Predicting resistance to anticancer drugs

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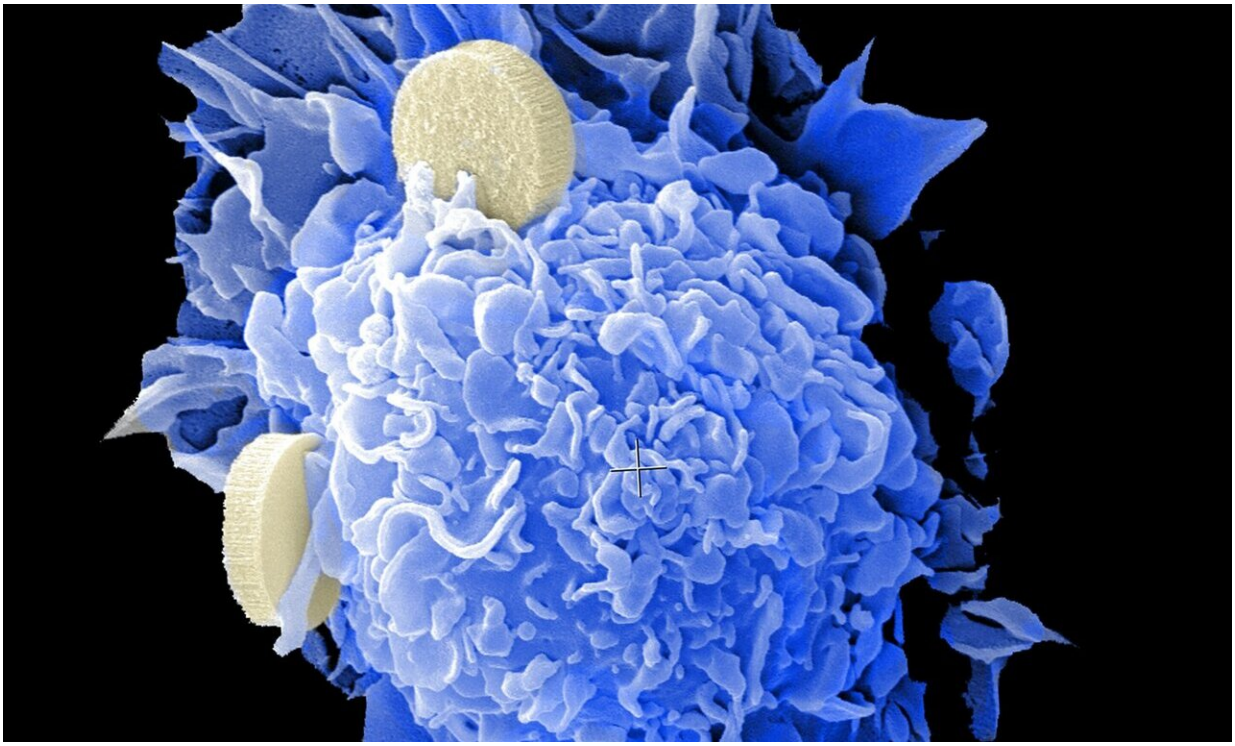

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Cancer cells can develop resistance to therapy through both genetic and non-genetic mechanisms. But it is unclear how and why one of these routes to resistance prevails. Understanding this 'choice' by the cancer cells may help us devise better therapeutic strategies. Now, the team of Prof. Jean-Christophe Marine (VIB-KU Leuven Center for Cancer Biology) shows that the presence of certain stem cells correlates with the

development of nongenetic resistance mechanisms. Their study is published in the prestigious journal *Cancer Cell*.

Two routes to resistance

Even though cancer therapy has made great strides in the last few years, resistance remains a major problem. When cancer cells develop resistance against the drugs targeting them, they can continue to spread, even when the patient is going through therapy.

Until recently, it was thought that this resistance arises exclusively through mutations—genetic alterations—in the cancer cells. However, new studies have suggested that resistance against cancer drugs can also arise via non-genetic mechanisms that change the expression of certain genes without altering the DNA sequence.

Prof. Marine explains that "the importance of nongenetic reprogramming as a driver of therapy resistance is not yet widely accepted in the field. Although my group has demonstrated that drug tolerance can be driven by nongenetic mechanisms, strong evidence that resistance can be acquired in absence of a genetic cause is still lacking."

In their study, the team of Prof. Marine firmly establishes that nongenetic mechanisms contribute to resistance to therapy in melanoma. The key question has become "how do cancer cells 'choose' between the different routes to resistance?"

Neural crest stem cells as key

Surprisingly, the team demonstrates that the road to resistance is predetermined and not randomly selected. They show that the presence of a specific group of cells, neural crest stem cells, leads to non-genetic

rather than genetic drug resistance in melanoma. A possible reason for this is that these neural crest stem cells exhibit 'epigenetic plasticity', which means that these cells have an increased ability to select which genes they express and how much. These cells literally reprogram themselves to evade the therapeutic pressure.

The researchers also identified the signaling pathway that drives the emergence of the neural crest stem cells and promotes their survival. This signaling pathway depends crucially on the protein Focal Adhesion Kinase (or FAK). By blocking the activity of this protein, the team was able to drastically reduce the occurrence of non-genetic drug resistance in patient-derived xenografts—tumor cells from human patients that were implanted in mice.

This combination of new basic insights into tumor cell biology and recently discovered non-genetic resistance mechanisms to cancer drugs has far-reaching clinical consequences.

Florian Rambow, senior postdoc who contributed to the study, explains that "these findings have several important clinical implications. Not only did we show a viable way to suppress non-genetic resistance, but we also demonstrated that the presence of specific cells dictates which resistance mechanism is likely to occur. This observation is the key to predicting potential resistance routes in patients and developing personalized therapies."

More information: Oskar Marin-Bejar et al, Evolutionary predictability of genetic versus nongenetic resistance to anticancer drugs in melanoma, *Cancer Cell* (2021). DOI: 10.1016/j.ccell.2021.05.015

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