinase (IKK) phosphorylates IκB, and then it undergoes proteolytic degradation by the proteasome-dependent pathway [7]. Nuclear translocation of NF-κB elevates the transcription of several inflammatory factors including chemokines, adhesion molecules, and cytokines [7, 8]. So, we suggest the treatment of hyperinflammation using existing, approved therapies to decrease the rising mortality. One of the therapies that suppress inflammation is BAY 11-7082 (E) 3-[(4-methylphenyl)-sulfonyl]-2-propenenitrile that inhibits IKK and phosphorylation of IkB [9], so NF-κB remains in an inactive form. As a result, BAY 11-7082 blocks the expression of tumor necrosis factor-α (TNF-α), prostaglandin E2 (PGE_2), and nitric oxide (NO), famous inflammatory responses created by activated NF-κB [10]. The inhibitory effect of BAY-11-7082 is frequently shown as an investigation test to determine the involvement of IKK, and NF-κB, in a biological process, for instance, lung adenocarcinoma in mouse models [11]. Strickson et al showed that BAY-11-7082 suppresses the activation of IKK indirectly in response to interleukin-1 or lipopolysaccharide (LPS) in several cells such as T-cell leukemia and B-cell lymphoma [12]. Also, it is shown that BAY-11-7082 inhibits the NLR family pyrin domain containing 3 (NLRP3) inflammasome [13]. The inflammasome refers to

assemblies that activate caspase-1 [14], which changes inactive pro-interleukin-1β (pro-IL-1β) and pro-interleukin-18 (pro-IL-18) into active pro-inflammatory cytokines IL-1β and IL-18 [15, 16]. These processes are designed in the innate immune cells' cytoplasm due to threat signals [14]. The NLRP3 inflammasome is important as it is stimulated by danger signals, such as viruses, small molecule immune activators, bacteria, purified microbial products, crystalline or aggregated materials, and components of dying cells [14]. NLRP3 is expressed in the cytosol of dendritic cells, monocytes, lymphocytes, neutrophils, osteoblasts, and epithelial cells [17]. So, BAY-11-7082 by inhibition of the NLRP3 inflammasome prevents the expression of the pro-inflammatory cytokines, IL-18, and IL-1β in an NFkB-independent mechanism [13]. The investigations reported that serum IL-1β increased in COVID-19 patients [1]. According to this signaling pathway that is active in COVID-19 and the inhibitory influence of BAY-11-7082 on this pathway, we suggest that this drug can potentially be effective in treating COVID-19 (Figure **1**).

Competing Interests

None declared.

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