

Immunotherapy of COVID-19 with poly (ADP-ribose) polymerase inhibitors: starting with nicotinamide?

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Abstract

COVID-19 patients in China exhibit a proinflammatory environment that is stronger in severe cases requiring intensive care. The immunity modulators, the aryl hydrocarbon receptor (AhR) and the nuclear NAD⁺-consuming enzyme poly (ADP-ribose) polymerase 1 (PARP 1) may play a critical role in COVID-19 pathophysiology. The AhR is over-expressed in a variety of coronaviruses, including COVID-19 and, as it regulates PARP gene expression, the latter is likely to be activated in COVID-19. PARP expression is enhanced in other lung conditions: the pneumovirus respiratory syncytial virus (RSV) and chronic obstructive pulmonary disease (COPD). I propose that PARP 1 activation, which leads to cell death mainly by depleting NAD⁺ and ATP, is the terminal point in a sequence of events culminating in patient mortality and should be the focus of COVID-19 immunotherapy. Potent PARP 1 inhibitors are undergoing trials in cancer, but a readily available inhibitor, nicotinamide, which possesses a highly desirable biochemical and activity profile, merits exploration. It conserves NAD⁺ and prevents ATP depletion by PARP inhibition, enhances NAD⁺ synthesis, and hence that of NADP⁺ which is a stronger PARP inhibitor, reverses lung injury caused by ischaemia/reperfusion, inhibits proinflammatory cytokines, and is effective against HIV infection. Its unique biochemical properties qualify nicotinamide for therapeutic use initially in conjunction with standard clinical care or combined with other agents, and subsequently as an adjunct to stronger PARP 1 inhibitors.

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