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Highjacking of PI3K/AKT signaling pathway by Hepatitis C virus in TLR9-activated human plasmacytoid dendritic cells

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Background

Plasmacytoid dendritic cells (pDCs) are responsible for the production of type I IFN during viral infection. Viral elimination by IFN-alpha-based therapy in more than 50% of patients chronically infected with hepatitis C virus (HCV) suggests a possible impairment of production of endogenous IFN-alpha by pDCs in infected individuals. Recent studies in the HCVcc-exposed pDCs purified from healthy donors show that HCV is a weak inducer of IFN-alpha *in vitro* and that HCVcc blocks the TLR9-mediated IFN-alpha production. It has been also reported that PI3K/AKT is critical for type I IFN production by pDCs in response to TLR agonists. The specific aim of the present study is to investigate the effect of HCV on PI3K/AKT signaling.

Methods

To this end we exposed pDCs from healthy donors to insect cell-derived HCV-like particles (HCV-LP) or an insect cell control preparation in the presence or absence of TLR7 and TLR9 agonists and determined dynamics of PI3K/AKT phosphorylation by flow cytometry. By this approach we compared the early (AKT phosphorylation) and late (IFN-alpha production) steps of TLR7/TLR9-MyD88 signaling. The levels of cell-free supernatant-secreted IFN-alpha were determined by ELISA.

Results

Expression of TLR9 gene was analysed by quantitative RT-PCR. Whereas phosphorylation of AKT increased 4 times during 12-h culture of pDCs in the presence of IL-3 and it was increased further by 50% after stimulation with CpG-C, it dropped-down to the basal level, when pDCs were preincubated with HCV-LP. Expression of TLR9 during 12-h culture of pDCs in the presence of IL-3 was reduced 10^4 times, whereas it was reduced 10^6 times, when pDCs were stimulated with CpG-C. HCV-LP did not show any silencing effect on TLR9 expression.

Discussion

We conclude that HCV-LP block the TLR9-mediated IFN-alpha production upstream of PI3K/AKT pathway and that HCV-LP do not block transcription of TLR9 gene. These findings suggest that HCV impairs signalization *via* TLR9 upstream of PI3K/AKT pathway in pDCs. Furthermore, our model system will allow elucidating the mechanism of the blockade of TLR9 signaling by HCV in pDCs. (ANRS grant 2007/306).

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