Infectious Agents and Cancer

Oral presentation

An invasion mechanism for human papillomavirus related cancers: HPV 16 E6 degrades PTPN13 allowing enhanced map kinase signaling

AC Hoover*[1], GL Strand[2], PN Nowicki[3], ME Anderson[1], AJ Klingelhutz[4], AD Bossler[2] and JH Lee[5]

Address: [1]University of Iowa Roy J. and A. Carver College of Medicine Department of Otolaryngology, Iowa City, Iowa, USA, [2]University of Iowa Roy J. and A. Carver College of Medicine Department of Pathology, Iowa City, Iowa, USA, [3]University of Iowa Roy J. and A. Carver College of Medicine Department of Gynecologic Oncology, Iowa City, Iowa, USA, [4]University of Iowa Roy J. and A. Carver College of Medicine Department of Microbiology, Iowa City, Iowa, USA and [5]Sanford Department of Otolaryngology/Sanford Cancer Research, Sioux Falls, South Dakota, USA

* Corresponding author

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Oncogenic forms of human papillomavirus (HPV), most commonly HPV 16, are a causative factor in more than 90 percent of cervical and 25 percent of head and neck squamous cell carcinomas (HNSCCs). We have recently described a novel function of the PDZ binding motif of the high risk HPV 16 E6 protein in that it physically associates with and causes degradation of a non-receptor protein tyrosine phosphatase (PTPN13). Here, we describe an important synergy between PTPN13 loss and Ras activating oncogenes that results in enhanced signaling through the Ras/RAF/MEK/Erk cascade. We show that in a syngeneic mouse model of tonsillar squamous cell carcinoma, E6 or shRNA mediated PTPN13 loss synergizes with ErbB2 for invasive growth of mouse tonsil epithelial cells in vivo. Examination of signaling pathways downstream of ErbB2 and Ras revealed that in mouse and human epithelial cells, PTPN13 loss correlates with enhanced MAP Kinase activity. Transfection experiments in HEK 293 cells showed that co-expression of ErbB2, EGFR, or H-Ras^{V12} with PTPN13, as compared to an empty vector control, resulted in decreased levels of phospho-Erk and phospho-MEK, while a phosphatase null PTPN13 mutant was unable to inhibit MAP Kinase signaling. Through analysis of human tumor samples, we have identified a subset of HPV negative HNSCC's that have functionally significant PTPN13 phosphatase domain mutations. Finally, we have shown MAP Kinase inhibition by pharmacologic agent U0126 results in decreased phospho-Erk and inhibition anchorage independent growth in tumorigenic cell lines that have lost PTPN13, either through expression of E6 or down regulation by shRNA. These findings suggest an important synergy between PTPN13 loss and MAP Kinase activating cellular oncogenes commonly found in HPV related cancers. Inhibition of the MAP Kinase pathway may provide a potential therapy based on a viral mechanism of transformation.