Science News

A Protein Called cFLIP Makes Tumor Cells in Breast Cancer Resistant to Treatments

ScienceDaily (Dec. 14, 2010) — Researchers at the Andalusian Institute for Molecular Biology and Regenerative Medicine (CABIMER) and the University of Granada found that cFLIP -an inhibitor of death ligand-induced apoptosis- is not only essential in breast tumor cells resistance to TRAIL treatments (a death ligand with a potent therapeutic potential against cancer), but this protein is also key to the survival of such cancer cells.

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Researchers proved that a variation in the expression of this protein may lead to the normal development of breast epithelium. This is an important finding to be considered in the design of cFLIP-targeted therapies against cancer.

This finding might very useful for scientists, that could design cancer therapies aimed at interfering the action of this protein. Such was the conclusion drawn by the researchers at the Andalusian Institute for Molecular Biology and Regenerative Medicine (CABIMER), in collaboration with the University of Granada.

The research conducted by Rosario Yerbes Cadenas, PhD candidate at the University of Granada, was led by professor Abelardo López Rivas, of CABIMER, and was aimed at analysing the potential of cFLIP inhibitors in cancer therapies.

At present, TRAIL is a death-ligand of the TNF family, with significant therapeutic potential against cancer, basically due to its ability to induce apoptosis in cancer cells without displaying significant toxicity toward normal cells. However, there are tumor cells that are resistant to TRAIL-induced apoptosis for unknown causes.

This study analysed the role of cFLIP in breast cancer cells' resistance to TRAIL-induced apoptosis. Thus, researchers concluded that cFLIP is key in these cells' resistance to TRAIL. Such conclusion was drawn from the evidence that the inhibition of their expression through treatments with Doxorubicin (anthracycline, widely used in chemotherapy) or with SAHA (Histone deacetylases inhibitor), as well as the silencing of its expression through cFLIP siRNA oligos (small interfering RNA), resulted in the sensitisation of breast cancer cells to TRAIL-induced apoptosis.

The authors of this research proved that cFLIP plays a survival role in tumorous and non-tumorous breast epithelial cells, since the inhibition of its expression induces apoptosis. This type of apoptosis requires the formation of the death-inducing signalling complex, which includes TRAIL-R2 receptor, adapter molecule FADD and procaspase-8- but is TRAIL-independent itself.

Conversely, in the light of the cFLIP relevance in controlling apoptosis, researchers studied the role of cFLIP in breast epithelial cells MCF-10A morphogenesis -a process where apoptosis plays an essential role. Thus, cFLIPL/cFLIPS overexpression inhibits lumen formation in acini from breast epithelial cells when they are cultured in a 3D extracellular matrix (3D cultures). Additionally, inhibition of cFLIP expression prevents the development of acini, since cells with low expression of cFLIP are unfeasible.

For this reason, regulation of cFLIP expression was very relevant to this research. Scientists determined that the PI3K/AKT signalling pathway is not the main responsible for cFLIP synthesis in breast cancer cell, but may be it is NF-kB pathway.

Additionally, this study revealed that the ubiquitin-proteasome system plays a key role in cFLIP cell degradation. At present, researchers are trying to identify E3-ubiquitin ligase protein, responsible for cFLIP degradation by such system.

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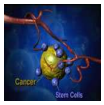

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