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Activation of RSK and ERK MAPK kinases by ORF45 of Kaposi's sarcoma-associated herpesvirus

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Kaposi's sarcoma-associated herpesvirus (KSHV) is a human DNA tumor virus etiologically linked to Kaposi's sarcoma, primary effusion lymphoma, and a subset of multicentric Castleman's disease. Infection and reactivation of KSHV activates multiple MAPK pathways. Noticeably, the ERK/RSK activation is sustained late during KSHV primary infection and reactivation from latency, but the responsible viral factors and underlying mechanism was unknown. Open reading frame 45 (ORF45) of KSHV is an immediate early, phosphorylated, and tegument protein. Its unique temporal and spatial expression put it in the forefront of coping with host cellular environment. We recently reported that ORF45 interacts with p90 ribosomal S6 kinases (RSKs), a family of serine/threonine kinases that lie at the terminus of the ERK pathway, and strongly stimulates their kinase activities. We found that binding of ORF45 to RSK increases the association of ERK with RSK, such that ORF45, RSK, and ERK form complexes. The complexes shield active pERK and pRSK from dephosphorylation. As a result, the complex-associated RSK and ERK are activated and sustained at high levels. We also demonstrated that RSK and ERK are activated biphasically during KSHV primary infection and lytic replication cycle. We provided evidence that the reciprocal activation of ERK and RSK by ORF45 contributes to the sustained activation of ERK/RSK in KSHV lytic replication. We further demonstrated that ablation of RSK expression by SiRNA or inhibition of kinase activity by specific RSK inhibitors lead to lower KSHV lytic gene expression, reactivation, and virus production, suggesting an essential role of the RSK in KSHV lytic replication. Therefore, inhibition of RSK is likely to disrupt KSHV infection and be a potent target for therapy of KSHV associated diseases.