PML NUCLEAR BODIES ORCHESTRATE ANTIVIRAL RESPONSE IN HBV-INFECTED HEPATOCYTES

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Promyelocytic leukaemia nuclear bodies (PML-NBs) play roles in various cellular functions and represent a key component of antiviral defense. In the case of hepatitis B virus (HBV), the antiviral activity of PML-NBs has been associated with the presence of SMC5/6 and epigenetic silencing of cccDNA. However, PML-NBs can have a pleiotropic effect on the life cycle of HBV and the role of PML-NBs needs to be further elucidated.

HBV infection does not induce formation of typical "antiviral" PML-NBs probably due to the missing IFN-signalling. Thus, we analyzed the antiviral role of IFN-α-induced PML-NBs in HBV-infected hepatocytes. We demonstrated that IFN-α treatment upregulates PML in HepG2-NTCP cells and in primary human hepatocytes. Furthermore, induction of the antiviral state in HepG2-NTCP cells by IFN-α led to inhibition of the formation of cccDNA in the early step of infection and the secretion of HBV antigens. We also analyzed the formation and composition of PML-NBs by confocal microscopy. We found, that a long IFN-α treatment (>24 hours) led to the reorganization of PML-NBs that was probably dependent on sumoylation. We also observed the association of HBV DNA with PML-NBs by FISH. Moreover, PML-NBs formed ring-shaped structures during the late phase of infection (5 dpi) that directly entrapped HBV capsids. Thus, we demonstrated that PML-NBs inhibits various steps of HBV lifecycle. Collectively, our results demonstrated that PML-NBs positionally orchestrate antiviral response in HBV-infected hepatocytes. These experiments have clinical relevance because of IFN-α therapy in chronically infected patients with HBV.

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