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

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Recognition of hepatitis C virus (HCV)-infected hepatocytes 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 IFN α 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 IFN α production. Depletion of pDCs from PBMCs attenuated IFN α release and purified pDCs produced high levels of IFN α after co-culture with FL replicons or JFH-1 infected cells. IFN α 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 IFN α 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 IFN α production from co-cultures. IFN α 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 IFN α 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 IFN α production.