A protein that 'rebels' against breast cancer treatment

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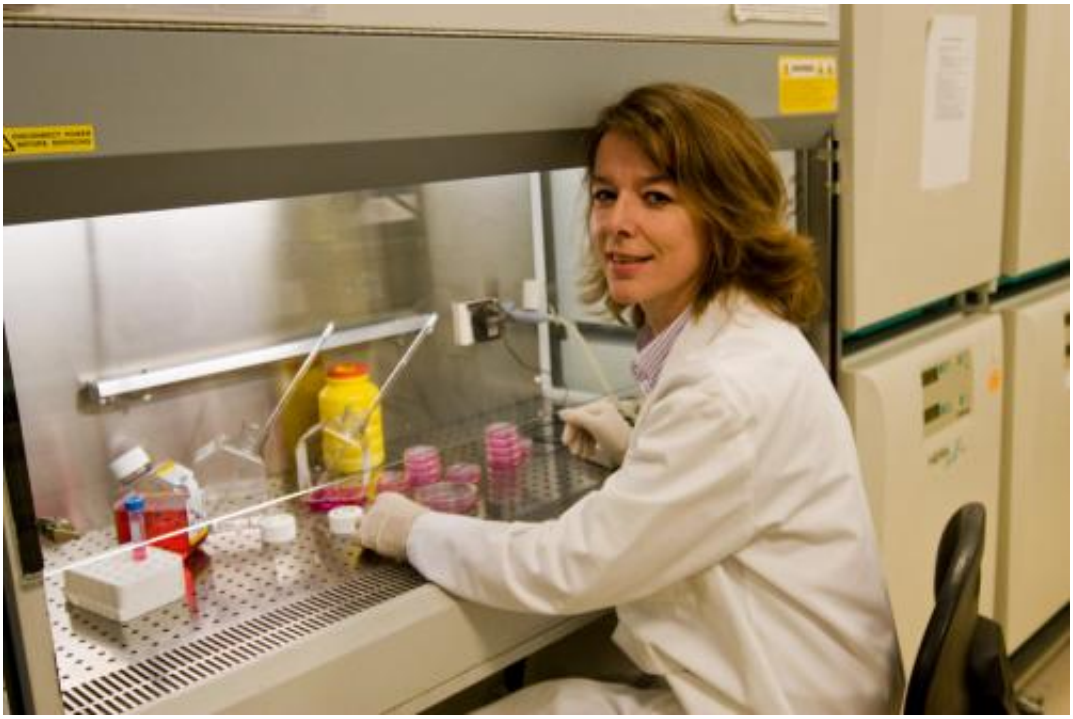

Despite the fact that the cure rate for breast cancer, the most common cancer in women, is very high (around 80%), this disease can nevertheless have very serious consequences. The majority of breast cancer-related deaths are caused by relapses, in other words reappearance of a malignant tumour after a longer or shorter disease-free period. In the most serious cases, the "new" tumour tends to be

resistant to treatment and is more invasive and aggressive than the primary tumour, thus resulting in a serious clinical problem.

A study led by the researcher María Vivanco at the Basque bioscience research centre CIC bioGUNE, in which the Galdakao Hospital and the clinic Preteimagen have also participated, has identified a cellular mechanism that could explain the resistance of these tumours to treatment. This research, which was published recently in the prestigious journal *EMBO Molecular Medicine*, has shown that a protein known as SOX2 leads a rebellion against hormone-based cancer treatment by desensitising tumour cells to such treatment.

It has also been found that the levels of this protein are higher in tumours from patients in whom hormone therapy has failed. Similarly, a higher concentration has been found in primary tumours from these patients compared with tumours that did respond to treatment. These results highlight the importance of SOX2 in the development of tamoxifen resistance while also suggesting the potential use of this protein as a biomarker for treatment resistance.

The term breast cancer covers a heterogeneous set of diseases, in other words several different types of cancer can be distinguished on the basis of their different molecular compositions. These types require different treatments. The most common treatment is endocrine (hormone-based) and, in the vast majority of cases, involves the use of a drug known as tamoxifen.

The new findings reported by Dr. Vivanco's group help to explain exactly how resistance to this treatment occurs. Tamoxifen normally inhibits the growth and multiplication of tumour cells. However, in the event of a relapse, these cells often no longer respond to treatment and continue to develop.

"We have demonstrated both in vitro and in vivo that altering the SOX2 levels also affects the sensitivity of cells to tamoxifen", explains Dr. Vivanco, who adds that "this lack of sensitivity of tumour cells to treatment occurs upon activation of the so-called Wnt signalling pathway, therefore we believe that inhibition of this pathway, together with hormone therapy, could represent a novel strategy for fighting treatment-resistant cancers".

Cancer stem cells

Recent studies have shown that some tumours reappear due to the fact that a small population of cells, known as cancer stem cells, which are more resistant to treatment and can cause the tumour to return, remains in the body. As well as its relevance as regards desensitisation of tumour cells to tamoxifen, it has also been found that SOX2 helps to maintain these carcinogenic stem cells.

Consequently, this protein has a twofold effect by making the cells more resistant to treatment and helping those cells that can cause a relapse to survive. According to these researchers, this makes SOX2 a potential biomarker for treatment resistance. In other words, its concentration in the tumour could indicate its level of risk.

Experience

Dr. Vivanco specialises in breast cancer research and has participated in many other studies in this field, such as that published in the journal *Proceedings of the National Academy of Sciences* (*PNAS*) in 2012, which describes how the protein HOXB9 helps cancer cells to survive radiotherapy.

According to Dr. Vivanco, this new research represents "a breakthrough in our long-term study of one of the most important aspects of cancer

research, namely the need to gain a better understanding of why some tumours reappear and to try to find a way of preventing this".

More information: "Sox2 promotes tamoxifen resistance in breast cancer cells." Marco Piva, Giacomo Domenici, Oihana Iriondo, Miriam Rábano, Bruno M. Simões, Valentine Comaills, Inmaculada Barredo, Jose A. López-Ruiz, Ignacio Zabalza, Robert Kypta, Maria dM Vivanco. *EMBO Molecular Medicine* (2013) 5, 1-14.

Provided by CIC Biogune