Aim of our program is the analysis of the molecular mechanisms by which the human papillomavirus type 16 (HPV16) E5 protein modulates activation of the epidermal growth factor receptor and the effects of this modulation on gene transcription. Further, we started a new approach concerning activation of the phospholipases in E5-expressing cells. This approach is based on the observations that E5 is associated with cellular membranes, and that this association results in changes in the phospholipid composition of cellular membranes.

Effect of The Human Papillomavirus Type 16 E5 Protein on Signal Transduction


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The human papillomavirus type 16 E5 (HPV16-E5) protein is a membrane protein, extremely hydrophobic and mainly localized at the endosomes and the Golgi membranes. Its physiological function is unknown but it has been suggested that it is related to growth factor-mediated signal transduction. E5 seems to be enriched in CINIII lesions but published reports show that its presence is not necessary for maintaining the transformed phenotype in well developed carcinomas.

We have already shown that HPV16 E5 is able to control gap-junction-mediated cell-cell communication by modulating connexin43 phosphorylation. Since this gap junction protein was phosphorylated in a src- and a MAP kinases erk1/2-dependent process, we started with a series of experiment aiming to analyze the effect of the viral protein on growth factor-mediated and -independent signalling. We first demonstrated that in vaginal keratinocytes transcription of E5 is associated with increased cellular life span, suggesting that the protein is involved in the first stages of cellular transformation [1]. Since in keratinocytes an autocrine/paracrine system is probably responsible for proliferation, we analyzed the effects of E5 on the activation of the members of the EGFR family in human keratinocytes in dependence of the ligand used [2, 6]. Our results showed that HPV16 E5 is responsible for an increased EGF-mediated signalling by a mechanisms involving increased receptor tyrosine phosphorylation [2]. This effect seems to be independent on the culture conditions, since in raft cultures produced with human keratinocytes expressing HPV16 E5, we also could demonstrate a strong modulation of EGF receptor activation [8]. This modulation was proved to be independent on the binding of HPV16-E5 to the endosomal 16K subunit (proteolipid) of the proton ATPase as postulated by other authors. Using mutant deletions we could show that E5 binds the proteolipid but this binding has no effects on EGFR activation modulation [11].

These results were extended by showing that E5 expression is not accompanied by gross changes in protein glycosylation, although most of the viral proteins were localized at the Golgi apparatus [10]. Interestingly, we observed also an effect of E5 on the cell-cell communication when using raft cultures instead of monolayer cultures, although the molecular mechanisms mediated by E5 were different, thus demonstrating that the effects shown in monolayer were not due to the culture conditions used [9].

Since E5 is a membrane protein, we decided to start with a new approach concerning the behaviour of the phospholipases in E5-expressing cells. We observed that HPV16
E5 is able to modulate the activity of the PLC-γ1, and to increase the amount of DAG and IP₃, with the concomitant effects on PKC and calcium signalling [5].

Besides this program, we also analyzed the characteristics of the promoter of a low-risk virus type, HPV11, in transgenic mice. We observed that HPV11 is able to trigger the expression of a heterologous gene in the hair follicle epithelium in a specific manner [3, 4]. This results open the possibility to use this promoter fragment to precisely express genes in potential skin epithelial stem cells.

Publications (* = external co-author)