Nemati M, Asl ER, Pouya FD, Rasmi Y. Curcumin, an Inhibitor of PAK1, Potential Treatment for COVID-19. J Infectiology. 2020; 3(2): 1-3

Journal of Infectiology

Journal of Infectiology

Commentary Open Access

Curcumin, an Inhibitor of PAK1, Potential Treatment for COVID-19

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Article Info

Article Notes
Received: June 15, 2019
Accepted: July 09, 2020

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On 31st December 2019, 27 cases of pneumonia with unknown etiology were recognized in Wuhan City, Hubei province in China. These patients had clinical symptoms including dyspnea, dry cough, fever, and bilateral lung infiltrates on imaging[1]. However, some patients had different fatal complications such as septic shock, organ failure, severe pneumonia, pulmonary edema, and Acute Respiratory Distress Syndrome (ARDS)[2]. The ARDS is an immunopathologic event. The major mechanism of ARDS is an uncontrolled systemic inflammatory response subsequently releasing pro-inflammatory cytokines such as interleukins (IL), interferons (IFN), chemokines, and tumor necrosis factor (TNF)-α followed by a cytokine storm[3,4]. The agent that causes this status was identified from throat swab samples by the Chinese Centre for Disease Control and Prevention (CCDC) on 7th January 2020[5]. It named, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses[6], and coronavirus disease of 2019 (COVID-19) by the World Health Organization (WHO)[5]. On 30th January 2020, the WHO reported the Chinese prevalence of COVID-19 to be a Public Health Emergency of International Concern[7].

There are currently insufficient studies that describe the pathophysiological features of COVID-19[8]. SARS-CoV-2 belongs to the RNA virus family called "corona"[9,10]. Treatment of COVID-19, needs particular agents that targets a specific "host" enzyme critical for viral infection, but not for the normal physiology of hosts. This enzyme is the p21-activated kinase 1 (PAK1), the most "pathogenic" of mammalian family kinases, a serine-threonine protein kinase, cloned more than 25 years ago. Abnormal activation of PAK1 is responsible for various diseases including inflammation, cancers, immuno-suppression, viral infection, malaria, and ageing[11]. In this signaling pathway, after stimulation of epidermal growth factor receptor (EGFR), the PAK1 stimulates by binding to the Rho family small G proteins ras-related C3 botulinum toxin substrate 1 (Rac1) and cell division control protein 42 homolog (Cdc42) which both are activated by phosphorylation[12,13] and promotes the activity of the transcription nuclear factor-κB (NF-κB) by an inhibitor of kappa B kinase (IKK)-independent mechanism. The NF-κB regulates a great number of genes important for immune and inflammatory responses, apoptosis, transformation, and cell growth. In response to different stimuli, IκB (inhibitory protein of NF-κB complex) phosphorylates and inactivates by the IKK subunits (IKKα and IKKβ), which permits the release of NF-κB. At this time, NF-κB translocates to the nucleus and binds to regulatory DNA sequences[14]. The NF-κB activates by coronavirus infections. In mice model, inhibition of NF-κB reduces

