Mouse hepatitis virus liver pathology is dependent on ADP-ribose-1'-phosphatase, a viral function conserved in the alpha-like supergroup

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Viral infection of the liver can lead to severe tissue damage when high levels of viral replication and spread in the organ are coupled with strong induction of inflammatory responses. Here we report an unexpected correlation between the expression of a functional X domain encoded by the hepatotropic mouse hepatitis virus strain A59 (MHV-A59), the high-level production of inflammatory cytokines, and the induction of acute viral hepatitis in mice. X-domain (also called macro domain) proteins possess poly-ADP-ribose binding and/or ADP-ribose-1'-phosphatase (ADRP) activity. They are conserved in coronaviruses and in members of the "alpha-like supergroup" of phylogenetically related positive-strand RNA viruses that includes viruses of medical importance, such as rubella virus and hepatitis E virus. By using reverse genetics, we constructed a recombinant murine coronavirus MHV-A59 mutant encoding a single-amino-acid substitution of a strictly conserved residue that is essential for coronaviral ADRP activity. We found that the mutant virus replicated to slightly reduced titers in livers but, strikingly, did not induce liver disease. In vitro, the mutant virus induced only low levels of the inflammatory cytokines tumor necrosis factor alpha and interleukin-6 (IL-6). In vivo, we found that IL-6 production, in particular, was reduced in the spleens and livers of mutant virus-infected mice. Collectively, our data demonstrate that the MHV X domain exacerbates MHV-induced liver pathology, most likely through the induction of excessive inflammatory cytokine expression.