Analysis of the relationship between human papillomavirus and the cellular survivin gene

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Carcinoma of the uterine cervix is one of the most common malignant diseases among women worldwide. Several oncogenic, or high-risk human papillomaviruses (HPVs) are thought to play a critical role in the development of the carcinoma. More than 90 percent of the cervical lesions contain different types of HPV, in half of the cases HPV 16 is detected.

Besides HPV infection, other factors are involved in the development of cervical carcinoma. These factors include the genetical and immunological characteristics of the host, cellular processes, and different co-factors, such as hormonal effects, smoking, nutrition, sexual habits.

A potential co-factor may be a recently discovered cellular protein, called survivin, a novel member of the inhibitor of apoptosis protein (IAP) family. The product of survivin gene not only suppresses apoptosis but also controls cell division. Survivin is undetectable in most terminally differentiated normal tissues but is expressed in embryonic and fetal organs and is present in most malignant tumours. Human papillomaviruses (HPV) are thought to play an important role in the development of cervical cancer. By interfering in the cell cycle, the viral oncoproteins (E6 and E7) can induce the immortalization of the host cell. The transcriptional effects of the HPV-16 E6 and E7 proteins on the survivin promoter in transiently transfected cell lines using luciferase tests were examined. HPV-16 E6, but not E7, was found to significantly transactivate the survivin promoter. Experiments performed in different cancer cell lines and with different E6 mutants indicated that the effect of E6 on the survivin promoter is largely dependent on p53 status. In accordance with this, the p53 tumour suppressor protein downregulated the expression of survivin. As E6 is able to interact with p53 and induces its ubiquitin-dependent degradation, it appears that the transactivation effect of E6 on survivin is mediated by the p53 degradation pathway. Transduction of HPV-16 E6 and E7 into human embryonic fibroblast cells showed that the HPV oncoproteins can upregulate endogenous survivin mRNA. Importantly, synchronization experiments of the cell cycle showed that the effect of HPV-16 E6 on survivin transcription is independent of the cell cycle.

A common polymorphism at the survivin gene promoter (G/C at nt -31) was shown to be correlated with survivin gene expression in cancer cell lines. Our aim was to investigate whether this polymorphism could be involved in the development of HPV associated cervical carcinoma. Survivin promoter polymorphism was detected in patients with cervical cancer, patients with equivocal cytologic atypia and in a control population using PCR-RFLP (restriction fragment length polymorphism) and PCR-SSCP (single strand conformation polymorphism) analysis. HPV was typed in cervical cancer and cytologic atypia patients using PCR-RFLP. We could not find any statistically significant differences in the genotype distributions of the survivin promoter variants among our study groups. Our findings suggest that the survivin promoter polymorphism at nt -31 may not represent an increased risk for the development of cervical cancer, at least in the population studied here.