PIR/NF-kB activation by Human papillomavirus-16 E7 is mediated through EGFR/PI3K/AKT signaling pathway in epithelial oral cancer cells

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Oral squamous cell carcinoma (OSCC) is in part, associated with high-risk human papilloma virus 16 (HPV16) infection. The viral life cycle implies the expression of two viral oncoproteins, E6 and E7 that promote degradation of key regulators of apoptosis and cell cycle: p53 and pRb. It has been suggested that HPV contributes to poor prognosis of this disease by acting directly on the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway to induce a metastatic phenotype. Previously, we have found that HPV16 E7 oncoprotein promotes an increase of pirin levels, a regulator of NF-κB. In addition, since pirin protein positively regulates epithelial-mesenchymal transition (EMT) and migration, this is associated with tumor progression. However, signaling pathways and mechanisms involved are unclear. Methods.Molecular markers associated to the oncogenic role of HPV16 E7 were evaluated using transcriptase-reverse quantitative PCR (RT-qPCR) and Western Blot (WB). In addition, migration ability of the cells was evaluated using transwells. On the other hand, we performed Luciferase reporter assays for evaluating NF-κB activation. Finally, EGFR/MAPK activation was evaluated by WB and Proteome Profiler Human Phospho-Kinase Array Kit.Results. Our datasuggest that EGFR and PI3K/AKT1 are involved in PIR regulation induced by E7, mainly related to response to oxidative stress. We also showthat EGFR/PI3K/AKT is activated in the presence of HPV16 E7. Through the use of reporters and array kit we observed that HPV16 E7 regulates the activation of NF-κB. Conclusion. These findings suggest that HPV16 E7 regulates PIR/NF-κBand EGFR/PI3K/AKT1pathways in human oral cells. The characterization of the mechanism involved in PIR activation opens the possibility of new therapeutic targets in HPV-associated oral cancer.

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