Accumulation of a product of cell metabolism found to be linked with kidney tumor growth

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Researchers funded by the Medical Research Council (MRC) have shown that when the metabolite fumarate accumulates in a hereditary form of renal cancer it leads to an epigenetic reprogramming that drives cancer, according to a study published in *Nature*. The tumour growth mechanism seen here could be similar in other cancers, such as lung and bowel cancer, where the enzyme that breaks down fumarate is not present or not fully functional.

Fumarate is found naturally in fruits and vegetables. It is also produced artificially for use as a food additive to act as an acidity regulator and flavouring agent. It usually acts as an intermediately product during the citric acid cycle, which the cells use to produce energy.

Hereditary leiomyomatosis and renal cell cancer (HLRC) is a rare form of cancer that results in skin tumours and can lead to kidney cancer. It was already known that the disease was related to a mutation in the gene that codes for the enzyme fumarate hydratase (FH), found in the mitochondria, but until now it was unclear how this leads to tumour growth.

Researchers from the MRC Cancer Unit at Cambridge University used a combination of RNA sequencing and metabolomics, the study of small molecules resulting from metabolism, to find out what was causing tumour growth.

The team found that the excess fumarate that results from the loss of FH led to epigenetic changes to a micro RNA. This caused the micro RNA to be suppressed, which functions in the prevention of metastasis.

These epigenetic changes resulted in the expression of genes that initiated epithelial to mesenchymal transition. This is the process whereby normal cells become cancerous and metastasise, spreading around the body.

Now that the mechanism of tumour growth related to FH loss is known, future work can focus on how fumarate is involved in other cancers. For instance, it has been shown that FH is lost in other types of tumours, including non-hereditary renal cancer, neuroblastoma, and tumours of the adrenal gland. Given that metastasis is the primary cause of death in cancer patients, understanding how to block metastasis caused by fumarate could be a key strategy for cancer therapy. Future work would also need to be done to further understand the action of fumarate in normal conditions.

Lead researcher, Dr Christian Frezza from the MRC Cancer Unit, says: "The findings of our study suggest that the disruption of FH and the resulting fumarate accumulation have roles in this type of kidney cancer. This could also be a feature of other tumour types where FH loss has been reported, including neuroblastoma, colorectal and lung cancer."

Dr Nathan Richardson, head of molecular and cellular medicine at the MRC, says: "The results of this research give us a clearer insight into how fumarate is involved in this form of renal cancer. It now gives us the opportunity to see if this also applies to other common forms of cancer and also how metabolism is related to the progression of the disease."

More information: Marco Sciacovelli et al, Fumarate is an epigenetic modifier that elicits epithelial-to-mesenchymal transition, *Nature* (2016). DOI: 10.1038/nature19353

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