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Association between cellular RNA splicing machinery and human papillomavirus E4

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Human papillomaviruses (HPV) are ubiquitous DNA tumour viruses in the human population and are the aetiological agents for epithelial cancers such as cervical cancer. The HPV infectious cycle is linked to the differentiation programme of the host cell - the keratinocyte - with permissive replication restricted to differentiating cells. HPV E4 is an abundant protein in infections and its actions are necessary for permissive replication. Using a proteomic approach, we show that HPV E4 associates with the host RNA splicing machinery and suggest that this action facilitates permissive HPV replication. One of the identified targets of E4 is the central splicing regulator SRPK1, a protein-specific kinase involved in the phosphorylation and regulation of the serine/arginine (SR) rich family of RNA splicing factors. Significantly, the association with this kinase is conserved with E4 proteins derived from diverse HPV types, including types 1, 16 and 18. Biochemical and microscopic studies have confirmed colocalisation of E4 and SRPK1 in human keratinocytes grown in tissue culture and notably, in superficial cells of HPV1-induced warts. *In vitro* kinase assays indicate that E4 proteins are phosphorylated by SRPK1. Evaluation of the effect of E4 on SRPK1 function is in progress, but identification of enzyme activities necessary for HPV infection could offer excellent therapeutic targets.

SRPK1 phosphorylates the splice factor ASF/SF2, which has been implicated in the regulation of HPV late gene expression. Thus, we hypothesize that E4, *via* its association with SRPK1, modifies the activity of host cell RNA splice factors to regulate viral gene expression.