The 3' region of Human Papillomavirus type 16 early mRNAs decrease expression

Background: High risk human papillomavirus (HR-HPV) infects mucosal surfaces and HR-HPV infection is required for development of cervical cancer. Accordingly, enforced expression of the early HR-HPV proteins can induce immortalisation of human cells. In most cervical cancers and cervical cancer cell lines the HR-HPV double stranded DNA genome has been integrated into the host cell genome. Methods: We have used a retroviral GUS reporter system to generate pools of stably transfected HaCaT and SiHa cells. The HPV-16 early sequences that are deleted upon integration of the HPV-16 genome was inserted into the 3' UTR of the reporter mRNA. Pools containing thousands of independent integrations were tested for the steady state levels of the reporter mRNA by Real Time PCR and reporter protein by a GUS enzymatic activity assays. In addition, we tested the cellular distribution and half lives of the reporter mRNAs. The integrity of the reporter mRNAs were tested by northern blotting. Results: We show that the 3' region of the HPV-16 early mRNAs (HPV-16 nucleotide (nt.) 2582-4214) act in cis to decrease both mRNA and protein levels. This region seems to affect transcription from the exogenous minimal CMV promoter or processing of the reporter mRNA. The observed repression was most pronounced at the protein level, suggesting that this sequence may also affect translation. For the HPV types: 2, 6, 11, 13, 18, 30, 31, and 35 we have investigated the regulatory effect of the regions corresponding to the HPV-16 nt. 3358 - 4214. For all types, except HPV-18, the region was found to repress expression by posttranscriptional mechanisms. Conclusion: We find that the 3' region of HPV-16 early mRNAs interfere with gene expression. It is therefore possible that the deletion of the 3' part of early HPV-16 mRNAs occurring during cervical oncogenesis could contribute to transformation of cells through deregulation of the viral oncogene synthesis. Moreover, we find that the corresponding region from several other HPV types also repress expression, suggesting that the repression by this region may be a general feature of the HPV life cycle.

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