P049 TLR9 and RIG-I co-ordinately induce cytokine expression during herpes simplex virus type 2 infection in macrophages

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During viral infections, pattern recognition receptors (PRR)s sense the presence of infection and initiate signalling pathways in the infected cells. Three pathways with important functions in antiviral defense lead to activation of interferon (IFN) regulatory factor (IRF), nuclear factor κB (NF-κB), and the mitogen activating protein kinases (MAPK)s, respectively. These pathways regulate expression of cytokines, chemokines, and IFNs. The aim of the present study was to characterize the requirement for different PRRs in the expression of cytokines during infection with the DNA virus herpes simplex virus (HSV)-2 in macrophages. Toll like receptor (TLR) 2, and 9 have been reported to recognize HSV infection, and we have previously shown that double-stranded RNA accumulates in HSV-2-infected cells. To investigate the role of these TLRs as well as the RIG-I-like RNA helicases in the immediate cellular response to HSV infection, we blocked these PRRs in RAW264.7 macrophage-like cells and looked for activation of signalling pathways and expression of cytokines. While no role for TLR2 was found, blockage of either TLR9 or RIG-I reduced expression of IL-6, RANTES, and IFN-α/β, whereas the induction of TNF-α was inhibited only when TLR9 was blocked. At the level of signal transduction we found TLR9 to be responsible for activation of MAPK p38, RIG-I to mediate the NF-κB response, and both PRRs to participate in activation of IRF-3. Overall the data suggest a dual recognition of HSV-2 by TLR9 and RIG-I, which co-ordinately regulate cytokine expression in response to this virus.