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Opinion

New insights into the effects of hydroxychloroquine in COVID-19

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ABSTRACT

In late 2019 until 2021, the novel coronavirus disease (COVID-19) has become pandemic. This disease is related to severe inflammatory symptoms of the respiratory epithelial cells and the dysfunction of several organs. One of the suggested drugs to reduce the inflammation caused by COVID-19 is hydroxychloroquine. Studies have shown this drug blocks the inflammatory pathway of nuclear factor-κB by blocking P21 activated kinase 1. Also, nanoparticle vaccines Poly Lactide-Glycolide) Acid (PLGA) containing hydroxychloroquine are effective in cancer by stimulating CD8T + cells responses. This study assumed that hydroxychloroquine was effective in inhibiting COVID-19 with these mechanisms.

***Keywords*:** COVID-19; hydroxychloroquine; P21 activated kinase 1; CD8T + cells

INTRODUCTION

In late 2019 and early 2020, many people in Wuhan, China, and then around the world were infected by the acute respiratory syndrome coronavirus 2 SARS-CoV-2 (COVID-19) [1]. Common symptoms in patients with COVID-19 are Acute Respiratory Distress Syndrome (ARDS) and dysfunction of various organs of the body. One of the most important results of the COVID-19 clinical picture is the increase of inflammatory cytokines, Cytokine Release Syndrome (CRS), which play an essential role in the progression of the disease [2]. In infected or damaged tissue, the inflammation

caused by the immune response is manifested by symptoms such as redness, swelling, heat, pain, and function abnormally [3]. Nuclear Factor-κB (NF-κB) is one of the main regulators of genes involved in the immune system and inducers of inflammatory responses [4,5]. In a COVID-19 viral infection, the production of proinflammatory cytokines interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) increase, and this increase is dependent on the NF-κB signaling pathway; therefore, NF-κB is essential by causing inflammation and fever in this disease [6]. In COVID-19, influenza, Human Immunodeficiency Virus (HIV), and other diseases such as cancer, inflammation, and malaria, the most important factor involved is abnormal P21 activated kinase 1 (PAK1) [7]. To activate PAK1, first, the Epidermal Growth Factor (EGF) binds to Epidermal Tyrosine Kinase Receptor (EGFR) and activates guanosine-nucleotide-binding protein (RAS). PAK1 can activate inflammatory or survival pathways by NF-κB [8]; therefore, compounds suppressing PAK1 can be a good treatment option for inflammatory disorders [9]. Chloroquine (CQ) and Hydroxychloroquine (HCQ), used in malaria and autoimmune diseases such as Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) [10], identified as PAK-1 blockers, have anti-inflammatory properties [7]. To precisely assess the antiviral performance of HCQ and CQ, in vitro studies have shown that HCQ has lower drug toxicity and good potential for COVID-19 inhibition than CQ. However, long-term and high doses consumption of HCQ can be associated with poisoning [11]. Major anti-inflammatory and anti-viral functions for HCQ include suppression of phospholipase A2, [12] decreased expression of IL-1 and IL-6 cytokines by macrophages, TNF-α inhibition, prevention of toll-like receptor signals, and inhibition of T and B cell receptors [13,14]. HCQ is an endosomal membrane disruptor that promotes vesicular instability, endosomal membrane permeability, and the release of therapeutic agents into the cytoplasm [15]. In vivo studies have shown that HCQ can reduce the virus load and inhibit the entry of SARS-CoV-2 into lung cells. But, side effects such as retinopathy, hypoglycemia, and cardiac toxicity are factors that cast doubt on the safety of HCQ. Using nanotechnology to deliver this drug in the respiratory system by reducing the effects of drug toxicity through controlled release can play a prominent role in treating COVID-19 [16]. Nowadays, nanotechnology is used to develop vaccines against cancer and infectious diseases. One of these nanoparticles is PLGA. It is a biodegradable copolymer, approved by the

Food and Drug Administration (FDA) [17-19]. In one study, Jiale Liu et al. developed a nano-vaccine that physically is mixing OVA (a model antigen) and HCQ. This compound was encapsulated by PLGA nanoparticles and then assessed cytosolic delivery of antigens and T cell responses to inhibit tumor growth. The study results showed an increase in CD8 + T cellular response with inducing apoptosis of tumor cells [15]. On the other hand, another function of CD8T + cells is to detect virus-infected cells through the T cell receptor (TCR). They then reduce cell infection and virus production by killing infected cells through lytic or non-lytic (secretion of cytokines such as Interferon-gamma (IFN) and TNF [20]. Figure 1 depicts that to treat COVID-19 patients, HQC can act as an inhibition of NF-κB and the generator of cytotoxic CD8+ T-cell responses.

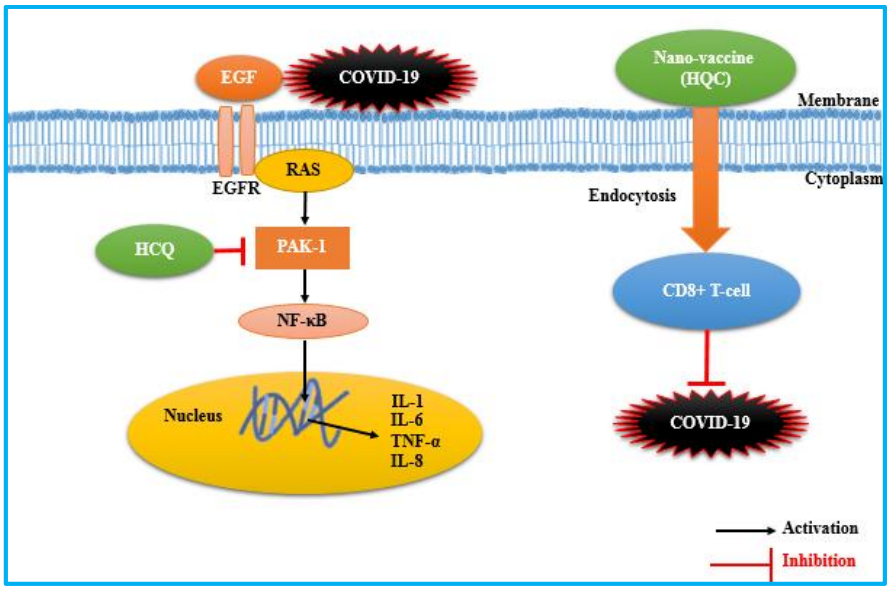

Figure1. Anti- inflammatory signaling pathway by HCQ. Abbreviations: COVID-19, Coronavirus disease 2019; EGF, Epidermal growth factor; EGFR, Epidermal growth factor receptor; RAS, Guanosine-nucleotide-binding protein; PAK1, P21 activated kinase 1; HCQ, Hydroxychloroquine; NF-κB, Nuclear factor-κB; IL-6, Interleukin- 6; IL-1, Interleukin- 1; IL-8, Interleukin- 8; TNF-α, Tumor necrosis factor-alpha.

CONCLUSION

To treat inflammation in patients with COVID-19, HCQ, as a PAK-1 inhibitor, can act through the RAS signaling pathway. This drug prevents the activity of NF-κB by inhibiting PAK-1 leading to the suppression of the IL-6, IL-1, and TNF-α genes, as important cytokines at the onset of inflammatory reactions. Furthermore, HCQ can stimulate CD8+ T-cell responses by nano-vaccine PLGA in treating patients with COVID-19.

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