Abstract

Host sensors that recognize pathogen associated molecular patterns and the mechanisms of innate immune response to mouse polyomavirus (MPyV) infection were the main topics of current work. We found that MPyV did not induce interferon (IFN) production during early events of infection, but induced interleukin-6 (IL-6) and other cytokine production without inhibiting virus multiplication. Cytokine microenvironment changed the phenotype of adjacent non infected fibroblasts toward the cancer-associated fibroblast (CAF)-like phenotype. We identified Toll-like receptor 4, a sensor of the innate immunity system, to be responsible for infection dependent IL-6 production. In an effort to determine whether and where virions are released from endosomal compartments into the cytosol, we found that the hydrophobic domains of minor capsid proteins, exposed on the surface of virions after their partial disassembly in the ER, play an important role in effective escape of virions from the lumen part of endoplasmic reticulum into the cytosol, Although naked, partially disassembled virions appear before translocation to the nucleus in the cytosol, viral DNA is not recognized by cytosolic sensors at this phase of infection Sensing of MPyV resulting in IFN production occurs first during viral replication. Mutant virus, defective in nuclear entry, was not able to induce interferon. Both, p204 and cGAS DNA sensors, but not endosomal sensor of methylated DNA -Toll like receptor 9, were involved in recognition of replicating phase of MPyV infection. Although p204 and cGAS colocalized in the nucleus with MPyV genomes, only p204 sensed DNA in the nucleus. Unexpectedly, cytosolic viral DNA leaked from the nucleus and micronucleus-like bodies (induced by genotoxic stress during MPyV infection) were the targets for cGAS and induced its activation. The absence of cGAS in cells did affect IFN production but not interaction of p204 with viral DNA. The outcome of results highlights the complex interactions between the virus and the host innate immunity sensors.

Key words: polyomaviruses; innate immunity, DNA sensing ; TLR4; cGAS, p204; IFI16; interferon-β; interleukin-6