MedicalXpress

Scientists find promising new approach to preventing progression of breast cancer

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February 15, 2013 – Doctors currently struggle to determine whether a breast tumor is likely to shift into an aggressive, life-threatening mode—an issue with profound implications for treatment. Now a group from The Scripps Research Institute (TSRI) has identified a mechanism through which mitochondria, the powerhouses of a cell, control tumor aggressiveness. Based on their findings, the team developed a simple treatment that inhibits cancer progression and prolongs life when tested in mice.

The research team, which describes its results February 15, 2013, in an article published online ahead of print by *The* Journal of Clinical Investigation, hopes to proceed quickly to human clinical trials to test this new approach using drugs already in use for other conditions.

Looking at Clues

The TSRI laboratory of Associate Professor Brunhilde H. Felding studies cancer, especially the mechanisms that control metastasis, the spread of cancer from its primary site to distant organs in the body.

Past research suggested that mutations affecting mitochondria, which are key to energy production in cells, strongly influence whether a tumor becomes aggressive. But the mechanism was not clear.

"We decided to investigate a specific protein complex, called

mitochondrial complex I, that critically determines the energy output of cellular respiration," said the study's first author, Antonio F. Santidrian, a research associate in Felding's laboratory. To do this, the group teamed up with Akemi and Takao Yagi at TSRI, who are leading experts in complex I research. Using unique reagents from the Yagi group, the Felding team discovered that the balance of key metabolic cofactors processed by complex I—specifically, nicotinamide adenine dinucleotide (NAD+) and NADH, the form it takes after accepting a key electron in the energy production cycle—was disturbed in aggressive breast cancer cells.

Exciting Results

To find out if the balance of NAD+ and NADH was critical for tumor cell behavior, the team proceeded to insert a yeast gene into cancer cells that caused a shift toward more NAD+. To the scientists' amazement, this shift caused the tumor cells to become less aggressive.

"It was a really happy moment for me," said Santidrian. But the more exciting moments, he said, were yet to come.

To confirm and extend the initial findings, the team altered genes tied to NAD+ production. The resulting shift again showed that higher NADH levels meant more aggressive tumors, while increased NAD+ had the opposite effect.

The next logical step was to find a simple way to enhance the critical NAD+ level therapeutically. So the team explored what would happen if mice with breast cancer were fed water spiked with nicotinamide, a precursor for NAD+ production. The scientists found cancer development was dramatically slowed down, and the mice lived longer

"In animal models at various stages, we see that we can actually prevent

progression of the disease," said Felding.

Next Steps

Now the group is working toward human trials to learn whether nicotinamide or other NAD+ precursors will have similarly impressive results in humans. Since NAD+ precursors are already used for other purposes, such as controlling cholesterol levels, achieving approval for human clinical trials should be simpler than is normally the case.

"It is not a totally new treatment that would need to be tested for toxicity and side effects like a new drug," said Felding. "And we already know the precursors can be easily ingested."

If manipulating the NAD+/NADH ratio in humans has the same effect as in mice, the results could be profound. Such treatment could benefit people at risk of developing aggressive breast cancer, offer complimentary treatment to chemo and radiation therapy to avoid disease recurrence, and maybe even provide a preventive treatment for women with a family history of breast cancer.

Provided by Scripps Research Institute