Cancer cells circumvent immune system, but reveal themselves in the process

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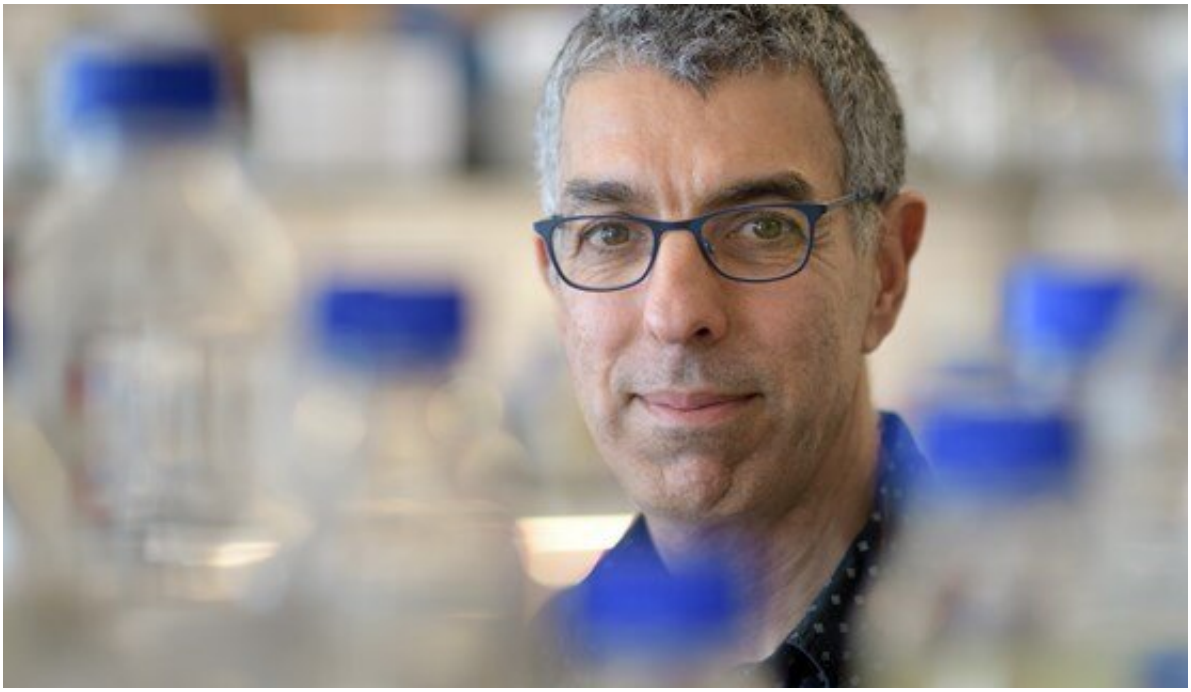

Reuven Agami, group leader, oncogenomics. Credit: Netherlands Cancer Institute

In their move to circumvent the immune system, melanoma cells end up with a deficiency of the crucial nutrient tryptophan. Unlike healthy cells, these cancer cells can continue to synthesize proteins to survive, but this comes at a price: they will be much more easy to detect by the immune system.

This discovery is outlined in a publication in *Nature* by researchers led by Reuven Agami (Netherlands Cancer Institute) and Yardena Samuels (Weizmann Institute), in collaboration with the University of Oslo.

Finding the cancer cell's vulnerabilities

Cancer cells behave differently from healthy cells. They adapt rapidly, take greater risks than healthy cells, and manage to survive under dire circumstances that would kill healthy cells. But these things come at a cost: they make mistakes and develop new vulnerabilities. And those vulnerabilities are exactly the types of things cancer researchers are trying to uncover. Such as the exceptional mechanism that is described in the *Nature* publication.

Tryptophan

Healthy cells in our bodies stop synthesizing proteins if they lack a certain nutrient, the amino acid tryptophan, which is found in food. Without tryptophan, a cell cannot survive. If the ribosomes, the protein factories in the cell, stumble upon the three letter sequence (the codon) for tryptophan, they will quit reading and synthesizing until the tryptophan is replenished.

Frame shifting

But in melanoma—an aggressive type of skin cancer—the ribosomes continue to read the mRNA sequence, consisting of three letter codons: every codon corresponds with a specific amino acid. Except these cancer cells skip the first letter of the codon corresponding with tryptophan. As a result, the reading frame changes completely. This is called frame shifting. The easy to understand sentence "if still possible" becomes: "Fst ill pos sib le" In other words, gibberish.

Aberrant peptides

The cancer cells continue to synthesize proteins. However, these are built out of aberrant peptides based on a faulty code. The melanoma cell continues to function, but at a cost: it betrays its presence to the immune system's T cells. The melanoma cells present these abnormal protein fragments on the outside of the cell, as cells tend to do when dealing with foreign elements.

Immunotherapy

This paves the way for new types of immunotherapy, the researchers suspect. Therapies involving T cells from healthy people that can be trained to recognize these foreign protein fragments.

The irony is that melanoma cells depleted their tryptophan stock in their very move to circumvent the immune system. To halt the deadly effects of T cells in the tumor, melanoma cells produce an enzyme that synthesizes a substance that will inhibit the T cells from killing cancer cells. During the process, tryptophan is broken down, which causes the nutrient deficiency.

Attempts to halt this enzyme with a targeted drug, to improve the success rates of immunotherapy based on checkpoint inhibition, .unexpectedly proved ineffective in clinical trials. The effects of the immunotherapy did not improve.

Researchers from the Agami lab and their colleagues stumbled upon their new discovery about frame shifting and the production of aberrant peptides while investigating the mechanism behind this clinical failure—a discovery which will hopefully lead the way to new forms of immunotherapy.

"We think that such flexibility in mRNA translation stimulates tumor growth and aggressive behavior, at the expense of the quality by which cancer cells produce proteins when nutrients are sparse," says Reuven Agami.

More information: Osnat Bartok et al. Anti-tumor immunity induces aberrant peptide presentation in melanoma, *Nature* (2020). DOI: 10.1038/s41586-020-03054-1

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