EXPOSURE OF HPV-31b INFECTED KERATINOCYT TO CIGARETTE SMOKE CARCINOGEN BENZO[A]PYRENE RESULTS IN ALTERATION OF HOST CELL CYCLE PROFILE AND VIRAL LIFE CYCLE

Samina Alam, Brian S. Bowser, Michael J. Conway, Horng-Shen Chen, Craig Meyers
Penn State College of Medicine, Hershey, United States

Background: Epidemiological studies suggest that cigarette smoke carcinogens are cofactors which synergize with Human Papillomaviruses (HPV) to increase the risk of cervical cancer progression. Benzo[a]pyrene (BaP), a major carcinogen in cigarette smoke, is detected in the cervical mucus, and may interact with HPV.

Materials and Methods: We generated raft cultures using a HPV31-infected cell line and treated them with increasing concentrations of BaP, a well characterized cigarette smoke carcinogen.

Results: High concentrations of BaP treatment were cytotoxic to HPV31-infected raft cultures but not to primary raft cultures generated using human foreskin keratinocytes (HFK). Exposure to 1μM BaP resulted in a tenfold increase in viral titer, which correlated with accumulation of ppRb, p16INK4, and p27KIP1 proteins and increased CDK1 kinase activity. Similarly BaP treated HPV-16- and HPV-18-infected raft cultures also resulted in a significant increase in viral titers. Under these conditions the expression of the differentiation marker involucrin was increased, whereas the expression of keratin-10 expression was decreased. Treatment with a lower concentration (0.001μM) of BaP resulted in increased HPV genome replication, but did not increase viral titers. Additionally, this BaP treatment correlated with decreased p21WAF1 levels, increased CDK4 kinase activity and increased keratin 14 expression.

Conclusions: Overall, BaP modulation of the HPV life cycle and host cell cycle profile may potentially enhance virus persistence, increase host tissue carcinogenesis, and permissiveness for cancer progression.