Compounds outsmart solid tumors' malfunctioning machinery

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Molecular biologists in the School of Medicine at The University of Texas Health Science Center San Antonio have found a novel way to fine-tune the activity of cells' protein-disposing machinery, with potentially cancer-fighting effects.

This machinery, the proteasome, is deregulated in cancer. Agents called protease inhibitors are viewed as potential anti-cancer therapies, but they indiscriminately curb proteasome activity, which also includes protein recycling. Such strategy is effective to kill cells in aggressive blood cancers but leads to drug resistance and excessive toxicity in solid tumors.

Fine-tuning

The new strategy may change that. By basically outsmarting the cell's machinery, compounds called allosteric regulators are able to fine-tune the proteasome actions instead of block them. "The result is that cell lines from solid tumors, which are resistant to existing therapy, are sensitive to these agents," said Pawel Osmulski, Ph.D., assistant professor of molecular medicine at the Health Science Center. He and Maria Gaczynska, Ph.D., associate professor of molecular medicine, co-authored a report in *Molecular Pharmacology* that provides a basis for this approach.

'Highly beneficial'

Deregulation of the proteasome's actions is noted in cancer or during aging and contributes to intracellular pathologies. "It is easy to envision that precise adjusting of the proteasome activities with therapeutic molecules would be highly beneficial in many human conditions," Dr. Osmulski said.

Inhibition and activation

"Allosteric regulators are better than proteasome-affecting agents used in clinics because they do not induce classical drug resistance," Dr. Gaczynska said. "They bind to sites on the proteasome molecule used by natural regulatory proteins. They are more specific and are not restricted to proteasome inhibition but can activate the proteasome under certain conditions."

The new strategy was serendipitously found during experiments with rapamycin, a drug that in a highly publicized study by the UT Health Science Center's Barshop Institute for Longevity and Aging Studies was found to extend life span in mice.

Potential

The *Molecular Pharmacology* report and follow-up studies describe the unexpected and highly desired effects that rapamycin and similar compounds elicit on the proteasome. Based on these studies, it would be possible to design a new line of proteasome regulators with anti-cancer properties, Drs. Osmulski and Gaczynska said. This work is in progress in their laboratory. Drs. Osmulski and Gaczynska are affiliated with the Barshop Institute and with the Cancer Therapy & Research Center at The University of Texas Health Science Center San Antonio.

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