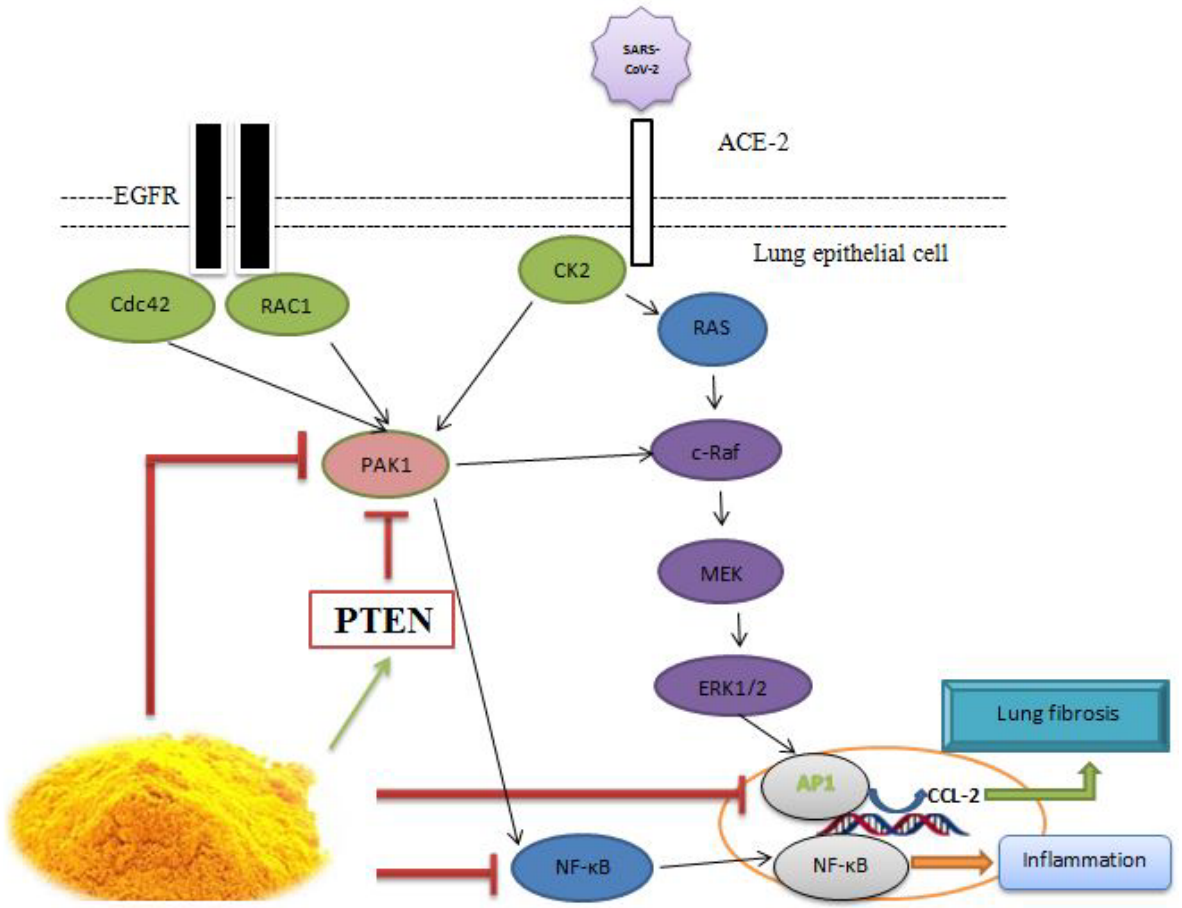

Figure 1: Inhibitory effect of curcumin of PAK1 signaling induced by SARS-CoV-2. The EGF binds to EGFR and activates Rac1 and Cdc42. Stimulation of PAK1 by binding to Rac1 and Cdc42, induce the activation of NF- κB. Curcumin inhibit the NF- κB, PAK1 and up-regulates PTEN that inactive the PAK1. In another pathway, SARS-CoV-2 via ACE-2 and activates CK2/RAS-PAK1-RAF-AP1.Curcumin inhibit AP1.

Abbreviations: EGFR: Epidermal growth factor receptor; Cdc42: Cell division control protein 42 homolog; RAC1: Ras-related C3 botulinum toxin substrate 1; PAK1: P21 (RAC1) Activated Kinase 1; PTEN: Phosphatase and tensin homolog ; ACE-2: Angiotensin-converting enzyme-2; CK2: Casein kinase 2; MEK: Mitogen-activated protein kinase kinase; ERK1/2: Extracellular signal-regulated kinases 1 and 2; AP1: Activator protein 1; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cell.

lung infection and enhances survival after SARS-CoV-2 infection[15].

In the another signaling pathway of COVID-19, it was showed that, a tumor-suppressing phosphatase called phosphatase and tensin homolog (PTEN), inactivates PAK1 and inhibits the coronavirus-induced CCL2 (C-C motif chemokine ligand 2)-dependent fibrosis[16]. It should be noted that expression of CCL2 depends on the coronavirus Angiotensin-converting enzyme 2 (ACE2) receptor induced casein kinase 2 (CK2)/RAS (Guanosine-nucleotide-binding protein)-PAK1- rapidly accelerated fibrosarcoma (RAF)-activator protein 1 (AP1) signaling pathway[17,18].

Curcumin is one of the compositions that inhibit the activity of PAK1[19], AP1 and NF-κB[20]. Curcumin is the prominent yellow pigment in turmeric with anti-inflammatory properties[21]. The therapeutic benefits of curcumin have been revealed in multiple chronic diseases: arthritis, inflammation, liver disease, metabolic syndrome, neurodegenerative diseases, obesity, and cancer[22]. Curcumin suppresses NF-κB activation via direct changes on the NF-κB/IκB complex and inhibition of IκB degradation that NF-κB remains in its inactive cytoplasmic form[23-25]. Curcumin also interferes with NF-κB binding to DNA, therefore, it prevents NF-κB driven expression of pro-inflammatory factors[26-28] and upregulates PTEN[29] by non-genomic mechanisms, such as post transcriptional regulation[29] (Figure 1).

So, we can conclude that curcumin with anti-inflammatory properties and inhibition of PAK1, AP1 and NF-κB that create an inflammation status could be a potentially beneficial treatment for COVID-19 related ARDS.

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