# Resistance to therapy and tumor relapse attributed to specific cancer cell population

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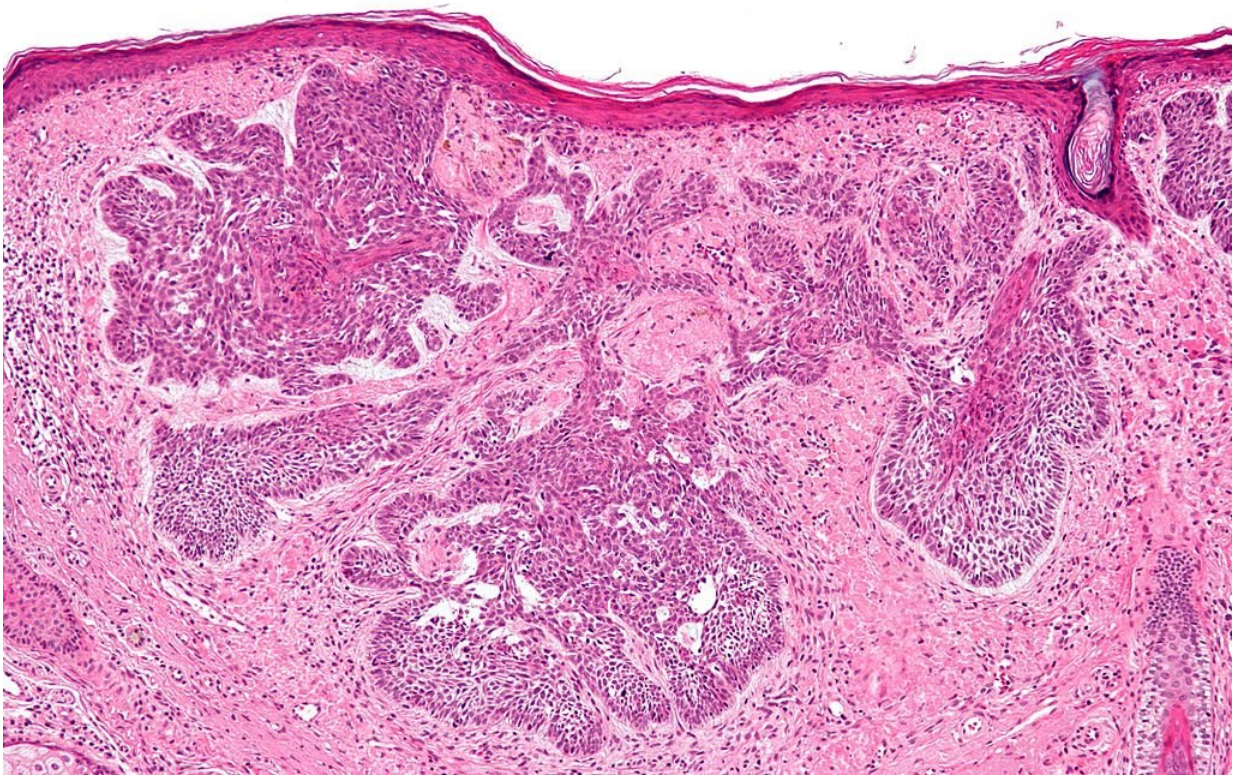

Intermediate magnification micrograph of a basal cell carcinoma. H&E stain. Wikimedia Commons CC BY-SA 3.0

Resistance to therapy is a major problem in cancer patients, as resistant cells are at the root of tumour relapse and are associated with high

morbidity and mortality. A better understanding of the mechanisms associated with resistance to therapy is essential for the development of strategies to definitively eradicate cancer and prevent tumour relapse.

In a study published in *Nature*, researchers lead by Pr. Cédric Blanpain, MD/Ph.D., WELBIO investigator and Professor at the Université libre de Bruxelles, Belgium identified a population of tumour cells that persist following drug treatment, leading to cancer relapse after treatment discontinuation in basal cell carcinoma, the most frequent skin cancer. The study also identifies a combination of drugs that can eliminate this resistant tumor population, thereby preventing tumour relapse.

Basal cell carcinoma is the most common human cancer, affecting several million new patients each year around the world. Vismodegib, an FDA-approved drug is used for the treatment of locally advanced and metastatic basal cell carcinoma in humans. Many patients treated with vismodegib experience tumour regression during treatment, but very often, those tumours relapse following treatment discontinuation. The precise mechanisms are poorly understood.

In this new study, Adriana Sánchez-Danés of the Université libre de Bruxelles, ULB, Laboratory of Stem Cells and Cancer and colleagues identified the mechanism by which vismodegib leads to tumor regression and uncovered the cause of the relapse observed upon treatment discontinuation. They found that vismodegib promotes the differentiation of the bulk of tumour cells, leading to their elimination. Vismodegib treatment led to the emergence of a population of dormant tumour cells characterized by active Wnt signaling that persists despite continuous drug administration.

In collaboration with the groups of Pr. Tabernero (Barcelona, Spain) and Pr. del Marmol (Brussels, Belgium), the researchers demonstrated that this population of tumor cells with Wnt signaling was also found in

patients with basal cell carcinoma treated with vismodegib.

Adriana Sánchez-Danés and colleagues found that inhibition of Wnt signaling, together with vismodegib eliminates persisting tumor lesions, leading to tumor eradication in the vast majority of the cases. "It was really exciting to identify a combination of drugs already available in clinics that lead to the eradication of resisting tumor cells and avoiding tumor relapse in the most frequent cancer in humans," says Sánchez-Danés.

The study illustrates that vismodegib promotes tumour regression by promoting the differentiation of tumour cells. This demonstrates for the first time that inducing tumour differentiation is a safe and efficient strategy to treat solid tumours such as basal cell carcinoma. "This is the first example of an FDA-approved drug used to treat solid tumours that induces tumor regression through differentiation. Tumour differentiation is an exciting route to treat cancer as it is non toxic for normal cells and was proved to be a revolutionary treatment in certain leukemias," said Cédric Blanpain, the senior author of study.

"Our study also identifies a new mechanism of resistance to therapy in basal cell carcinoma and demonstrates that the administration of two existing drugs is sufficient to prevent tumor relapse in the vast majority of the cases. The next step would be to conduct clinical trials using the combination of these two drugs in patients with relapsing basal cell carcinomas and possibly other cancers characterized by the activation of the two signaling pathways identified here," explains Cédric Blanpain, the corresponding author of the *Nature* paper.

**More information:** Adriana Sánchez-Danés et al, A slow-cycling LGR5 tumour population mediates basal cell carcinoma relapse after therapy, *Nature* (2018). DOI: 10.1038/s41586-018-0603-3

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