Gene Associated with Rare Adrenal Disorder Appears To Trigger Cell Death

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(PhysOrg.com) -- A gene implicated in Carney complex, a rare disorder of the adrenal glands, appears to function as a molecular switch to limit cell growth and division, according to a study by researchers at the National Institutes of Health and other institutions. Mice lacking functional copies of the gene in the adrenal glands developed an overgrowth of adrenal tissue and were more susceptible to tumors in the gland.

The adrenal glands — one located on top of each kidney — produce hormones which help control heart rate, blood pressure, and other important body functions.

The researchers discovered that the normal process by which cells in the adrenal gland grow old and die is put on hold when the gene, known as Prkar1a, is deactivated. The Prkar1a gene is known to be involved in how the cell regulates its activities.

“Loss of Prkar1a appears to lead to unchecked cell growth in the adrenal glands,” said Dr. Constantine A. Stratakis, M.D., acting director of the Division of Intramural Research of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and an author of the paper. “Our hope is that future studies of the gene and its functions will lead to a greater understanding of how certain types of cancer develop and ways to limit their growth.

The findings were published online in PLoS Genetics. The study’s

first author is Isabelle Sahut-Barnola of Clermont University, France. Other authors include researchers at Ohio State University, Columbus and at three French institutions.

Carney complex is a rare disorder of the adrenal glands. Individuals with Carney complex typically develop Cushing's syndrome, a combination of weight gain, high blood pressure, diabetes, and other symptoms stemming from the overproduction of the hormone cortisol, which is produced by the adrenal glands. People with Carney complex are also predisposed to developing benign tumors of the heart and connective tissue, as well as benign and cancerous tumors of the adrenal and other glands. Previous studies have shown that people with Carney complex are likely to have a mutation in the Prkar1a gene.

To conduct the study, the researchers developed a strain of mice lacking functional copies of the Prkar1a gene in the adrenal glands. As the mice grew, they developed characteristics similar to those of people with Carney complex, including Cushing's syndrome.

Dr. Stratakis explained that the study results suggest that in adrenal tissue, the Prkar1a protein ensures that normal hormone-producing functions develop. In mice with functioning copies of Prkar1a, stem cells in the adrenal glands are retained after birth in a region of the gland called the X-zone. This zone disappears when female mice have their first litter, or at puberty in males.

However, among mice lacking the Prkar1a gene, 10-month-old females that had given birth still retained the stem-cell-like X-zone tissue. This zone was even larger in 18-month-old mice.

In other sections of the gland, researchers also detected new stem cell-like cells in 5-month-old mice. These cells grew in a band that was progressively thicker in 10- and 18-month-old mice.

These findings suggest that the Prkar1a protein plays a role in curtailing the further growth and development of these stem cells into tumors.

It is possible that mutations in Prkar1a play a role in the development of other kinds of tumors as well, Dr. Stratakis said. In a previous study, he and his colleagues found that mice with disruptions in the Prkar1a gene developed bone tumors. These studies also may have important implications in understanding how unregulated stem cells may lead to tumor development in various organs, Dr. Stratakis said.

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