

## Public Abstract

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Title:Regulation of BK Virus DNA Replication by Transcription Factors and Noncoding RNAs

Human polyomavirus BK (BKV) asymptomatically infects most people during early childhood, and establishes a life-long persistent infection without causing overt clinical symptoms. High level BKV replication occurs predominantly in urogenital tracts of immune-suppressed patients following renal transplantation and bone marrow transplantation, which cause polyomavirus associated nephropathy (PVAN) and hemorrhagic cystitis, respectively. Epidemiological studies indicate that around 30% of kidney transplantation patients are at risk of developing PVAN and 50% of PVAN patients are at risk of transplantation failure.

This dissertation explores the mechanisms by which the genomic noncoding control region (NCCR) regulates BKV DNA replication in cell culture and might be related to the establishment of BKV persistent infection and pathogenesis of PVAN.

These studies indicate that cellular transcription factor NFI interacts with the BKV NCCR and stimulates BKV DNA replication, perhaps through interaction with BKV large T antigen (Tag) and DNA polymerase- $\alpha$  primase (pol- $\alpha$  primase). In contrast, PCAF/GCN5 histone acetyltransferases inhibit BKV DNA replication, possibly by targeting component(s) of DNA replication machinery other than Tag. A search for these targets is proposed, and possible functions of acetylation on BKV Tag are discussed.

In addition, small noncoding RNAs, termed srRNAs, that inhibit BKV DNA replication have been discovered in murine cells. Surprisingly, srRNAs from human cancer cells stimulate BKV DNA replication, suggesting cell type specific expression of srRNAs has distinct role in regulation of BKV DNA replication. We propose that the expression of srRNAs may have implication in the viral tropism, establishment of persistent infection and reactivation.