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Citation: *Journal of Biological Chemistry (JBC Papers in Press* published Nov. 30, 2005 online): “A Peroxisome Proliferator-activated Receptor-gamma (PPAR-gamma) agonist, Troglitazone, facilitates caspase-8 and -9 activities by increasing the enzymatic activity of Protein Tyrosine Phosphatase-1B on human glioma cells”

HIGHLIGHTS:

Using a drug originally intended for diabetes treatment, researchers at Cedars-Sinai Medical Center’s Maxine Dunitz Neurosurgical Institute have modified a series of intracellular biochemical events to decrease malignant brain cells’ resistance to therapies that are designed to trigger a natural process of cell death.

RESEARCHERS BREAK CHAIN OF BIOCHEMICAL EVENTS THAT BRAIN CANCER CELLS USE TO EVADE THERAPY

LOS ANGELES (Feb. 3, 2006) – In their quest to find and exploit vulnerabilities in the natural armor that protects malignant brain tumors from destruction, researchers have found a way to decrease the cells’ resistance to therapies that are designed to trigger cell death. The findings resulted from laboratory experiments conducted at Cedars-Sinai Medical Center’s Maxine Dunitz Neurosurgical Institute and are based on the manipulation of a series of intricate biochemical events taking place within brain tumor cells.

“We have described and are exploiting a biochemical pathway to make brain cancers much more sensitive to common therapeutic agents that cause a natural process of cell death called apoptosis,” said John S. Yu, M.D., co-director of the Comprehensive Brain Tumor Program at the Institute, adding that the researchers are applying for Food and Drug Administration approval to translate their findings into patient clinical trials as soon as possible.

Although most types of cells can be dismantled and cleared by apoptosis – a “programmed” and necessary cell death mechanism – gliomas and other cancer cells have genes that enable them to thwart apoptosis and continue to grow unchecked even when subjected to therapies that are designed to initiate or enhance apoptosis.

One such therapy, which Institute researchers have studied and are developing, centers on a protein called TRAIL (tumor necrosis factor related apoptosis inducing ligand). TRAIL has been shown to cause cell death in several types of cancers, with negligible damage to normal cells. The new findings should increase the effectiveness of TRAIL and other agents that trigger a “caspase cascade” – a specific biochemical chain reaction resulting in cell death.

In the normal process of apoptosis, the enzymes caspase-8 and caspase-9 activate caspase-3, which initiates cell breakdown, leading to cell death. In gliomas, however, several proteins that modulate these enzymes are overexpressed, resulting in down-regulation (reduction) of enzyme activity. With caspase-3 activation blocked, apoptosis is halted and cancer cells grow uncontrolled.

(more)

The Cedars-Sinai researchers theorized that a diabetes drug called troglitazone would limit the effects of the overexpressed proteins, reinstating the caspase activity and the process of apoptosis. In patient trials, pioglitazone will be used instead of troglitazone, which was the ingredient in Rezulin®, removed from the market because of safety issues. Pioglitazone acts in cancer cells in the same way as troglitazone, but without the associated liver concerns. Both are in a family of drugs called thiazolidinediones, given in tablet form to patients with Type 2 diabetes to improve cells' responsiveness to insulin.

Although Yu and his colleagues usually are hesitant to prescribe more than one anti-cancer medication, this appears to be an ideal situation for a two-drug attack.

“When you combine two therapeutic agents, you usually get the toxicity of both, which is additive. But this strategy is different in that we are using a common diabetes drug that does not have the toxicity of a therapeutic agent. We have medications that are designed to induce apoptosis in tumor cells. Now we have a drug that appears to lower thresholds for induction of apoptosis,” said Yu, senior author of a paper describing the study in the *Journal of Biological Chemistry*, published online Nov. 30, 2005. The article is expected to be published in the print version of the journal in late January.

“This study shows that as we begin to dissect the biochemistry of cancer, we can design therapies that interact within the critical pathways that are important for cancers to survive,” said Keith L. Black, M.D., director of the Institute and the Division of Neurosurgery at Cedars-Sinai. “One of the things we have learned is that there probably will not be one ultimate pathway in cancer that we can block and be curative. A more likely scenario is that we will need to develop multiple pathways for interaction. The understanding we gain from translating basic research into patient care allows us to build upon what we already know and begin to block additional pathways to make our current therapies more effective.”

The study was supported by National Institutes of Health grant 1RO1 NS048959.

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