E7 takes the foot off the brake

Human papillomavirus (HPV) can transform epithelial cells and cause cervical cancer. Two recent articles published in *The Journal of Virology* explore the role of the HPV E7 protein in this process.

The ability of HPV to transform host cells requires the viral E6 and E7 proteins. Overexpression of E7 in eukaryotic cells causes genomic instability through several mechanisms, including the induction of polyploidy, a condition that predisposes the cell to cancer. The mechanisms by which E7 exerts this effect are unclear; an interaction between E7 and the tumour suppressor protein retinoblastoma (Rb) has previously been speculated to play a part. Eukaryotic cell checkpoints ensure that the correct number of chromosomes is maintained. During mitosis, the spindle checkpoint ensures that the onset of anaphase is delayed until the chromosomes are correctly attached to the mitotic spindle, whereas the post-mitotic checkpoint allows cells to arrest at G1

in response to a range of insults after adaptation to the spindle checkpoint. In the first study, Heilman and colleagues expressed the E7 protein in primary keratinocytes and epithelial cells, and detected a small increase in the percentage of polyploid cells, an effect that was exacerbated by the addition of nocodazole or monastrol, compounds that induce the mitotic spindle checkpoint. Using markers of cell cycle progression and fluorescence microscopy assays, they were able to conclude that the spindle assembly checkpoint was still active in the presence of E7 and that expression of E7 did not significantly affect the overall length of mitosis. Despite not having undergone cytokinesis, the nocodazole-treated cells were in a G1-like state, in which the post-mitotic checkpoint should prevent initiation of DNA replication. However, the authors showed that a large proportion of E7-expressing cells initiated DNA replication prior to cytokinesis. The authors speculate that this bypass of the post-mitotic

checkpoint is the source of the polyploidy in HPV-infected cells. Based on the known interaction of Rb with E7 and the similarity of the phenotypes of E7-transfected cells and Rb^{-/-} cells, the authors further speculate that E7 might inactivate Rb, leading to polyploidy.

In the second report, Nguyen and Münger show that the E7 protein can also trigger the spindle checkpoint. Having previously shown that E7 can cause dynein to delocalize from the mitotic spindles, they now show that the carboxy-terminal region of E7 can interact with the nuclear mitotic apparatus protein (NuMA), a protein that plays a part in mitotic spindle organization and stabilization. Expression of E7 increased the number of disorganized mitoses, which the authors suggest may have an accessory role in causing aneuploidy. In contrast to Heilman *et al.*, Nguyen and Münger show that these disorganized mitoses represent cells in prometaphase and detected a mitotic delay. The source of the difference in the findings is unclear but may represent differences in the methodologies that were used and the number of cells that were analysed.

E7 can therefore affect the process of mitosis through multiple mechanisms. How these mechanisms contribute to the induction of aneuploidy and cancer development remains to be discovered.

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ORIGINAL RESEARCH PAPER Heilman, S. A. *et al.* Abrogation of the postmitotic checkpoint contributes to the polyploidization in HPV E7 expressing cells. *J. Virol.* 7 Jan 2009 (doi:10.1128/JVI.02149-08) | Nguyen, C. L. & Münger, K. The human papilloma virus E7 protein deregulates mitosis via an association with the nuclear mitotic apparatus protein-1 (NuMA). *J. Virol.* **83**, 1700–1701 (2009)