A stem cell strategy for boosting testosterone levels tested in rodents

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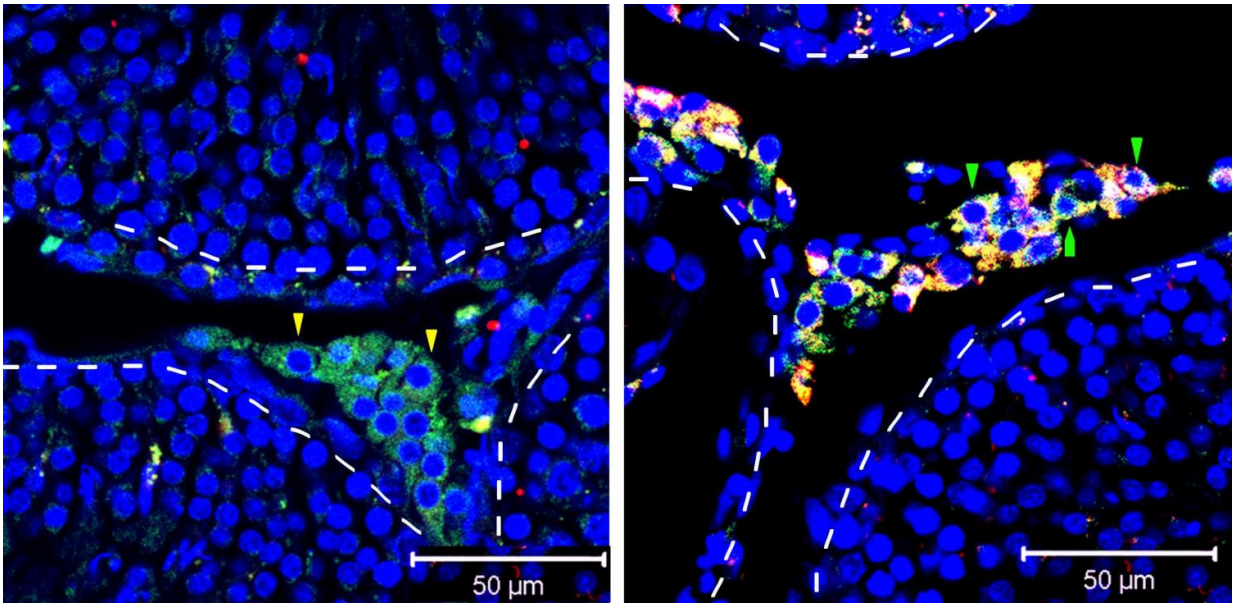

In this image, the GFP-expressed fibroblasts (yellow arrows, left) and the induced Leydig-like cells (green arrows, right) immigrate into the interstitial regions of seminiferous tubules (indicated by the "white bracket") after transplatation. The induced Leydig-like cells express all essential enzymes of steroidogenesis and synthesize the testosterone triggered by Luteinizing hormone. Credit: Zhijian Su

Male hypogonadism is a condition that diminishes testosterone levels in approximately 30% of older men, but currently available therapies can produce serious side effects. In a study published December 22 in *Stem*

Cell Reports, researchers developed an alternative approach involving the direct conversion of adult skin cells into functional testosterone-producing cells. When transplanted into male rodents with hypogonadism, these so-called Leydig-like cells survived and restored normal testosterone levels.

"Our study is the first to report a method for generating Leydig cells by means of direct cell reprogramming," says senior study co-author Yadong Huang of Jinan University. "This alternative source of Leydig cells will be of great significance for basic research and provides the attractive prospect of clinical application in the field of regenerative medicine."

Male hypogonadism is characterized by symptoms such as mood disturbances, sexual dysfunction, decreased muscle mass and strength, and decreased bone mineral density. One primary cause is the dysfunction of testosterone-producing Leydig cells in the testes. Testosterone replacement therapy can alleviate some symptoms resulting from Leydig cell failure, but it may also increase the risk of prostate and cardiovascular complications, such as the formation of blood clots.

Leydig cell transplantation could be a promising alternative to hormone replacement therapy, providing physiological patterns of hormone for a longer period of time. However, stem cell-based approaches are costly, time-consuming, and limited by ethical concerns and the risk of tumor formation. Huang and co-senior study author Zhijian Su of Jinan University reasoned that the direct conversion of adult skin cells into Leydig cells would be a faster, safer regenerative medicine approach.

To test this idea, the researchers screened 11 transcription factors that could affect the ability of Leydig cells to produce testosterone. Using lentiviral vectors to force the expression of three of these transcriptional factors, Dmrt1, Gata4, and Nr5a1, they were able to directly reprogram

mouse skin cells into functional Leydig-like cells, which showed normal gene activity and were capable of producing testosterone. When transplanted into the testes of rats or mice with hypogonadism, these cells survived and restored normal testosterone levels.

According to the authors, future studies should aim to improve the efficiency of the approach to generate a pure population of cells that closely mimic adult Leydig cells. For their own part, the researchers are examining in more detail the mechanisms underlying the direct conversion of skin cells into Leydig-like cells. To make the findings more relevant to patients, they are also examining direct cellular conversion strategies using small molecules and other non-viral methods. "In the end, we are hopeful that this research will pave the way for clinical trials testing a novel regenerative medicine approach to treat androgen deficiency in men," Su says.

More information: *Stem Cell Reports*, Yang et al.: "Direct reprogramming of mouse fibroblasts toward Leydig-like cells by defined factors" www.cell.com/stem-cell-reports … 2213-6711(16)30272-7 , DOI: 10.1016/j.stemcr.2016.11.010

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