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

17 December 2020

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.