Disrupting a destructive duo: Researchers inhibit cancer proteins

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A research team led by U of T Mississauga scientists has developed a new way to split up a dangerous pair of cancer proteins, a finding that could ultimately lead to chemotherapy that is more effective and has fewer side effects.

Working with scientists at the University of Central Florida and the Princess Margaret Hospital, Professor Patrick Gunning of the Department of Chemical and Physical Sciences has created several molecules that inhibit Stat3, a protein that--in cancer cells--pairs with another copy of itself and goes haywire. The findings appear in the September issue of the journal *ChemBioChem: A European Journal of* Chemical Biology.

"The molecules we have created are particularly nice because they're showing selectivity against cancer cells but not against healthy cells," says senior author Gunning. "This molecule could be used in conjunction with typical chemotherapeutics, and it could mean that drugs will have less resistance—so you could use lower dosages and cause fewer side effects."

The Stat3 protein is involved in almost all cancers, and is known to contribute to the resistance of cancer cells to current drug therapies. "Most currently available therapeutics aim to induce cell death," says Gunning. "We wanted to make small molecules that could try and stop this protein."

In cancerous cells, Stat3 proteins bind together to work as a lethal pair, and inhibitors work to prevent this. This type of protein-protein interaction is notoriously difficult to counter. Gunning's team targeted binding "hotspots" on a known Stat3 inhibitor called S3I-201. They chemically altered the inhibitor to produce several new variants, which they then tested on Stat3.

In in vitro studies, some variants proved to be even more powerful than S3I-201, and showed activity against prostate, breast and acute myeloid leukemia cancer cell lines. "These are some of the most potent inhibitors in the literature so far for this particular protein," says Gunning. "In some cases, they were more than twice as effective as the existing inhibitor."

When the team used more complex cancer cell models, they found the inhibitors survived the passage across the cell membrane and still targeted the Stat3 cancer proteins inside. Gunning and his colleagues are working to make the new inhibitors even more effective, as well as more metabolically stable, meaning that they can survive the chemical defense mechanisms within the cell.

Source: University of Toronto (news : web)

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