Targeting 2A protease by RNA interference attenuates coxsackieviral cytopathogenicity and promotes survival in highly susceptible mice.

BACKGROUND: Enteroviridae such as coxsackievirus B3 (CVB3) are important infectious agents involved in viral heart disease, hepatitis, and pancreatitis, but no specific antiviral therapy is available. METHODS AND RESULTS: The aim of the present study was to evaluate the impact of RNA interference on viral replication, cytopathogenicity, and survival. Small interfering RNA (siRNA) molecules were designed against the viral 2A region (siRNA-2A), which is considered to be highly conserved and essential for both virus maturation and host cytopathogenicity. siRNA-2A exhibited a significant protective effect on cell viability mediated by marked inhibition of CVB3 gene expression and viral replication. In highly susceptible type I interferon receptor-knockout mice, siRNA-2A led to significant reduction of viral tissue titers, attenuated tissue damage, and prolonged survival. Repeated siRNA-2A transfection was associated with a further improvement of survival. Various control siRNA molecules had no protective effect in vitro or in vivo. CONCLUSIONS: RNA interference directed against the 2A protease encoding genomic region effectively confers intracellular immunity toward CVB3-mediated cell injury and improves survival, suggesting a potential role for RNA interference for future treatment options targeting enteroviral diseases.