Mechanism that may trigger degenerative disease identified

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Jon Oatley

(PhysOrg.com) -- A mechanism that regulates stem-cell differentiation in mice testes suggests a similar process that may trigger degenerative disease in humans, according to a Penn State College of Agricultural Sciences reproductive physiologist.

Research involved manipulating a protein called STAT3 that signals stem cells to decide whether to differentiate into a specialized type of cell or self-renew and remain stem cells. By manipulating STAT3, researchers identified a key regulator of spermatogonial stem cell self-renewal.

The STAT3 protein, which is active in tissues throughout the body and is essential for life, regulates genes that are involved in cell growth and division, cell movement, and the self-destruction of cells. All tissue and

organs within the body are based on a specific differentiated cell type, and these cells are constantly lost through cell death and aging. For the testis, the differentiated cell type is sperm.

Every time a stem cell divides, it produces two new cells. Self-renewal is the process by which this division results in a stem cell duplicating itself, thus maintaining a stem cell pool. Differentiation is when the stem cell division produces cells that will become the differentiated cells that maintain the function of the tissue or organ. Impairment of either of these stem-cell functions manifests as tissue and organ failure, so deciphering the mechanisms that regulate stem-cell activity is of utmost importance for devising treatments for degenerative diseases.

"We looked at a mechanism that is involved in the differentiation of stem cells, and we were actually able to shift that decision away from differentiation into self-renewal," said Jon Oatley, assistant professor of reproductive physiology, who led the study. "Right now we are at the ground level -- we discovered this in a mouse, and we hope we can start to look at it in human disease to see whether this pathway still holds true. We hope that down the line, as we study it further, we may be able to tie it to human disease."

Several key regulators of spermatogonial stem cell self-renewal have been identified, but knowledge of molecules that control spermatogonial stem cell differentiation is lacking, Oatley explained.

"In this study, we found that impairment of STAT3 signaling enhances spermatogonial stem cell self-renewal without affecting general proliferation of the cells. That indicates an alteration in the balance of spermatogonial stem cell fate decisions that inhibited differentiation in favor of self-renewal."

Much stem-cell research is done of necessity with mice, noted Oatley,

who pointed out that scientists who use the mouse as a model for human biology make the assumption that what they learn about in a mouse is identical to what happens in a human.

"Ideally, any of us who work with mice would love to translate our work into humans, but the problem is that you can't get the tissue samples from humans, and you can't manipulate the genetics of humans to show what we want to learn," he said.

Oatley said he believes his research is a solid first step in helping scientists learn how to regulate STAT2 levels to treat or control degenerative disease in humans.

The findings were published in the June online issue of *Biology of Reproduction*.

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