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Genomic instability induced by the HPV E7 Oncogene

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Infection by specific types of human papillomavirus (HPV) is strongly associated with development of cervical cancer. However, HPV infection is necessary but not sufficient for cervical carcinogenesis. Genomic instability caused by HPV allows cells to acquire additional mutations required for malignant transformation. Genomic instability in the form of polyploidy has been demonstrated for an important role in cervical carcinogenesis. We have recently found that HPV-16 E7 oncogene induced polyploidy in response to DNA damage yet the mechanism is not known. Here we present evidence demonstrating that HPV E7 induces endoreduplication, a process of successive rounds of host DNA replication without an intervening mitosis. Interestingly, the DNA replication initiation factor Cdt1, whose uncontrolled expression induces endoreduplication in human cancer cells, was up-regulated during E7-induced endoreduplication. Moreover, down-regulation of Cdt1 impaired the ability of E7 to induce endoreduplication. Cdt1 has been shown to subject to cyclin-dependent kinase (Cdk)-mediated phosphorylation that is followed by degradation. Consistent with this notion, we demonstrated that inhibition or down-regulation of mitotic kinase Cdk1, but not Cdk2 that normally functions at the G1/S transition, induced endoreduplication in E7 expressing cells. These results demonstrate an important role for Cdt1 in HPV E7-induced endoreduplication and Cdk1 in regulation of this process. These studies shed light on mechanisms by which HPV induces genomic instability.

Biography

Jason J Chen has completed his Ph.D from Columbia University and postdoctoral studies from Tufts University School of Medicine. He is an Associate Professor of Medicine at University of Massachusetts Medical School and a Guest Professor at Shandong University, China. Dr. Chen's major research interests include cancer biology, virology, anti-viral/cancer therapy. He has worked on HPV for nearly 20 years. His current research focuses on modulation of cell cycle checkpoints by HPV oncogenes. He has published more than 30 articles in reputed journals and serving as an editorial board member of several journals.