Pathway that degrades holiday turkey fuels metastasis of triple negative breast cancer

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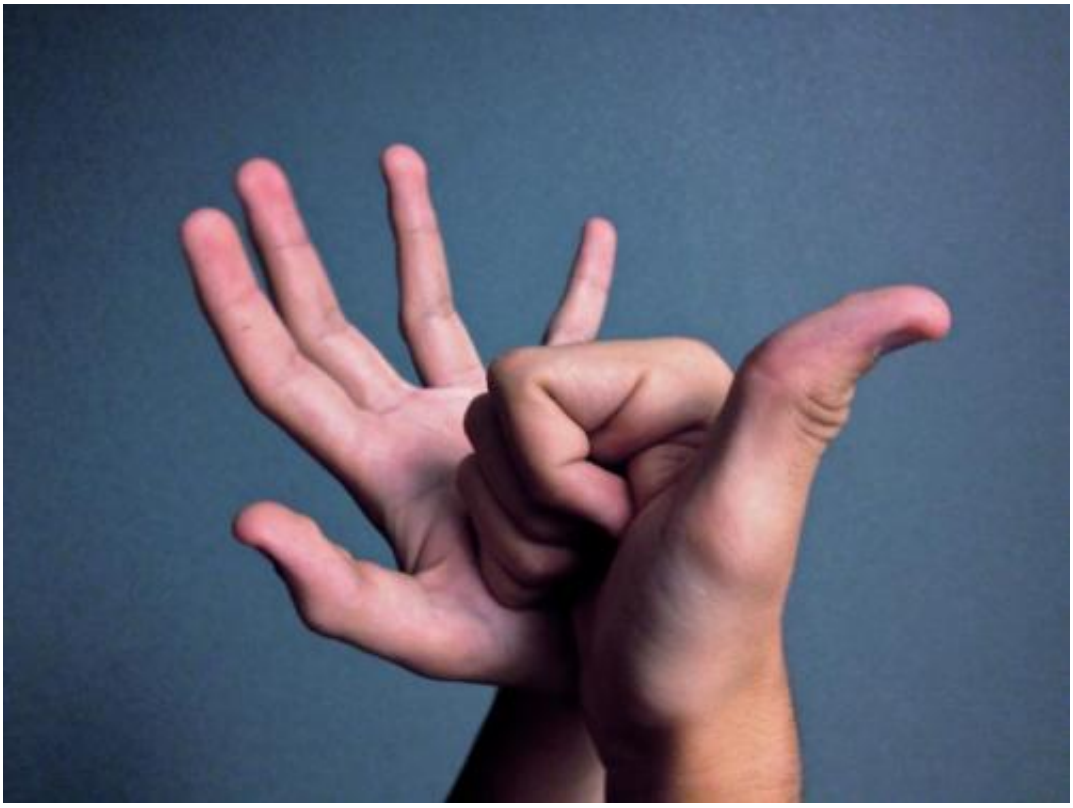

Tryptophan, the same essential amino acid that famously makes people sleepy after holiday meals, wakes up the ability for cancer to metastasize through the body. Image: Flickr/JDHancock cc license.

A University of Colorado Cancer Center study being presented at the San Antonio Breast Cancer Symposium shows that triple negative breast cancer cells process tryptophan to promote survival while traveling

through the body in order to seed new tumor sites.

"I'm not saying that people with metastatic breast cancer shouldn't eat turkey during the holidays, but triple-negative breast cancer appears to have found a way to process tryptophan more quickly, equipping cancer cells to survive while in circulation, which allows them to metastasize," says Thomas Rogers, the paper's first author and PhD candidate in the laboratory of CU Cancer Center investigator, Jennifer Richer, PhD.

When healthy cells become detached from the foundation on which they grow, they are programmed to undergo cell death through a process known as anoikis ("without a home" in Greek). This means that in order to metastasize, cancer cells have to evade anoikis - they have to survive while in suspension, unattached from a foundation. The current study used a gene array to discover which genes were upregulated in triple negative breast cancer cells that were able to grow in suspension compared with cells that were still attached to a substrate.

"Basically, we asked what is different in cells that are able to survive being detached," Rogers says.

Many of the gene expression changes in the triple negative breast cancer cells that had learned to survive detachment were in a single metabolic pathway - the kynurenine pathway, which is responsible for degrading the essential amino acid tryptophan. The faster the kynurenine pathway, the faster tryptophan is degraded. Controlling the speed of the kynurenine pathway is the enzyme TDO2 - which happened to be the most upregulated gene in detached compared to attached triple-negative breast cancer cells.

In other words, it may be that cancer cells over-express TDO2, which speeds up the whole kynurenine pathway, and degrades more tryptophan - all of which helps these cells to escape anoikis, which allows them to

survive long enough to pick up roots and move to other places in the body.

"When a cancer cell detaches and cranks up this catabolic pathway, it can metabolize tryptophan faster and promote survival," Rogers says.

Currently, drugs targeting other enzymes in the complex chain of the kynurenine pathway are already in clinical trials. For example the drug indoximod by New Link Genetics is being tested in combination with chemotherapy against metastatic breast cancer (clinicaltrials.gov number NCT01792050). This drug adjusts features within the pathway to help the body's immune system more effectively target cancer cells.

"We hope that looking at other targets in this pathway could create a more effective therapy," Rogers says. "Indoximod or other compounds like it could be used in combination to not only boost the immune system to target free-floating cancer cells, but also to re-sensitize cancer cells to the programmed cell death of anoikis."

Provided by University of Colorado Denver

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