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SARS-CoV-2 non-structural protein nsP3 macrodomain and viral replication: functional characterization and inhibitor screening

Initiative: Innovative Ansätze in der antiviralen Wirkstoffentwicklung

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Viruses belonging to the family of Coronaviridae, Togaviridae, and Hepeviridae contain genes that encode a conserved protein domain, referred to as macrodomain. However, the role of this domain during infection is in need of clarification. Mammalian macrodomain proteins remove enzymatically ADP-ribose, a common post-translational modification, from substrates. ADP-ribosylation is particularly relevant to activate vital stress signaling pathways, like e.g. during viral infection. Studies describing both the enzymatic activity and function of viral macrodomains have defined these domains as de-ADP-ribosylating enzymes, indicating that these viruses have evolved a mechanism to counteract host ADP-ribosylation. In particular, SARS, MERS and SARS-CoV-2 macrodomain enzymes can modulate the host's innate immune response. Indeed, inactivation of the macrodomains of SARS-CoV and several alphaviruses reduces pathogenicity in interferon-proficient cells. This project's goal is to define the function of the SARS-CoV-2 nsP3 macrodomain and to find specific inhibitors. Therefore, virtual screening and crystal structure-based fragment analysis as well as HTP screens will be performed. Next, the project team will refine these by hit-to-lead computational approaches and define interacting proteins and substrates. This preclinical project will herald therapies to prevent severe lung disease triggered by SARS-CoV-2 showing a strategy that can potentially be applied also to other viruses.

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