How breast cancer cells evade therapeutic attacks

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Tumour cells depend upon estrogens to survive and proliferate in about 70% of all breast cancer cases. The most frequently used treatment to fight this variety of tumours relies on anti-estrogens such as tamoxifen. However, resistance to this type of therapy develops in more than 30% of the patients.

Understanding the mechanisms involved in the appearance of resistance to tamoxifen is thus essential to develop new therapeutic approaches. The research done by the team of Didier Picard, professor at the University of Geneva (UNIGE), provides key answers in the 1st of April 2010 edition of *Genes & Development*. Their study reveals how cancer cells become impervious to the drug by activating a specific biochemical cascade. The latter, normally triggered by a chemical messenger called cyclic AMP, is permanently stimulated in cells refractory to the treatment.

Breast cancer, which is characterized by an enhanced and anarchic proliferation of mammary cells, is one of the main causes of cancer-related mortality in women. In over two thirds of the cases, estrogens play an active part in the progression of the disease, due to the presence of receptors for this hormone in the nucleus of malignant cells. Estrogens indeed modulate the expression of genes necessary to cell survival and proliferation through their interaction with these receptors.

The most frequent treatment for this type of breast cancer, called hormone-dependent, relies on anti-estrogens such as tamoxifen, which

block tumour cell growth by inhibiting the activity of the receptor. However, the cancer eventually becomes resistant to the therapy in more than 30% of the patients.

The second messenger's key role

"Estrogen receptors, notably the one called ERα, are also activated by other molecules that operate in an indirect way, without interacting with them", explains Didier Picard, professor at the Faculty of Sciences of UNIGE. "We aim precisely at understanding the mechanisms involved in the indirect stimulation of ERα in cancer cells".

Researchers from his team have studied a molecule, cyclic AMP, which is able to convey various types of signals within the cell. Called a "second messenger", this molecule acts as an intermediary to transmit information between the exterior and the interior of the cell. Different growth factors, neurotransmitters or hormones, incapable of crossing the cell barrier, thus communicate their message by activating intracellular signalling pathways via cyclic AMP.

A novel mode of regulation

"During this project, we have studied how cyclic AMP could turn on ERα in breast cancer cells in the absence of estrogens", says lead author Sophie Carascossa. In this case, the second messenger triggers a specific biochemical signalling cascade in which a protein called CARM1 is involved. The protein then binds ERα and this in turn activates the receptor. "The interaction with CARM1 occurs in a domain of the receptor near the one that normally binds estrogens. This mode of regulation was completely unknown until now", specifies the scientist. The study also reveals that the signalling pathway is stimulated in a constitutive way in malignant cells resistant to tamoxifen, thus evading

control in these cells.

Although the molecular mechanisms implicated in the resistance process are probably numerous, the interaction between CARM1 and ERα could represent a promising therapeutic target in the long run.

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