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Activation of cell cycle checkpoints by human papillomavirus E4 protein

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Human papillomavirus (HPV) infections are a serious problem for human health; inducing genital warts and respiratory papillomatosis, and epithelial cancers.

HPV early proteins E6 and E7 disrupt host cell checkpoints that control proliferation and apoptosis. In contrast, HPV E4 can activate G1/S and G2/M cell cycle checkpoints. Examination of the molecular action of E4 has shown that HPV1 E4 mediates inhibition of G2-to-M transition by more than one mechanism. Distinct protein forms of E4 orchestrate the individual G2 arrest functions. When two forms are co-expressed, G2 arrest is associated with inactivation of the regulatory kinase Cdk1 by tyrosine15 phosphorylation. Cdc25C and Wee1 compose a phosphatase/kinase switch by which Cdk1 is activated. The E4-arrest function correlates with stabilized Wee1 levels and Wee1 overexpression enhanced the extent to which E4-expressing cells arrest in G2. Depletion of Wee1 by siRNA alleviated the G2 block indicating that maintenance of Wee1 activity is necessary for E4 inhibition of cell division. G2 arrest function encoded by another modified form of E4 is associated with loss of cyclin B1-cdk1 complexes. Our study indicates that different forms of E4 exhibit distinct biological actions on the cell cycle.

Because E4 acts as a major regulator of permissive HPV replication, we hypothesize that differential expression of E4 proteins during the viral life cycle determines the host cell cycle status and these actions support HPV replication. Moreover, the opposing effects on cell cycle progression between E4 and HPV oncoproteins may necessitate loss of E4 expression for malignant progression of infected cells.