Researchers identify a critical growth factor that stimulates sperm stem cells to thrive

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Researchers at the University of Pennsylvania School of Veterinary Medicine and Pennsylvania State University have identified for the first time a specific "niche factor" in the mouse testes called colony stimulating factor 1, Csf1, that has a direct effect on sperm stem cell self-renewal. Moreover, the study shows that the origin of this growth factor is the Leydig cell — located in the testes and stimulated by the pituitary gland to supply testosterone — that secretes Csf1 and enhances self-renewal of the stem cells.

The finding, based upon a decade of related research, shows that stem cells are influenced to increase divisions by this growth factor, which provides a powerful new model in the study of stem cells and shows they interact with their microenvironment called the "niche." Future studies can now be performed in a stem cell-niche system that provides a quantitative functional end point for assessment.

"This appears to be the first identified factor in a stem cell niche with a specific effect on self-renewal of stem cells, as well as the first cell found to be the origin of such a niche factor in any mammalian adult stem cell system," Ralph Brinster, professor of physiology at Penn Vet, said. "The growing recognition of the profound control the niche has on stem cell function, including aging, makes our result of interest to scientists not only in reproduction but in all adult stem cell systems."

All stem cells reside in a microenvironment generated by the cells that surround them, known as the stem cell "niche." The stem cell and niche

interact and influence each other, forming an interdependent, functional unit that results in stem cell self-renewal, differentiation, aging and other stem cell functions, including stem cell death. Brinster and his research team have for decades focused on spermatogonial stem cells, SSCs, that are the foundation of spermatogenesis and production of spermatozoa in the testes of adult males, whether man or mouse. The SSCs' self-renew throughout adult life, providing cells that differentiate into the spermatozoa needed in reproduction.

Based upon research focusing on the niche and the SSC, the team previously discovered that the niche in the testis of a newborn male mouse supported stem cells and their ability to produce spermatogenesis much better than the niche in the mature adult male testis. In subsequent studies, Brinster looked at what happened to SSCs as the male mouse aged and became infertile, which occurs at about age 2. That finding showed that all the SSCs in the testes had disappeared or died by the onset of infertility.

Hoping to identify the specific factor that led to the disappearance of SSCs and subsequently infertility, the team transferred the SSCs of young mice — 6 months old and still virile — into the testes of young mice every three months. The SSCs survived for more than three years in these mice, a greater than 50 percent increase in the life of the stem cells. This finding demonstrated that it was the SSC niche in the testis that was failing in older males long before the stem cells, which were relatively long-lived.

Self-renewal and differentiation of SSCs provides the foundation for testis function and fertility. Using DNA microarray transcript profiling to identify specific genes whose expression are augmented in the SSC-enriched Thy1+ germ cell fraction of mouse pup testes, the research team found that the receptor for Csf1 is enriched in Thy1+ germ cells. By adding Csf1 to cultures, SSC self-renewal was significantly enhanced

in Thy1+ spermatogonial cultures over a 63-day period without affecting expansion of other non-stem cell spermatogonia.

In vivo, expression of Csf1 in both pre-pubertal and adult testes was localized to clusters of Leydig cells and select peritubular myoid cells in the interstitial space between seminiferous tubules. Collectively, these results identify Csf1 as an extrinsic stimulator of SSC self-renewal and implicate Leydig and myoid cells as contributors of the testicular stem cell niche.

Source: University of Pennsylvania

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