Anal and cervical cancer are caused by human papillomavirus (HPV) infection, and affect a large number of female patients. HPV infection of epithelial cells of the anus and the cervix results in cellular transformation over time to precancerous lesions that can progress to cancer.

Current therapies to treat these precancerous lesions, to prevent cancer development, are not specific to HPV-infected cells and thus are not very effective or well tolerated. We have been examining the molecular pathways that are important in HPV-associated carcinogenesis of the genital tract to develop better targeted, more effective therapies to prevent anogenital cancer.

One of the pathways that we have identified as important is the mTOR/PI3K pathway, which is an upstream inhibitor of the autophagic pathway. Autophagy is a catabolic process that occurs in all cells to breakdown damaged/dysfunctional organelles and proteins to maintain cellular health. The objective of this study was to evaluate if both mTOR and PI3K inhibition is necessary for anal cancer prevention or if single pathway inhibition is effective.

Based on our previous work with these transgenic mice, at 5 weeks of age, most mice have normal histology, at 15 weeks of age, greater than 75% of mice have low-grade dysplasia and at 20 weeks of age, greater than 75% have high-grade dysplasia. Thus, mice were started into the study at 5 weeks of age for normal histology, 15 weeks of age for low-grade dysplasia, and 25 weeks of age for high-grade dysplasia. Mice were treated locally at the anus with a topical carcinogen, (7,12-Dimethylbenz[a]anthracene (DMBA)) for 20 weeks, which promotes the development of progressive anal dysplasia to carcinoma. For this study, mice at various ages were randomized into six treatment groups: control, DMBA only, topical Sapansertib (TAK) only, DMBA with topical TAK (DMBA+TAK), topical Pictilisib (GDC) only, DMBA with topical GDC (DMBA+GDC). The mice underwent weekly observations for anal tumor development. Fischer’s two-sided exact t-test was used to determine differences between treatment groups in tumor incidence at 20 weeks.

Mice treated with topical GDC with DMBA had 100% (24/24) tumor development, like the DMBA only group (p-value=1). Only 40% (6/15) of mice treated with topical TAK and DMBA developed tumors (p-value<0.05). For mice starting with low-grade dysplasia, those treated with DMBA only 100% (16/16) developed overt tumors. 75% (15/20) of mice treated with topical GDC with DMBA had tumors (p-value=0.053) while only 40% (8/18) of TAK with DMBA developed tumors (p-value<0.05). For mice starting with high-grade dysplasia treated with DMBA alone 67% (12/18) developed overt tumors. Mice treated with topical GDC and DMBA had 86% (19/22) tumor development (p-value=0.25) while 19% (3/16) of mice treated with topical TAK and DMBA developed tumors (p-value<0.05).

Topical mTOR inhibition decreases anal cancer development in HPV transgenic mice, regardless of starting histology.

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