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Abstract

ADAR1 Function Regulates Innate Immune Activation and Susceptibility to Viral Infections †

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Abstract: Viral infection induces innate intracellular antiviral defenses, aimed at restricting virus replication and spread. Therefore, understanding the role and function of innate immune modulators can help to establish novel strategies for viral control. Here, we explore the role of ADAR1 as a regulator of the HIV, HCV, and HPV infections, both in vitro and in vivo, in a genetic association study. Depletion of *ADAR1* induced innate immune activation, observed by a significant increase in *IFNB1* mRNA and CXCL10 expression. Further characterization of *ADAR1* knockdown also showed upregulation of the RNA sensors MDA5 and RIG-I, increased IRF7 expression, and phosphorylation of STAT1. ADAR1 deficiency had differential effects depending on the virus tested: siADAR1 cells showed a significant reduction in HIV-1 infection, whereas *ADAR1* knockdown suggested a proviral role in HCV and HPV infections. In addition, genetic association studies were performed in a cohort of 155 HCV/HIV individuals with chronic coinfection, and a cohort of 173 HPV/HIV-infected individuals was followed for a median of six years (range 0.1–24). Polymorphisms within the *ADAR1* gene were found to be significantly associated with poor clinical outcome of HCV therapy and advanced liver fibrosis in a cohort of HCV/HIV-1-coinfected patients. Moreover, we identified the low-frequency haplotype AACCAT to be significantly associated with recurrent HPV dysplasia, suggesting a role for ADAR1 in the outcome of HPV infection in HIV+ individuals. In conclusion, we show that ADAR1 regulates innate immune activation and plays a key role in susceptibility to viral infections by either limiting or enhancing viral replication. Overall, ADAR1 could be a potential target for designing immune-modulating therapeutic strategies.

Keywords: ADAR1; innate immunity; IFN; HIV; HPV; HCV