A new approach to improving cancer chemotherapy

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(Medical Xpress) -- Chemotherapy kills tumor cells, but it also wreaks havoc on the rest of the body. A team of researchers led by Igor Roninson of the South Carolina College of Pharmacy just reported the discovery of a new class of drugs that reduces the adverse effects of cellular damage from chemotherapy.

The advance appears to be applicable to a wide range of cancers and has the potential to improve the efficacy of and increase the time of remission after chemotherapy. It may also be developed into a promising new therapy for age-related diseases, such as Alzheimer's.

"Conventional anticancer drugs, while essential for current cancer therapy, have side effects that can damage healthy cells and cause them to promote the growth of surviving cancer cells," said Roninson, the SmartState Endowed Chair of Translational Cancer Therapeutics at the South Carolina College of Pharmacy, who has appointments with both the University of South Carolina and the Medical University of South Carolina. "We needed to find a way to interrupt that process."

The cancer-supporting activity of conventional drugs appears to occur, in part, because these drugs damage both tumor cells and the patient's normal tissues, causing numerous changes in drug-damaged cells, including the onset of senescence. Cellular senescence, or aging, can result from changes in the chromosomes that develop with age, or it can be induced by DNA damage caused by traditional anticancer drugs and other factors. The senescent cells and other damaged cells have been

shown to produce cancer-supporting molecules as well as proteins implicated in other diseases of old age, such as Alzheimer's disease and arthritis.

The importance of these secretory activities of senescent cells has been convincingly demonstrated in recent studies, but no practical method for blocking this pattern was previously known. Roninson's team has just reported in the *Proceedings of the National Academy of Sciences* the development of Senexin A, the first of a series of chemicals that inhibit the secretory pattern of the senescent and other damaged cells. This inhibition is key to reducing the cancer-promoting effects of chemotherapy.

In one of the experiments reported, carried out by co-author Hippokratis Kiaris at the University of Athens (Greece), mice were treated with a commonly used anticancer drug. After the mice recovered from this treatment, both drug-treated and untreated mice were injected with cancer cells.

Strikingly, mice pretreated with the anticancer drug developed tumors much more efficiently than the untreated mice. Furthermore, the blood of mice pretreated with the anticancer drug had a higher content of proteins that stimulate the growth of tumor cells.

But treating mice with Senexin A neutralized the cancer-supporting effects of the anticancer drug, blocking the increase both in the tumor growth and in the production of tumor supporting growth factors. Senexin A also increased the antitumor effectiveness of the conventional drug.

The molecular target of Senexin A was identified as a protein kinase (an enzyme that modifies other proteins by adding a phosphate) called CDK8 (cyclin-dependent kinase 8). Senexin A is the first selective

inhibitor of CDK8 and its nearest relative, CDK19. CDK8 is involved in the regulation of gene expression; that is, the changing in the balance of proteins produced in a cell. Unlike better known kinases of the CDK family, CDK8 does not have a role in the process of cell division.

CDK8 was already known to play an important role in colon cancer and melanoma. The team reported a striking correlation between the gene expression of CDK8 and the duration of relapse-free survival in patients with breast and ovarian cancer. For example, breast cancer patients with below-median expression of CDK8 survived without the disease approximately seven years longer than patients who had above-median expression of CDK8. The new results implicate CDK8 in damage- and senescence-induced production of cancer-supporting proteins, and suggest that the new class of drugs may provide benefit in many different types of cancer.

The research represents a collaboration between Senex Biotechnology (a Columbia, S.C., company founded by Roninson), USC, and the University of Athens (Greece), together with several other institutions. The study was based on Roninson's discovery in 2000 that p21, a protein that stops the division of damaged and aging cells, induces the production of multiple proteins implicated in cancer, Alzheimer's and other aging-related diseases. The team has now demonstrated that p21, which was known to inhibit other members of the CDK family, in contrast, promotes the activity of CDK8 and stimulates CDK8-regulated genes.

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