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Dual Effect of Auranofin Drug on SARS-CoV-2

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Description

In response to pro-inflammatory cytokines, the central element of the NF-κB activation pathway called NEMO (NF-κB Essential Modulator) is located in supramolecular structures [1]. This observation led Robert Weil's laboratory to search for chemical compounds potentially regulating the formation of these complexes, which are essential for the activation of NF-κB, by high-throughput screening and using the Prestwick library (a collection of 1520 small molecule; 95% of approved-off-patent drugs). This approach identifies not only already known NF-κB inhibitors, but also anti-cancer and anti-inflammatory agents, in addition to other compounds that are listed in our published manuscript on the subject [1,2]. Among them, Auranofin, a gold-based salt with anti-inflammatory properties, approved 33 years ago by the FDA for the treatment of rheumatoid arthritis and currently in phase II and III for clinical trials in cancer therapy, has shown promising activities against several microbial infections [2].

Despite the development of vaccines against SARS-CoV-2, we face new waves of COVID-19 which appear following the emergence of variants diverging from the initial strain and resistant to current vaccines [3]. To fight the spread of these new variants, pharmaceutical companies have developed specific antibodies or antiviral therapies for the prevention and treatment of COVID-19 [4]. Thus, several products targeting virus entry or replication have obtained emergency marketing authorizations. However, due to this exceptional situation, we lack perspective on their safety and effectiveness. Moreover, their cost and their mode of administration restrict their use. In this context, our strategy has been to search for a drug capable of both inhibiting the systemic inflammation that creates the severity of the disease, using our expertise on the NF-κB pathway (controlling inflammation) and slow down virus replication in vitro. In order to find novel NF-κB inhibitors, a high-throughput screening of an FDA-approved drug library was developed which allowed the identification of Auranofin, a gold-based salt with anti-inflammatory properties, among NF-κB inhibitors. The latter has shown promising effects against several microbial infections and recent studies suggested that Auranofin inhibits the replication of SARS-CoV-2, although no mechanism of action was proposed [5-7]. In this context, our study shows a dual role for Auranofin by preventing SARS-CoV-2 cell entry and blocking the activation of NF-κB [8]. Using biochemistry experiments and state-of-the-art imaging techniques, it was shown that Auranofin alters cell membrane lipid properties and consequently inhibits the receptor dependent-endocytosis of SARS-CoV-2, having an effect on several variants, including Omicron. It was also observed that Auranofin impacts the lateral diffusion of ACE2, the receptor of SARS-CoV-2, on the cell plasma membrane. In addition, Auranofin acts at early steps of the NF-κB signalling pathway and inhibits its activation in response to viral infection and to cytokine hyperproduction ("cytokine storm") that correlates with multi-organ systemic complications eventually leading to death [4].

Having shown that Auranofin presents a dual effect on SARS-CoV-2 infection, work is currently in progress for testing Auranofin on SARS-CoV-2 infection in vivo with the purpose to its use as a treatment against COVID-19.

Conclusion

In summary, using model cell lines we show that Auranofin acts at several levels to interfere with SARS-CoV-2 entry by endocytosis and through the inflammatory response, which is a source of morbidity in COVID-19. We thus propose that Auranofin could be an attractive therapeutic option to improve severe forms of COVID-19. In vivo studies using animal models as well as clinical studies would make it possible to validate the therapeutic potential of Auranofin.

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