Fragments of tRNA suggest a novel mechanism for cancer progression

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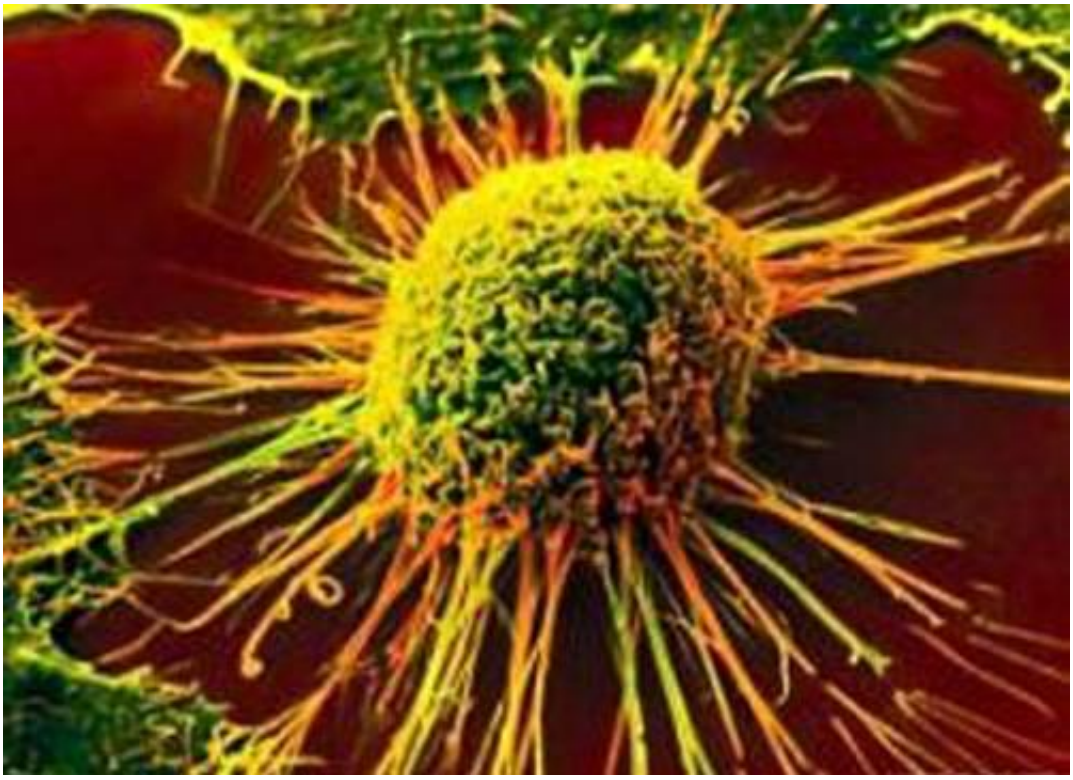

For years, scientists have been puzzled by the presence of short stretches of genetic material floating inside a variety of cells, ranging from bacteria to mammals, including humans. These fragments are pieces of the genetic instructions cells use to make proteins, but are too short a length to serve their usual purpose. Reporting in this week's *Cell*,

researchers at Rockefeller have discovered a major clue to the role these fragments play in the body—and in the process, may have opened up a new frontier in the fight against breast cancer.

Specifically, Sohail Tavazoie and his colleagues discovered that these particular genetic fragments, of a type of RNA known as transfer RNA (or tRNA), appear to be capable of reducing the growth and spread of breast cancer cells. "This is a new basic mechanism the body uses to control the growth of cancer," says Tavazoie, Leon Hess Associate Professor and head of the Elizabeth and Vincent Meyer Laboratory of Systems Cancer Biology. "We plan to explore it further, so hopefully it will open up new ways of curbing cancer that we have never tried before and reveal new basic insights on how genes are regulated inside our cells."

Scientists have found tRNA fragments in all walks of life, and they consistently increase in number when cells are exposed to low oxygen levels and other forms of cellular stress. But their purpose in the body has remained mysterious. "What those fragments are there for, and their role, is poorly defined," says Tavazoie.

The research, led by postdoctoral fellow Hani Goodarzi, discovered that breast cancer cells generate tRNA fragments when exposed to low levels of oxygen. And cancer cells that carry more of these particular genetic fragments are less likely to metastasize. What's more, adding these fragments to cells reduced the growth and progression of cancer; blocking the fragments, in turn, led to the opposite effect.

Looking closer, the researchers saw that tRNA fragments that come from specific tRNAs (glutamic acid, aspartic acid, glycine, tyrosine) bind to a key player in the life cycle of a cancer cell. This key player, known as an oncogene, normally binds to other RNAs and increases their numbers, causing them to make more of the oncogenes that help cancer

cells divide and spread. "These tRNA fragments bind the oncogene—called YBX1—and push out the other RNAs that encode for oncogenes, reducing cancer cells' ability to grow and metastasize. By doing so, they represent a new class of molecules in the cell we call tumor suppressors," says Goodarzi.

These tRNA fragments are demonstrating an entirely novel way of regulating gene expression, Tavazoie says. By blocking YBX1's ability to bind other RNAs whose expression YBX1 increases, tRNA fragments are playing a part in how the body expresses genes.

It makes sense that the number of tRNA fragments would increase in periods of cellular stress, such as when the cell is exposed to low oxygen levels, says Tavazoie. "Cells can sense whether they don't have sufficient energetic currency that occurs during low oxygen states, and tRNA fragments help suppress cells' growth rate so they can preserve their energy and nutrients for when the stress resolves."

Of course, aggressive breast cancer cells often find ways to sidestep the body's efforts to control them, including those involving these tRNA fragments. "We're very interested in figuring out how aggressive breast cancer cells stop the production of tRNA fragments," Tavazoie says. "It's exciting that these cancer cells are revealing a completely new way by which expression of oncogenes is regulated as a means of controlling cancer growth."

More information: Endogenous tRNA-Derived Fragments Suppress Breast Cancer Progression via YBX1 Displacement, *Cell* 161, 790–802 (online May 7, 2015)
www.cell.com/cell/abstract/S0092-8674(15)00318-9