TARGETING LYMPHOCYTE Kv1.3-CHANNELS TO SUPPRESS CYTOKINE STORM IN SEVERE COVID-19: CAN IT BE A NOVEL THERAPEUTIC STRATEGY?

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SUMMARY In the midst of a pandemic, finding effective treatments for coronavirus disease 2019 (COVID-19) is the urgent issue. In "chronic inflammatory diseases", the overexpression of delayed rectifier K⁺-channels (Kv1.3) in leukocytes is responsible for the overactivation of cellular immunity and the subsequent cytokine storm. In our previous basic studies, drugs including chloroquine and azithromycin strongly suppressed the channel activity and pro-inflammatory cytokine production from lymphocytes. These findings suggest a novel pharmacological mechanism by which chloroquine, with or without azithromycin, is effective for severe cases of COVID-19, in which the overactivation of cellular immunity and the subsequent cytokine storm are responsible for the pathogenesis.

Keywords COVID-19, cytokine storm, lymphocyte, Kv1.3-channels, chloroquine

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Most patients are either asymptomatic or develop only mild to moderate symptoms, such as fever, dry cough and shortness of breath, which often improve spontaneously with supportive treatment alone. However, some patients develop fatal pneumonia with acute respiratory distress syndrome (ARDS) or are occasionally complicated by multiple organ failure due to generalized thrombotic microangiopathy as the result of systemic vasculitis (1). Concerning the mechanisms, the over-activation of leukocytes and the uncontrolled release of pro-inflammatory cytokines, such as interleukin (IL)-6, IL-1, IL-2, IL-10, tumor necrosis factor (TNF)-α and interferon (IFN)-γ, are thought to be responsible (2, 3). This phenomenon is termed "cytokine storm" characterized by an excessive response of the immune system.

"Chronic inflammatory diseases" is a disease category in which over-stimulated cellular immunity is responsible for the pathogenesis (4). Besides infectious diseases and autoimmune disorders, studies indicate that common diseases, such as metabolic disorders and cancer, are also included in this disease category. Recently, we have demonstrated in animal studies that the cytokine storm can occur in advanced-stage kidney diseases, such as end-stage renal disease and interstitial nephritis (5, 6). In these animal models, leukocytes including T-lymphocytes and macrophages were markedly increased within the kidneys and the cytokine levels, such as IL-2 and TNF-α, were actually elevated. In these leukocytes, since delayed rectifier K⁺-channels (Kv1.3) were over-expressed, and since pharmacological blockade of the channels actually ameliorated the disease progression, they were thought to be the primary trigger of the overactivation of cellular immunity and the subsequent cytokine storm.

In the midst of a pandemic, finding effective treatments for COVID-19 is an urgent issue. Despite the limited evidence, some clinical studies have suggested the efficacy of chloroquine with or without azithromycin for COVID-19 patients with severe respiratory failure (7-9). In addition to the direct effect of chloroquine on reducing the viral replication (10), in vitro studies demonstrated its inhibitory effect on the production of cytokines from leukocytes (7, 11). Regarding the mechanisms of such anti-inflammatory properties of chloroquine, recent reports suggest the involvement of glycogen synthase kinase-3β (GSK3β) or Toll-like receptors (TLRs) (12, 13). In our previous patch-clamp studies using murine thymocytes, both chloroquine and azithromycin strongly suppressed the activity of lymphocyte Kv1.3-channels and thus reduced the production of inflammatory cytokines (14, 15). These findings provide an additional pharmacological mechanism by which chloroquine with or without azithromycin was effective for severe cases of COVID-19, where the overactivation of cellular immunity and the subsequent cytokine storm were responsible for their pathogenesis (Figure 1). Additionally, in our series of patch-clamp studies
Kv1.3-channels promote calcium influx and trigger the proliferation and activation of lymphocytes (4). The increased cytosolic calcium concentration stimulates the phosphatase calcineurin, which de-phosphorylates the nuclear factor of activated T cells (NFAT), causing its accumulation in the nucleus and binding to the promoter region of cytokine-encoding genes. Both chloroquine and azithromycin inhibit Kv1.3-channels (14,15).

so far, we also revealed the inhibitory properties of nonsteroidal anti-inflammatory drugs, anti-hypertensive drugs, anti-cholesterol drugs and anti-allergic drugs on lymphocytes Kv1.3-channels (16-18). Considering such pharmacological properties, these commonly used drugs may also be beneficial in the treatment of COVID-19, since the channel blockade reduces the cytokine production and thus suppresses the cytokine storm.

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References


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