UNDERSTANDING THE INTERPLAY BETWEEN BK POLYOMAVIRUS AND CELULAR RESTRICTION FACTORS

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The most important human polyomavirus are the Merkel cell polyomavirus, the etiological agent of 80% of Merkel cell carcinoma, JCPyV that causes progressive multifocal leukoencephalopathy and BKPyV which causes nephropathy. After initial primary infection and dissemination in the organism, persistence of polyomavirus is, by not well-known mechanism. Local innate immune response and other cellular restriction factors such as macromolecular protein complexes such as the PML nuclear bodies (PML NB) can play a role in the outcome of the infection and promote viral persistency. Our reseach focus on the understanding the molecular mechanisms of innate immune response activation and modulation in response BKPyV.

For this we use two cellular models the human microvascular endothelial cells (HMEVC) from the bladder (bd) which respond to BKPyV by producing interferon (IFN), and the renal proximal tubular epithelial cells (RPTEC), which although do not respond to BKPyV infeciton by producing IFN, PML NBs are reorganized/modifeid during infection, the PML NB are less and larger.

To understand the role of viral replication in the IFN innate immune responses and in the PML NB remodeling induced by the virus, we designed, prepared and characterized a replication-defective BKPyV by introducing a point mutation in the LT helicase domain. The innate immunity response of cells to the mutant virus was studied by quantifying the expression of IFN-β and interferon stimulated genes and analyzing the phosphorylation of STING. In addition, the genomes of the mutant virus were visualized by fluorescence in situ hybridization and their distribution compared with the localization of PML NBs. Our results indicate that HMVECs bd can lauch moderate innate immune response to the nonreplicating virus although the response differ from the response to the wt virus. Furthermore, non-replicating BKPyV genomes associate with PML NBs, thus suggesting that replication is dispensable for interaction bwteeen PML and viral genomes. Further studies are being carried out to fully characterize the cell responses launched by both cell lines to the mutant virus.

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