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No brakes on breast cancer cells

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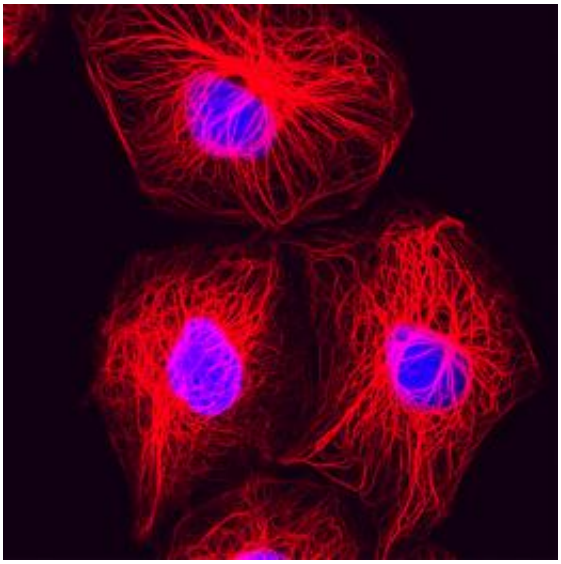

Breast cancer cells; proteins of the cytoskeleton are shown in red. Source: Lutz Langbein, German Cancer Research Center

Scientists of the German Cancer Research Center have discovered a tiny RNA molecule, called miR-520, which at once blocks two important pathways in the development of cancer in cells. In estrogen receptor-negative breast cancer, the production of this microRNA is often reduced and this is correlated with malignant behavior of tumor cells. The DKFZ team has found out that tumors with low levels of miR-520 have a particularly strong tendency to metastasize.

MicroRNAs or miRNAs are tiny RNA molecules that have only about 20 nucleotides and do not code for proteins. They regulate many

important processes in cells by binding to target messenger RNAs - the instructions for protein production - , thus blocking production of the respective protein. In cancer, the production of some miRNAs is often reduced or amplified. This particularly affects miRNAs that regulate the activity of cancer-promoting genes.

A key molecule in the development of cancer is a transcription factor called NFkappaB, which is an important switch for many genes with inflammation-promoting effects. At DKFZ, Professor Dr. Stefan Wiemann and collaborators have now investigated whether microRNAs that affect NFkappaB production are deregulated in breast cancer. Jointly with colleagues at Heidelberg and Tuebingen University Hospitals, the DKFZ team studied over 800 miRNAs and discovered a family of RNA molecules known as miR-520, which particularly strongly reduce the production of NFkappaB. "If the cells produce less NFkappaB, the production of inflammation-promoting signaling molecules is reduced. This puts a brake on cancer growth, because these signaling molecules promote invasive capacity, formation of new vessels and metastasis," says Ioanna Keklikoglou, a doctoral student Wiemann's department, explaining this mechanism.

However, miR-520 does not only act like a cancer brake by suppressing NFkappaB. In addition, Wiemann's team discovered that this microRNA also blocks another cancer-promoting signaling pathway that is triggered by growth factor TGF-beta. TGF-beta signals cause malignant cells to be less firmly anchored in the tissue and, thus, better able to invade surrounding organs - a characteristic feature of cancer cells.

Subsequently, the DKFZ researchers studied the question of whether the findings obtained in cancer cells in the culture dish are also involved in breast cancer. Studying tumor tissue samples of 76 patients, the team discovered that tumors which have already spread to the lymph nodes produce less miR-520 than those which have not yet spread. However,

this connection was only found in tumors that do not produce receptors for the female sexual hormone, estrogen (ER-negative tumors).

"Our findings clearly demonstrate that miR-520 is a genuine cancer brake that suppresses the malignant behavior of tumor cells in two different ways at once," said Stefan Wiemann, commenting on the findings reported in his now published work. "This cancer brake appears to fail in many ER-negative breast tumors - and also in cells of other types of cancer, as colleagues have now demonstrated." ER-negative breast cancer is particularly difficult to treat in many cases. Developing a microRNA therapy that blocks several cancer-promoting signaling pathways at once may therefore be an interesting option.

More information: I Keklikoglou, C Koerner, C Schmidt, JD Zhang, D Heckmann, A Shavinskaya, H Allgayer, B Gückel, T Fehm, A Schneeweiss, Ö Sahin, S Wiemann and U Tschulena: MicroRNA-520/373 family functions as a tumor suppressor in estrogen receptor negative breast cancer by targeting NF-kappaB and TGF-b signaling pathways. Oncogene 2011, DOI: 10.1038/onc.2011.571

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