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"Adenosine analogs have a dual immunomodulatory and antiviral function and are potential therapeutic agents against SARS-CoV-2"

SARS-CoV-2 is a contagious virus that causes COVID-19, a disease that has affected millions of people worldwide and claimed over six million lives. The pandemic has unveiled an urgent need for new antivirals to control emerging infectious diseases and potential future pandemics. Classic antivirals are currently designed to directly interfere with pathogens. However, antivirals are often insufficient to rapidly clear infections in the absence of an effective immune response. Immunotherapy could complement the use of antivirals; however, its application to infectious diseases remains largely unexplored.

Adenosine analogs are antiviral drugs which resemble the structure of adenosine, a metabolite that derives from the breakdown of ATP and can suppress the immune response through activation of the Adenosine A2A Receptor (A2AR) in immune cells. Adenosine is overproduced in some infectious diseases, like COVID-19, where it restricts protective antiviral immune responses. Previous work from our lab showed that adenosine-mediated activation of A2AR causes suppression of CD8+ T-cells effector functions in COVID-19 mouse models. Importantly, our group showed that adenosine analogs could restore antiviral T-cell responses in COVID-19 models, through blocking the A2AR. Therefore, we propose that adenosine analogs that interact with A2AR may be endowed with dual – immunomodulatory and intrinsic - antiviral functions.

In this study, we used a drug discovery technique, Molecular Docking, to investigate possible adenosine analogs that could be used as antiviral and immunomodulatory dual agents. We screened adenosine analogs, known or predicted to inhibit SARS-CoV-2 replication, to test if they may bind to A2AR. Ten adenosine analogs were chosen and docked to the A2AR. Out of the ten analogs, three - forodesine, riboprine, and 8-chloroadenosine - were predicted by the docking modeling to bind with high affinity to the A2AR. We then tested whether forodesine could block A2AR activation. To investigate this, we treated CD8+ T cells from mouse spleen and lymph nodes with forodesine or CGS-21680 (CGS), an A2AR agonist, or a combination of the two. Then, we measured the proliferation of T-cells using flow cytometry. We found that forodesine treatment restored T-cell proliferation from the A2AR agonist CGS in CD8+ T-cells, suggesting that forodesine blocks A2AR. Our results indicate that adenosine analogs, like forodesine, may be endowed with immunomodulatory properties through A2AR, in addition to their intrinsic antiviral properties. In conclusion, adenosine analogs, like forodesine, could be used as novel dual – immunomodulatory and intrinsic – antiviral drugs. These compounds could represent game-changing therapies, not only to control COVID-19, but also other emerging viral diseases and future pandemics.