Letter

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Is GSK3β a molecular target of chloroquine treatment against COVID-19?

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SUMMARY The recent clinical trial reports pertaining to the efficacy of chloroquine and hydroxychloroquine against COVID-19 albeit yet to be validated with larger clinical trials, have sparked much interest globally to evaluate whether this anti-malarial drug can be repurposed for the treatment of COVID-19. In addition to its anti-viral activity, the anti-inflammatory activity of chloroquine may also contribute to its efficacy. Based on our data obtained from an animal infection model of melioidosis (a disease caused by the bacteria *Burkholderia pseudomallei*), treatment with chloroquine can result in the phosphorylation and consequent inhibition of glycogen synthase kinase-3β (GSK3β). This serine/threonine protein kinase is now recognised as a point of convergence for host inflammatory response. In view of this, it is plausible that the mechanism for the anti-inflammatory effect of chloroquine against COVID-19 involves inhibition of host GSK3β.

Keywords Chloroquine, COVID-19, GSK3β, anti-inflammatory

The molecular basis by which chloroquine dampens the host overwhelming inflammatory response (cytokine storm) during infection is still not fully understood. As in malaria, pathogenesis in viral infection may also be related to dysfunction in the regulation of pertinent signalling pathways; for example aberrant GSK3β signalling. Our notion is based on the understanding that GSK3β is a molecular hub linking numerous signalling pathways in the cell, including host-directed inflammatory response. Lithium chloride (LiCl) , a well-known GSK3 inhibitor, has been reported to suppress avian coronavirus infectious bronchitis where the anti-viral activity of lithium was attributed to its cellular effect (*1*). Most recently, Nowak & Walkowiak (2020) (*2*) proposed LiCl to be further explored as a potential therapeutic for the treatment of COVID-19. The reported efficacy of chloroquine in recent clinical trials to treat COVID-19 (*3,4*) may also be attributed to a mechanism of action that involve inhibition of GSK3β. In our laboratory, we have shown that chloroquine treatment in experimental animal melioidosis modulated cytokine levels and increased animal survivability *via* inhibition of GSK3β (*5*). Our analysis revealed that chloroquine resulted in phosphorylation and consequent inhibition of GSK3β in the liver. In a subsequent study (*6*), we concluded that chloroquine is a plausible candidate for repurposing in the treatment of melioidosis. It is possible that the mechanism for the anti-viral activity of chloroquine, specifically its anti-inflammatory effect involves inhibition of GSK3β in lung epithelial and immune cells. The lead author's 1980 publication (*7*) first identified GSK3 forty years ago. This kinase, initially described as a key enzyme involved in glycogen metabolism, is now known to regulate a wide array of cellular processes. Dysregulation of this kinase is implicated in several diseases including bipolar disorder, diabetes mellitus, Alzheimer's disease, inflammation, and cancer (*8,9*). Further research to better understand the molecular basis of the anti-viral effects of chloroquine can have far-reaching clinical implications.

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