

SUMMARY

EFFECT OF HUMAN PAPILLOMAVIRUS INFECTION ON EPIGENETIC REGULATORY MECHANISMS AND SIGNAL TRANSDUCTION IN KERATINOCYTES

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Cervical cancer is induced and maintained by oncogenic human papillomavirus (HPV) infection. Among various cofactors promoting cervical carcinogenesis, my research work targeted the mechanism of intratumoral IL-10 production and the activation of the Src-family non-receptor tyrosine kinases.

We have demonstrated that in keratinocytes and cells of cervical epithelial origin the IL-10 promoter is repressed by epigenetic regulatory mechanisms in a lineage specific manner. CpG methylation of the proximal promoter region and absence of acetylated H3 and H4 histones indicating closed chromatin state were identified as major determinants for transcriptional silencing of IL-10 expression in normal and neoplastic human epithelial cells. Regardless the presence of high-risk oncogenic HPV genomes, the lineage-specific epigenetic silencing of IL-10 expression was maintained uniformly in keratinocytes and in epithelial cell lines of cervical cancer origin. Our results support the notion that during cervical carcinogenesis, a possible source of topical IL-10 secretion are the leukocytes infiltrating the uterine cervix.

Elevated activity of Src kinase is accompanied with increased cell proliferation and invasivity in HPV-associated malignancies. Therefore, we used human keratinocytes transduced with HPV 16 E6, E7 or both oncogenes to investigate whether the activation of the Src-family kinases is a downstream effect of the papillomaviral oncoproteins. mRNA and protein expression as well as activation state (indicated by phosphorylation at specific tyrosine residues) of ubiquitously expressed SFKs, namely Src, Yes and Fyn, was investigated in both proliferating and differentiating keratinocytes. We have shown that HPV 16 oncoproteins upregulate Src family kinases Src and Yes via posttranscriptional mechanisms. Furthermore, HPV 16 E7 enhanced the activating phosphorylation of all expressed Src-family kinases in keratinocytes. The altered expression or activity of Src-family

kinases can serve as both initiating and maintaining oncogenic mechanisms during HPV-associated malignancies.

Keywords:

human papillomavirus, cervical carcinoma, promoter methylation, epigenetic regulation, Src-family kinase

Kulcsszavak:

humán papillomavírus, méhnyakrák, promóter metiláció, epigenetikai szabályozás, Src kináz