Cyclophilin inhibitors restrict Middle East respiratory syndrome coronavirus via interferon-λ in vitro and in mice

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ABSTRACT While severe coronavirus infections, including Middle East respiratory syndrome coronavirus (MERS-CoV), cause lung injury with high mortality rates, protective treatment strategies are not approved for clinical use.

We elucidated the molecular mechanisms by which the cyclophilin inhibitors cyclosporin A (CsA) and alisporivir (ALV) restrict MERS-CoV to validate their suitability as readily available therapy in MERS-CoV infection.

Calu-3 cells and primary human alveolar epithelial cells (hAECs) were infected with MERS-CoV and treated with CsA or ALV or inhibitors targeting cyclophilin inhibitor-regulated molecules including calcineurin, nuclear factor of activated T-cells (NFATs) or mitogen-activated protein kinases. Novel CsA-induced pathways were identified by RNA sequencing and manipulated by gene knockdown or neutralising antibodies. Viral replication was quantified by quantitative real-time PCR and 50% tissue culture infective dose. Data were validated in a murine MERS-CoV infection model.

Both CsA and ALV reduced MERS-CoV titres and viral RNA replication in Calu-3 cells and hAECs, improving epithelial integrity. While neither calcineurin nor NFAT inhibition reduced MERS-CoV propagation, blockade of c-Jun N-terminal kinase diminished infectious viral particle release but not RNA...
accumulation. Importantly, CsA induced interferon regulatory factor 1 (IRF1), a pronounced type III interferon (IFNλ) response and expression of antiviral genes. Downregulation of IRF1 or IFNλ increased MERS-CoV propagation in the presence of CsA. Importantly, oral application of CsA reduced MERS-CoV replication in vivo, correlating with elevated lung IFNλ levels and improved outcome.

We provide evidence that cyclophilin inhibitors efficiently decrease MERS-CoV replication in vitro and in vivo via upregulation of inflammatory antiviral cell responses, in particular IFNλ. CsA might therefore represent a promising candidate for treating MERS-CoV infection.