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### Abstract

Abrogation of p53 tumor suppressor protein function by human papillomavirus (HPV) E6 oncoprotein expression is a key event in the pathogenesis of cervical cancer. p53, a central regulator of apoptotic pathways, mediates responses to DNA damage and other cellular stresses. Loss of p53 function results in accelerated cell division rate and decreased sensitivity to proapoptotic signals.

The present study aimed to investigate whether disruption of E6-p53 interaction can sensitize cervical cancer cells to conventional cancer chemotherapy drugs *in vitro*. Various chemotherapy compounds were found to reduce E6 mRNA levels and activate p53 in several cervical cancer cell lines. The activated p53 was generally proapoptotic after these treatments, with one important exception: cisplatin-induced p53 was antiapoptotic. RNA interference-mediated E6 silencing (E6 RNAi) increased the p53 activation produced by concurrent chemotherapy, consequently enhancing the p53-mediated proapoptotic (or antiapoptotic) effect. Surprisingly, E6 RNAi alone induced only transient p53 activation despite continuous suppression of E6 mRNA. Instead of apoptosis, cell growth was inhibited. Several endogenous p53 antagonists – MDM2, COP1, Pirh2, and JNK – were found to be activated in response to E6 RNAi in non-stressed cervical cancer cells. This finding may at least partially explain the modest cellular responses to anti-E6 treatments in previous studies.

According to the present study, restoration of wild-type p53 function by targeting the E6-p53 interaction may have therapeutic potential in cervical cancer. Nevertheless, E6 targeting should be combined with conventional chemotherapy or approaches aimed at endogenous p53-antagonizing machinery to prevent quick fading of the p53 activation.

**Key words:** cervical cancer, human papillomavirus, E6, p53, chemotherapy, chemoradiation, chemosensitivity, cisplatin, RNA interference, MDM2