

# Keeping Oncogenic HPV in Check: How the Interplay between HPV Oncoproteins and microRNAs Affects Carcinogenesis

*For close to a century, researchers have known that certain viruses can cause cancer, but the molecular mechanisms by which this happens are far from understood. A class of molecules discovered relatively recently, microRNAs (miRNAs), appears to play a significant role in cell proliferation and differentiation, and aberrant miRNAs are associated with several cancers. In the April 2009 issue of RNA, Zhi-Ming Zheng, M.D., Ph.D., Investigator in CCR's HIV and AIDS Malignancy Branch, shows for the first time a link between oncogenic viral infection and miRNA expression, which controls cell growth.*

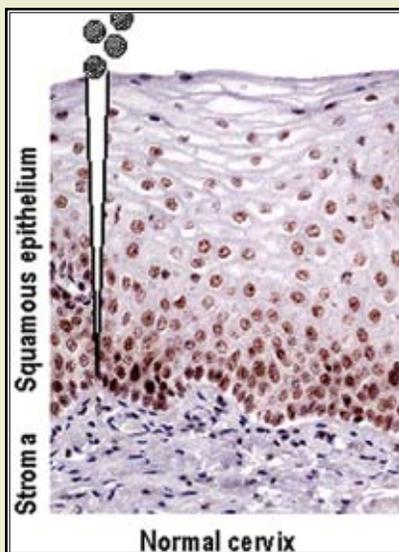
Human papillomavirus (HPV) is a leading cause of genital and anal cancers, accounting for more than 99 percent of cervical cancers and many anal and penile cancers, according to the American Cancer Society. We know that the viral oncoprotein E6 is a critical factor in tumor formation and that it acts to destabilize the tumor suppressor

p53. The p53 tumor suppressor protein, in turn, regulates the transcription of several genes that keep cell proliferation in check by inducing cell cycle arrest, DNA repair, or apoptosis. But which of these myriad targets of p53 are critical for the virus to promote tumor formation?

Tumor-suppressive miR-34a was recently identified as a direct target of the p53 transcription factor. Intrigued, Zheng and his colleagues decided to test the hypothesis that miR-34a might be a critical player in HPV induction of cervical cancer. They found that cervical cancer tissues and cell lines had reduced levels of miR-34a, that viral oncoprotein E6 was necessary for this reduction, and that boosting miR-34a levels in these cells retarded proliferation. "HPV infection controls the cell cycle progression through oncogene E6," said Dr. Zheng. "Previously, we only understood that the oncogene E6 downregulates p53; now we add one more layer to this understanding by finding that miR-34a is regulated by oncoprotein E6. So this is another way to interpret how HPV causes cancer."

Since the publication of this study, Dr. Zheng and colleagues have focused their research on the molecular targets of miR-34a, which remain largely unidentified. In May 2009, the team presented an abstract at the 25th International Papillomavirus Conference and Clinical Workshop in Sweden, revealing a newly identified target of miR-34a: p18, a tumor suppressor and checkpoint component of the cell cycle. Dr. Zheng noted, "By understanding how p18 is targeted by miR-34a, we may be able to use miR-34a and p18 as markers for the diagnosis and prognosis of cancer." He added, "Our study provides the first evidence that viral proteins regulate cellular miRNA expression. So this could be a clue to what proteins for other cancer-causing viruses—not just HPV—do."

*To learn more about Dr. Zheng's research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?Name=zheng>.*



(Image: Z. Zheng, CCR)

Human papillomavirus infects the cervix at the squamous epithelium.