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Anti-SARS-CoV-2 potential of RSK Inhibitors – Combining synergistic effectiveness and resistance prevention

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SARS-CoV-2 infections can have severe consequences, especially for elderly and immunosuppressed individuals. Identifying novel antiviral treatment strategies is an important task, especially in preventing the selection of resistant virus variants. Such treatment strategies include host targeting antivirals (HTAs) and direct acting antivirals (DAAs), each with distinct benefits. Here, we show that SARS-CoV-2 is susceptible to inhibition of the 90kDa ribosomal S6 (RSK) kinases. RSK inhibitors (BI-D1870, BRD 7389) were tested as monotherapies and in combination with the DAAs Remdesivir (RDV) and Nirmatrelvir (NTV). Both RSK inhibitors exhibited anti-SARS-CoV-2 properties in a stand-alone treatment, as well as synergistic effects with the DAAs. Serial passage of B.1.617.2 under increasing inhibitor concentrations (BI-D1870, BRD 7389, RDV, NTV) led to the selection of DAA drug-resistant variants, while the virus remained fully susceptible to RSK inhibitors. Moreover, synergistic combination therapy (BRD+NTV) likewise did not select for resistant viruses. Testing DAA resistant viruses against RSK-inhibitor + DAA drug combinations still revealed a synergistic mode of action, whereas the RDV + NTV combination therapy showed antagonistic effects. In summary, we identified RSK kinases as so far unknown SARS-CoV-2 proviral factor and could show that combining HTAs and DAAs can be a promising new antiviral approach to increase the antiviral efficacy and mitigate resistance selection.

Keywords

SARS-CoV-2, p90RSK kinases, RSK-inhibitors, Antiviral treatment, Combinational therapy, Synergy, Resistance

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No, I am not a Junior Scientist.

Author: Dr SCHREIBER, André (University of Muenster)

Co-authors: Mr AMBROSY, Benjamin (University of Muenster); Dr ANHLAN, Darisuren (University of Muenster); Dr BLETZ, Stefan (University Hospital Muenster); Prof. MELLMANN, Alexander (University Hospital Muenster); Prof. LUDWIG, Stephan (University of Muenster)

Presenter: Dr SCHREIBER, André (University of Muenster)

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