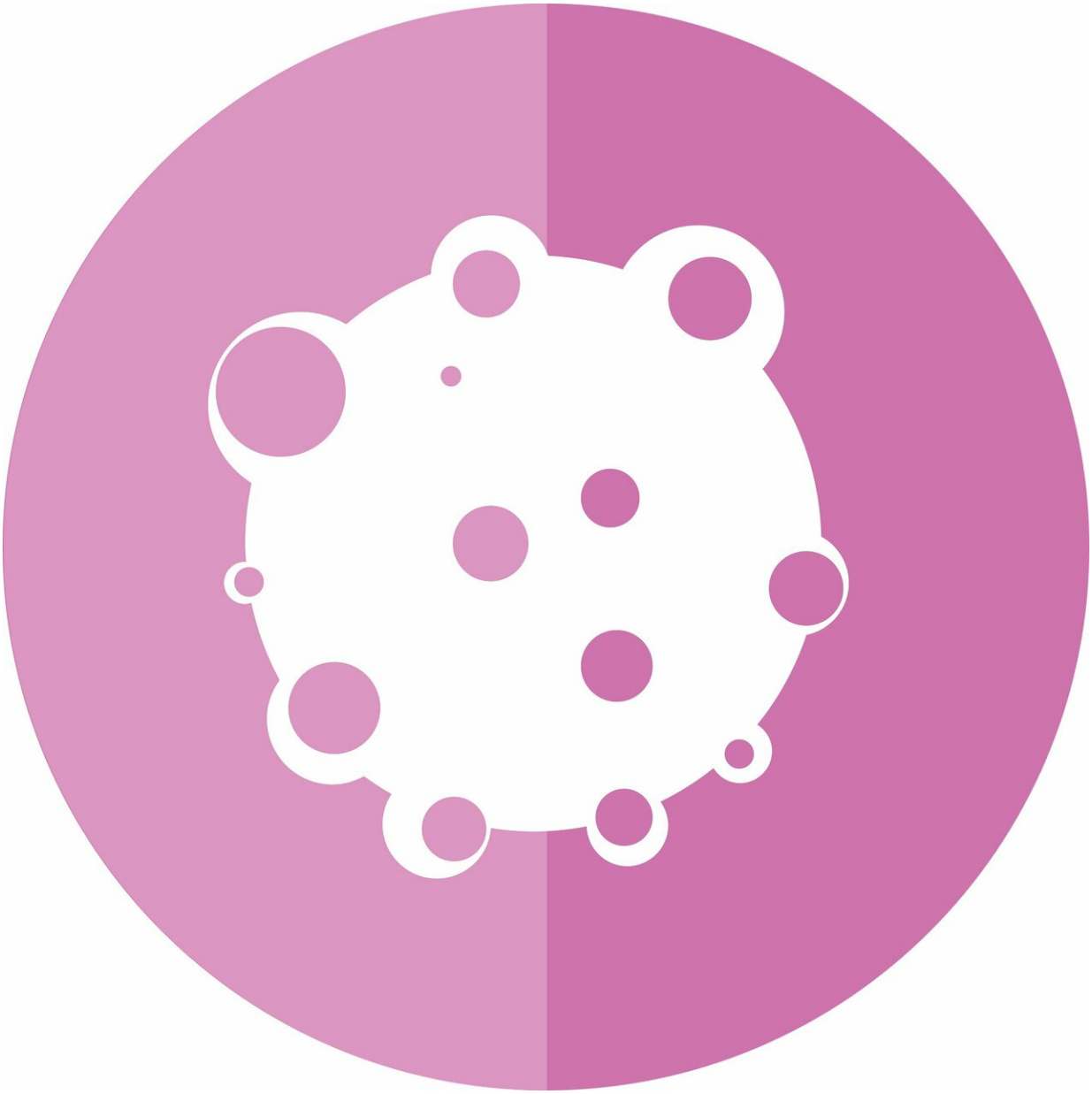
Novel therapeutic targets in cutaneous squamous cell carcinoma

March 30 2020



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Cutaneous squamous cell carcinoma (cuSCC) is the second most common diagnosed malignancy in the United States, with approximately 700,000 new cases each year. Cumulative exposure to ultraviolet light is the primary environmental risk factor that leads to cuSCC. While the majority of cuSCC cases are easily managed and treated, a small percentage of patients do not respond to treatment and have poor outcomes. Researchers at Moffitt Cancer Center want to devise better therapeutic strategies for this patient population by improving their understanding of how cuSCC develops. In a new article published online ahead of print in the journal *Cancer Research*, Moffitt scientists report on their identification of potential therapeutic targets for cuSCC.

The Flores Lab has been focused on identifying therapeutic targets for p53 mutant cancers. In this research, the team focused on the activity of the protein TAp63—a tumor suppressor protein that is part of the p53 family of tumor suppressors. This family of proteins normally function to inhibit tumor development and growth. TAp63 is also known to compensate for p53 loss and to play an important role in the creation of small segments of RNA called microRNAs that are present in the human genome. MicroRNAs contribute to many biological processes and are often deregulated in different diseases, including cancer.

The researchers wanted to determine whether the ability of TAp63 to function as a tumor suppressor and regulator of microRNAs could impact the development of cuSCC. They treated mice that were missing the TAp63 gene and normal mice with ultraviolet light and discovered that mice without the TAp63 gene developed a significantly higher number of cuSCCs than normal mice. These observations demonstrate that TAp63 also acts as a tumor suppresser protein in the skin.

Flores's team then performed a series of comparative studies in both mouse and human cuSCC tumor samples and discovered that two microRNAs—miR-30c-2* and miR-497—were expressed at much lower levels in tumors that lacked TAp63. When these microRNAs were reintroduced into tumor cells, the development of cuSCCs was significantly reduced. These observations suggest that miR-30c-2* and miR-497, similar to TAp63, may function by inhibiting the growth and development of cuSCC. The researchers verified this hypothesis by showing that miR-30c-2* contributes to cell death, while miR-497 inhibits cell growth and proliferation; therefore, when these miRNAs are missing, cuSCC growth can proceed unchecked.

The team also performed studies to assess how downstream targets of the microRNAs impacted cuSCC growth. They demonstrated that seven genes that are targets of the microRNAs are commonly deregulated in cuSCC tumors, including the AURKA gene. They confirmed the importance of AURKA by showing that inhibition of AURKA was able to reduce cuSCC growth in mouse models, suggesting that AURKA may be an appropriate therapeutic target.

"Our study establishes TAp63 as an essential suppressor of UV-induced cuSCC and reveals a previously undescribed functional network of microRNAs and targeted mRNAs," said Elsa Flores, Ph.D., chair of Moffitt's Department of Molecular Oncology and leader of the Cancer Biology and Evolution Program. "Given the lack of FDA approved targeted therapies for advanced cuSCC, our study provides preclinical evidence for the use of miR-30c-2*/miR-497 delivery or AURKA inhibition for the effective treatment approach."

Flores hopes this will lead to further investigations on these potential targets.

More information: Andrew John Davis et al, TAp63-regulated

microRNAs suppress cutaneous squamous cell carcinoma through inhibition of a network of cell cycle genes, *Cancer Research* (2020). DOI: 10.1158/0008-5472.CAN-19-1892