HPV-16 E7 CONFERS RESISTANCE TO THE ANTIPROLIFERATIVE EFFECT OF RAPAMYCIN IN ORGANOTYPIC CULTURES OF KERATINOCYTES.

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HPV infection has a prime etiologic role in development and progression of cervical cancer, one of the most frequent forms of cancer among women worldwide. HPV-16 E6 and E7 oncoproteins are able to induce degradation of p53 and pRb tumor suppressor proteins respectively. Moreover, the expression of these oncoproteins is related to alterations in the PI3K/AKT/mTOR pathway. Since it was demonstrated that E7 translation is dependent on mTOR activity we aimed to investigate the effect of mTOR inhibition on the proliferation of organotypic cultures of primary human keratinocytes (PHK) expressing HPV-16 E6 and E7 oncogenes. PHK were infected with retroviruses containing HPV-16 E6 or E7 genes. These cells were used to generate epithelial organotypic cultures. After 9 days, cultures were treated with 100ng/ml of Rapamycin (mTOR inhibitor) for 3 days. Immunohistochemical analysis was performed to evaluate proliferation. Proliferation of normal PHK was inhibited by rapamycin. The treatment also induced a flattened morphology in all cell layers. The same was observed for E6 expressing cultures. On the other hand, E7 expressing PHKs were resistant to rapamycin treatment in respect to proliferation. These results show for the first time that the rapamycin antiproliferative effect is bypassed by the expression of a viral oncogene.

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