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ABSTRACTS

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Novel antiviral activity of PAD inhibitors against human beta-coronaviruses HCoV-OC43 and SARS-CoV-2

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Question: The current SARS-CoV-2 pandemic, along with the likelihood that emerging viral threats will have to be tackled in the nearby future, highlights the urgent need to develop new effective antiviral agents. In this scenario, innovative host-targeting antivirals (HTAs), which act on host-cell factors essential for viral replication, are a promising class of antiviral compounds.

Methods: By using the HCoV-OC43 and SARS-CoV2 strains as models of infection in human lung fibroblasts (MRC-5) and monkey kidney cells (Vero-E6), we tested the antiviral activity of well characterized PAD inhibitors. We used real time quantitative PCR to quantify copies of the viral genomes, Western blot analysis to evaluate the expression of viral proteins, and plaque assay to evaluate the production of new virions. Furthermore, we assessed the pattern of citrullination upon infection by using a citrulline-specific rhodamine phenylglyoxal (RhPG)-based probe.

Results: Here we show that a new class of HTAs targeting peptidylarginine deiminases (PADs), a family of calcium-dependent enzymes catalyzing protein citrullination, is endowed with a potent inhibitory activity against human beta-coronaviruses (HCoVs). Specifically, we show that infection of many human cell lines with HCoV-OC43 or SARS-CoV-2 leads to enhanced protein citrullination through transcriptional activation of PAD4, and that inhibition of PAD4-mediated citrullination with either of the two pan-PAD inhibitors Cl-A and BB-Cl or the PAD4-specific inhibitor GSK199 curbs replication of both viruses.

Conclusion: Overall, our results demonstrate the potential efficacy of PAD inhibitors in suppressing HCoV infection, which may provide the rationale for the repurposing of this class of inhibitors for the treatment of COVID-19 patients and for consider their efficacy against emerging viral infections