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

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Objective
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
Cervical Dysplasia
Each year, approximately 3 million women in the United States are diagnosed with Human Papillomavirus (HPV)-associated low grade cervical intraepithelial neoplasia (cervical dysplasia). Low grade cervical dysplasia is a pre-cancerous lesion that, over the course of months to years, has the potential to develop into cancer. HPV oncogenes E6 and E7 aid in progression of cervical dysplasia. Despite HPV’s oncogenic potential, most individuals with low-grade cervical dysplasia will clear it naturally, but a few will progress to high-grade dysplasia which increases their risk of developing cervical cancer.

MicroRNA-4488

MicroRNAs (miRNAs) are single-stranded non-coding RNA molecules that contain approximately 22 nucleotides. They help control gene expression at RNA level and are present in many types of cancer. miR-4488 is a unique microRNA expressed in cervical dysplasia, as seen in Figure 3.

Methods

Wnt responsive luciferase reporter assay
Performed in the HPV negative cervical cancer cell line C-33A
- Transduced to express HPV-16 E6/E7 oncoproteins
- Vector controls maintained with Geneticin (G418)

HPV-16 oncogenes E6 and E7 promote Wnt signaling.

Wnt Activation Decreases miR-4488 Expression

HPV Oncogenes E6/E7 Downregulate miR-4488

- In primary ectocervical cells, expression of HPV-16 E6/E7 decreased miR-4488 expression 2-fold compared to GFP controls
- Confirms expression data of progressive cervical dysplasia
- Potential early infection phenotype

HPV Oncogenes Enhance Wnt Signaling

Wnt signaling is a cancer pathway that promotes cell migration, survival, and proliferation.
- Wnt agonist 1 (APE x Bio)
- HEK 293 cells stimulated with Wnt agonist 1

Results

Wnt-4488-Expression.png

HPV Oncogenes E6/E7 downregulate miR-4488 expression while enhancing Wnt signaling.

Conclusions

- HPV oncogenes E6/E7 downregulate miR-4488 expression while enhancing Wnt signaling
- Progressive cervical dysplasia promotes downregulation of miR-4488 and was confirmed as an early indicator of HPV oncogenic expression
- Wnt signaling activation decreases miR-4488 expression
- Both downregulation of miR-4488 and activation of Wnt signaling may be early indicators of oncogenic HPV E6/E7 overexpression and cervical dysplasia progression.

Future Work

- Examine putative targets of miR-4488 within the Wnt signaling pathway
- Examine the effects of downregulation and overexpression of miR-4488 on Wnt signaling activation
- Examine low-grade cervical dysplasia for markers of activated Wnt signaling
- Ultimate goal: to find a way to screen for these pathways and expressions in order to determine who will clear the cervical dysplasia on their own and who will progress to cancer.

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References


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