SIGNAL TRANSDUCTION PATHWAYS (MAPKs) ASSOCIATED WITH ORTHOPOXVIRUSES REPLICATION

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The Orthopoxvirus genus encompasses eight members of the Poxviridae family of viruses, from which *Vaccinia* virus (VACV) is the prototypic virus and is closely related to *Cowpox* virus (CPXV). VACV and CPXV are complex enveloped double-stranded DNA viruses that have the potential capacity of encoding more than 200 gene products along their ≈200 Kbp linear genomes. Their replication cycles occur entirely within the cytoplasmic compartment of infected cells. We have previously shown that VACV stimulates the mitogen-activated protein kinases (MAPKs) MEK/ERK. The signals transmitted downstream by these kinases target the ribosomal S6 kinase (RSK2) and the transcription factors Elk1, c-FOS, c-JUN and EGR-1. Genetic evidences either through dominant-negative approach (c-JUN) or gene silencing (siRNA) (EGR-1) have proved the relevance played by the pathway MEK/ERK/RSK/Elk/FOS//JUN/EGR in viral biology, because both the viral yield and plaque phenotype, but not viral morphogenesis, were significantly diminished under these circumstances. Viral DNA replication and gene expression was also dependent on the above cascade. Though the same pathway is also stimulated during CPXV infection it has been demonstrated not to impact CPXV biology. JUN seems to play distinct roles in VACV biology and integrates signals either emanated by MEK/ERK, which is devoted to virus replication, or MKK4/7/JNK1/2, which is associated with the viral egress of infected cells. The viral kinase B1 seems to be the upstream molecule that delivers the signal to MKK/JNK. VACV and CPXV replication also relies on the survival pathway since inactivation of the PI-3K/AKT pathway has a negative impact on viral biology.

Financial support: CNPq, CAPES, FAPEMIG

Keywords: Orthopoxvirus, Vaccinia vírus, signal transduction