'Longevity' protein SIRT1 may ward off precursor to prostate cancer

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Researchers from the Kimmel Cancer Center at Jefferson and two other institutions have discovered new evidence that suggests the "longevity" protein SIRT1, known for its life-spanning effects in different species, can inhibit the development of a known precursor to prostate cancer, prostatic intraepithelial neoplasia (PIN).

Results from the study could lead to new cancer prevention drugs that could not only block prostate cancer but promote longevity.

The study, published in the February 1 issue of *Cancer Research*, found that deletion of the Sirt1 gene in mice resulted in PIN lesion formation associated with reduced autophagy, which is the necessary degradation of a cell's own components and most likely essential for tumor suppression.

"Prostate cancer is one of the malignancies that has a very direct relationship to aging," says Richard G. Pestell, M.D., Ph.D., Director, Kimmel Cancer Center and Chairman of Cancer Biology at Thomas Jefferson University. "And these results provide a direct link for the first time between the onset of prostate cancer and the Sirt1 gene that regulate aging."

The results suggest that the Sirt1 gene promotes autophagy and further highlight the role of the protein SIRT1 (the human homologue of the yeast Silent Information Regulator 2 (Sir2) gene) as a tumor suppressor in the prostate. According to Dr. Pestell, "if you inactivate this gene,

then you get the prostate cancer precursor, known as PIN. So it tells you that this 'longevity' gene is normally blocking prostate cancer."

Previous studies have found that SIRT1—which was discovered about 15 years ago and found to have various life-spanning effects in yeasts, worms, mice and possibly humans—can both inhibit tumor growth in certain cancers as well as promote it by inactivating the tumor suppressor p53, but its role in regulating prostate gland development and androgen signaling in vivo was unknown.

To better understand SIRT1's role in the development of androgen-responsive tissues, such as the prostate, researchers from Thomas Jefferson University in Philadelphia, worked with the Herbert Irving Comprehensive Cancer Center at Columbia University in New York and the Ottawa Health Research Institute at the University of Ottawa. Dr. Pestell's laboratory carried out a genome-wide microarray, pathway analysis and histology on Sirt1 positive and negative transgenic mice and littermate controls.

The team found that deletion of the Sirt1 gene in mice resulted in PIN formation; features included cellular hyperplasia, increased Ki67 staining, hyperchromatic nuclei and prominent nucleoli, as well as a reduced size in prostate. Gene expression analysis further demonstrated that loss of endogenous Sirt1 inhibited autophagy, which regulates normal gland development.

Dr. Pestell's laboratory was the first to show that the androgen receptor is regulated by the deacetylase enzyme (SIRT1) in cell lines in a tissue culture. "So then we asked the question, 'if you take prostate cancer cell lines, and if the androgen receptor promotes growth, and acetylation promotes growth, does the deacetylase inhibit growth?'" After establishing that it in fact did, researchers applied their mouse model to establish the same relationship on the animal level.

Since the results of the study suggest that drugs that activate Sirt1 could block prostate cancer, Dr. Pestell explains, his team is now working to test various prevention drugs they've screened for testing in human prostate cancer cells.

Provided by Thomas Jefferson University

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