Androgen receptor signaling contributes to targeted therapy resistance in melanoma

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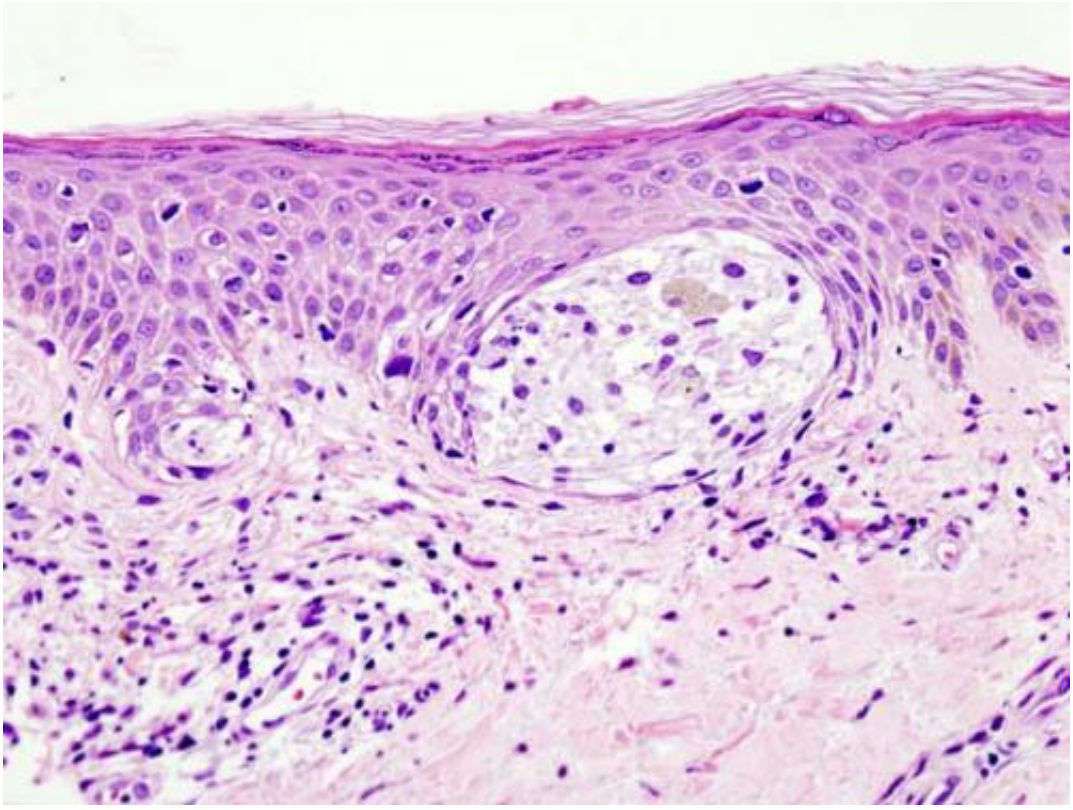

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Androgen receptor (AR) signaling affects response to BRAF/MEK inhibitor therapy in both males and females with melanoma, researchers from The University of Texas MD Anderson Cancer Center showed in a study published today in *Nature*. The findings provide a new target to

combat therapeutic resistance and one possible answer to why men face a poorer prognosis than women when diagnosed with melanoma.

The AR is a type of nuclear receptor that's activated by the male sex hormone testosterone. Females have lower levels of androgens, including testosterone. This research confirms the impact of biological sex on response to BRAF/MEK targeted therapy and shows for the first time that these inhibitors increase AR signaling, leading to therapeutic resistance and poor response to treatment. In preclinical models of melanoma, blocking the AR improved response to BRAF/MEK targeted therapy in both males and females.

"This study, coupled with other recent publications looking at the impact of AR signaling on response to other types of cancer therapies, such as immune checkpoint blockade, has enormous implications for the field," said senior corresponding author Jennifer Wargo, M.D., professor of Genomic Medicine and Surgical Oncology. "We know males and females get cancer at different rates and have different mortality. Our research raises the possibility that the AR and testosterone may be at play and offers a new target to improve response to treatment in both sexes."

Biological sex matters for targeted therapy response in melanoma

The study began with an observation from a neoadjuvant clinical trial for BRAF/MEK inhibitors in stage III melanoma (NCT02231775) where female patients had a higher rate of major pathologic response (MPR, defined as

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