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“HPV Oncogenes E6/E7 Promote Cervical Dysplasia Progression Through Suppression of miR-4488 and Activation of Wnt Signaling”

OBJECTIVES: This study aims to identify mechanisms involved in progression of low-grade cervical dysplasia to ultimately aid in early intervention and treatment of low-grade cervical dysplasia to prevent progression to cancer.

BACKGROUND: Each year, approximately 3 million women in the United States are diagnosed with Human Papillomavirus (HPV) -associated low grade cervical dysplasia, a pre-cancerous lesion. Most individuals with a low-grade dysplasia diagnosis will clear it naturally, however, a few women will progress to high-grade dysplasia which increases their risk of developing cervical cancer. HPV oncogenes E6 and E7 have been found to drive cancer progression. Our lab has found that microRNA-4488 (miR-4488) is downregulated in women with progressive cervical dysplasia ($p=0.0033$). This microRNA is predicted to regulate Wnt (Wingless and INT-1) signaling, a cancer pathway that promotes cell survival, migration, and proliferation that has been shown to be activated in cervical cancer. We hypothesize that HPV oncogenes E6/E7 promote cervical dysplasia progression by downregulating miR-4488 and promoting Wnt signaling.

METHODS: Changes in miR-4488 expression were analyzed in primary ectocervical cells expressing HPV-16 E6/E7 compared to vector controls using a TaqMan quantitative polymerase chain reaction (qPCR) assay. Wnt signaling activation was measured in an HPV negative cervical cancer cell line C-33A expressing HPV-16 E6/E7 oncogenes and were compared to vector controls using a Wnt-responsive luciferase reporter assay. Wnt signaling was stimulated in Hek293 cells by addition of Wnt agonist 1 (APExBIO). Total RNA, including microRNAs, were extracted from the stimulated cells along with controls (unstimulated Hek293) at various timepoints, and the effects of continuous Wnt signaling stimulation on miR-4488 expression were analyzed using a TaqMan qPCR assay.

RESULTS: MiR-4488 was downregulated 2-fold in primary cervical cells expressing HPV-16 E6/E7. Wnt signaling was upregulated in HPV-16 E6/E7 expressing C-33A cell line compared to the vector controls ($p = 0.0029$). HPV-16 E6/E7 expression induced Wnt signaling. Induction of Wnt signaling corresponded to decreased expression of miR-4488.

CONCLUSIONS: HPV oncogenes E6/E7 downregulate miR-4488 expression while enhancing Wnt signaling. Both downregulation of miR-4488 and activation of Wnt signaling may be early indicators of oncogenic HPV E6/E7 overexpression and cervical dysplasia progression.