RNA modifications in mitochondria promote invasive spread of cancer

Mitochondria are the power plants of cells, and they contain their own genetic material and RNA molecules. Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now discovered that certain modifications in mitochondrial RNA boost the invasive spread of cancer cells by supporting protein synthesis in mitochondria. They have established that a specific gene expression signature correlating with high levels of mitochondrial RNA modifications is associated with metastasis and poor prognosis in patients with head and neck cancer. When the researchers blocked the responsible RNA modifying enzyme in cancer cells, the number of metastases was reduced. Certain antibiotics that suppress protein synthesis in mitochondria were also able to prevent the invasive spread of cancer cells in laboratory experiments. The results have now been published in the journal Nature.

Cancer cells in aggressive tumors invade the surrounding tissue in an attempt to form a new tumor in other organs. During this journey, cancer cells have to survive unfavourable conditions such as shortage of oxygen or shortage in nutrients. To overcome these stress factors, cancer cells adapt their energy production accordingly. The molecular mechanisms allowing this flexibility were poorly understood until now. "However, we suspected that this metabolic plasticity must be a key to the successful spread of the cancer cells," says Michaela Frye; cell biologist at the German Cancer Research Center.

Mitochondria are tiny, membrane-enveloped structures known as the powerhouse of every cell in our body. For energy production, they use the so-called respiratory chain present in the mitochondrial membrane. Because mitochondria contain their own genetic material, they themselves produce key components of the respiratory chain.

The production of components of the respiratory chain is tightly regulated by a specific machinery in the mitochondria - with implications for the metastatic spread of cancer cells, as Michael Frye and her team have now discovered and published in the journal Nature. tRNA molecules are part of this machinery and are responsible for providing the individual amino acid building blocks during protein assembly. The research team identified the deposition of molecular modifications on mitochondrial tRNAs as the control mechanism to support production of proteins during metastasis.

RNA modifications regulate mitochondrial function and drive metastasis

Cancer cell invasion is a very energy consuming process. The team in Heidelberg discovered that a specific chemical modification found in mitochondrial tRNA, known as "m5C" (5-methylcytosine), is required for metastasis development. The m5C modification cranks up protein synthesis in the mitochondria. This enhances the production of components of the respiratory chain. As a result, the cell increases its pool of energy to fuel demanding cellular processes such as cancer cell dissemination from the tumour.

Cancer cells lacking m5C, on the other hand, obtain their energy through a comparatively less efficient mechanism called glycolysis and have a limited ability to spread metastatically. The researchers demonstrated this using human tumors grown in mice. However, cell viability or growth in the primary tumour was not affected by the loss of m5C.

RNA-modifying enzyme as a biomarker for metastatic tumours

A specific enzyme, the methyltransferase NSUN3, is responsible for the m5C RNA modification. When the scientists switched NSUN3 off, the mitochondrial tRNA was less modified and the invasive spread of the cancer cells decreased.

Could NSUN3 function as a biomarker for metastatic cancer? Gene expression signatures indicating high cellular NSUN3 levels and elevated m5C levels were indeed predictive for lymph node metastases and more severe disease progression in patients with head and neck cancer.

Antibiotics repurposed to block mitochondrial protein synthesis slow down metastasis

Certain antibiotics curb mitochondrial protein synthesis without affecting "general" protein synthesis in the cell's plasma. The researchers therefore assumed that these agents should affect cancer cells similarly to loss of NSUN3. Indeed, treatment with antibiotics such as chloramphenicol or doxycycline, reduced the invasive spread of cancer cells. Antibiotic administration also reduced the number of lymph node metastases in a mouse model.

"The importance of mitochondrial RNA modifications was previously studied in certain metabolic diseases. But we now show for the first time that there is a direct link between mitochondrial tRNA modifications and invasive spread of cancer," says Michaela Frye. The researcher is pleased that her group's work identified new approaches to potentially combat the spread of advanced cancers; she adds: "Inhibition of NSUN3 is a promising way to slow down metastasis because the enzyme is solely responsible for metastasis-promoting m5C RNA label. However, the potential long-term side effects of blocking mitochondrial protein synthesis must first be further explored."

Publication:

Sylvain Delaunay, Gloria Pascual, Bohai Feng, Kevin Klann, Mikaela Behm, Agnes Hotz-Wagenblatt, Karsten Richter, Karim Zaoui, Esther Herpel, Christian Münch, Sabine Dietmann, Jochen Hess, Salvador Aznar Benitah & Michaela Frye: Mitochondrial RNA modifications shape metabolic plasticity in metastasis
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Further information

- German Cancer Research Center (DKFZ), Heidelberg