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Et al.

CD81/CD9 TETRASPANINS AID PLASMACYTOID DENDRITIC CELLS IN RECOGNITION OF HCV-INFECTED CELLS AND INDUCTION OF IFNα

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Recognition of hepatitis C virus (HCV)-infected hepatocyes and interferon (IFN) induction are critical in antiviral immune response. We hypothesized that cell-cell contact between pDCs and HCV-infected cells was required for IFNα induction via involvement of cell surface molecules. Co-culture of human peripheral blood mononuclear cells (PBMCs) with genotype 1a full length HCV genomic replicon cells (FL) or genotype 2a JFH-1 virus infected hepatoma cells (JFH-1), not with uninfected hepatoma cells (Huh7.5), induced IFNα production. Depletion of pDCs from PBMCs attenuated IFNα release and purified pDCs produced high levels of IFNα after co-culture with FL replicons or JFH-1 infected cells. IFNα induction by HCV-containing hepatoma cells required viral replication, direct cell-cell contact with pDCs, and receptor-mediated endocytosis. We determined that the tetraspanin proteins, CD81 and CD9 and not other HCV entry receptors were required for IFNα induction in pDCs by HCV infected hepatoma cells. Disruption of cholesterol-rich membrane microdomains, the localization site of CD81 or inhibition of CD81 downstream molecule, Rac GTPase, inhibited IFNα production from co-cultures. IFNα production by HCV infected hepatoma cells was decreased in pDCs from HCV infected patients compared to normal controls. We found that pre-exposure of normal PBMCs to HCV viral particles attenuated IFNα induction by HCV infected hepatoma cells or TLR ligands and this inhibitory effect could be prevented by an anti-HCV E2 blocking antibody. **In conclusion,** our novel data show that recognition of HCV-infected hepatoma cells by pDCs involves CD81/CD9-associated membrane microdomains and induces potent IFNα production.