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Novel mechanism of the cervical carcinogenesis

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HPV infections are common in healthy women but only rarely cause cervical cancer, suggesting that individual genetic susceptibility may play a critical role in the establishment of persistent HPV infection and development of cervical cancer. We provide convincing *in vitro* and *in vivo* evidence showing that disruption of the Hippo pathway and subsequent hyperactivation of *YAP1* oncogene is a critical pathological event that determines individual susceptibility to HPV infection and cervical carcinogenesis. We found that hyperactivation of *YAP1* in mouse cervical epithelium was sufficient to induce malignant transformation of cervical epithelial cells and promote development of invasive cervical cancer. Cervical epithelial cell-

specific HPV16 E6/E7 and *YAP1* double knock-in mouse model demonstrated that HPV synergized with hyperactivated *YAP1* to promote the initiation and progression of cervical cancer. Our mechanistic studies indicated that hyperactivation of *YAP1* in cervical epithelial cells facilitated HPV infection via increasing the putative HPV receptor molecules and disrupting the host cell innate immunity. Our finding challenges the dogma that HPV is a necessary agent for the development of cervical cancer, uncovers a novel mechanism for the cervical carcinogenesis, and provides new targets for developing strategies to improve prevention and treatment of cervical cancer.

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