How Beta Hpvs Impede UVB-Induced DNA Damage Repair in Skin Cancer

September 17, 2012

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The papillomavirus family encompasses over 180 viruses that infect the cutaneous and mucosal epidermis and induce hyperproliferative lesions. More than 100 of these are human pathogens and include both viruses that have the potential to cause cancer and viruses that are associated with more benign conditions. For example, within the alpha genus of human papillomaviruses (HPVs), there are 'high risk' HPVs, so-called because they are the primary etiological agents of anogenital cancers, and 'low risk' HPVs, which are associated with genital warts. It is now known that the E6 and E7 proteins of high risk alpha viruses possess oncogenic activities required for tumor development and maintenance that are not observed with low risk alpha E6 and E7 proteins.

In the case of beta HPV, the oncogenic activity of E6 is less clear. Although beta viruses have been found in non-melanoma skin cancer (NMSC) cells, they do not appear to be required for tumor maintenance. Moreover, UVB is considered the primary causative agent of NMSC. Beta HPV has therefore been suggested to act as a cofactor that increases the carcinogenic potential of UVB exposure. Indeed, previous studies have shown that DNA damage induced by UVB exposure persists longer in E6-expressing cells than in negative controls. In addition, the Galloway Lab recently discovered that E6 proteins from beta HPV type 5 and 8 viruses (5E6 and 8E6, respectively) promote the degradation of p300, a protein involved in the UVB-induced DNA damage response. These findings spurred postdoctoral fellow Dr. Nicholas Wallace from the Galloway Lab and colleagues from both the Galloway and Grandori Labs in the Human Biology Division to examine how beta E6 destabilization of p300 affects the DNA damage response to UVB exposure, thus potentially promoting the development of NMSC.

Using human cells that are susceptible to HPV infection and immunohistochemistry, the authors confirmed that cells with UVB-induced DNA damage persist at elevated frequencies for hours longer in 5E6- and 8E6-expressing groups than in the negative control group. They also observed the subsequent accumulation of phosphorylated H2AX in 5E6- and 8E6-expressing cells, which serves as a molecular signal that unrepaired DNA damage deteriorates with time.

Importantly, the authors demonstrated that the DNA repair defects observed in 5E6- and 8E6-expressing cells result from an E6-induced deficiency in p300. As p300 is required for the activation

of ATR, and ATR activates tumor suppressor functions of p53 (e.g., arresting the cell cycle to prevent unwanted replication of damaged DNA), Wallace *et al.* also examined ATR levels and cell cycle arrest in 5E6- and 8E6-expressing cells following UVB exposure. They found that these cells were indeed deficient in ATR and that their cell cycles were not stalled in a phase prior to DNA replication.

Therefore, it appears that certain beta E6 proteins play a role in both impeding DNA repair and expanding DNA damage. As the above characteristics were not observed with the beta HPV type 38 E6 protein, which was also included in this study, it suggests that beta HPV viruses exhibit different oncogenic propensities similar to those of alpha HPV viruses.

Fortunately, the authors also observed that 5E6- and 8E6-expressing cells are more susceptible to DNA damaging chemotherapy agents than negative control cells as a result of their defective DNA damage repair, suggesting that NMSC may respond well to this class of chemotherapeutics.

Wallace NA, Robinson K, Howie HL, Galloway DA. 2012. HPV 5 and 8 E6 abrogate ATR activity resulting in increased persistence of UVB induced DNA damage. *PLoS Pathogens* 8:e1002807.

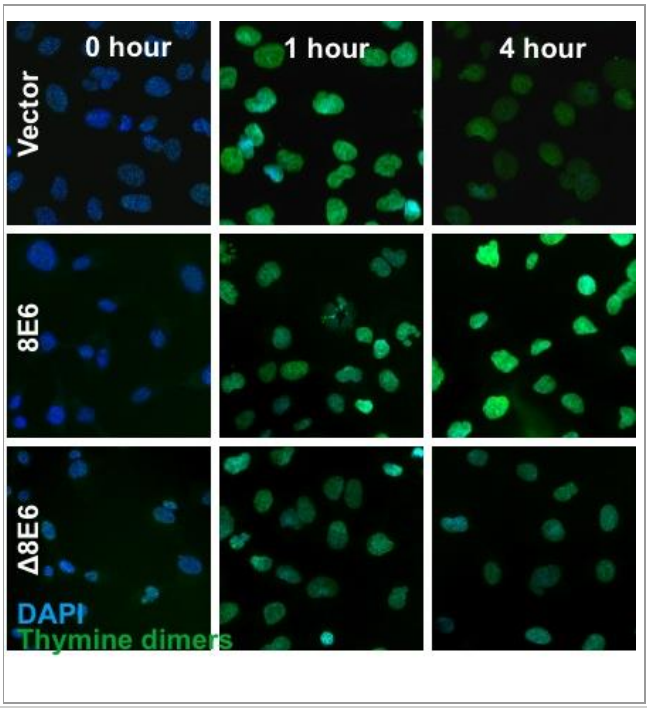

Image provided by Dr. Nicholas Wallace

Human cells transduced with a retrovirus to express the E6 protein from beta human papillomavirus type 8 (8E6, middle row) exhibit a diminished UVB-induced DNA damage response, resulting in the persistence of DNA damage as thymine dimers (green immunostaining). This observation is dependent upon the ability of 8E6 to promote the degradation of p300, a protein involved in the cellular response to DNA damage, as cells expressing a variant of 8E6 that does not degrade p300 (Δ8E6, bottom row) repair thymine dimers similar to negative control cells (vector, top row). Cell nuclei are stained blue with DAPI.