Scientists develop recipe for testosterone-producing cells

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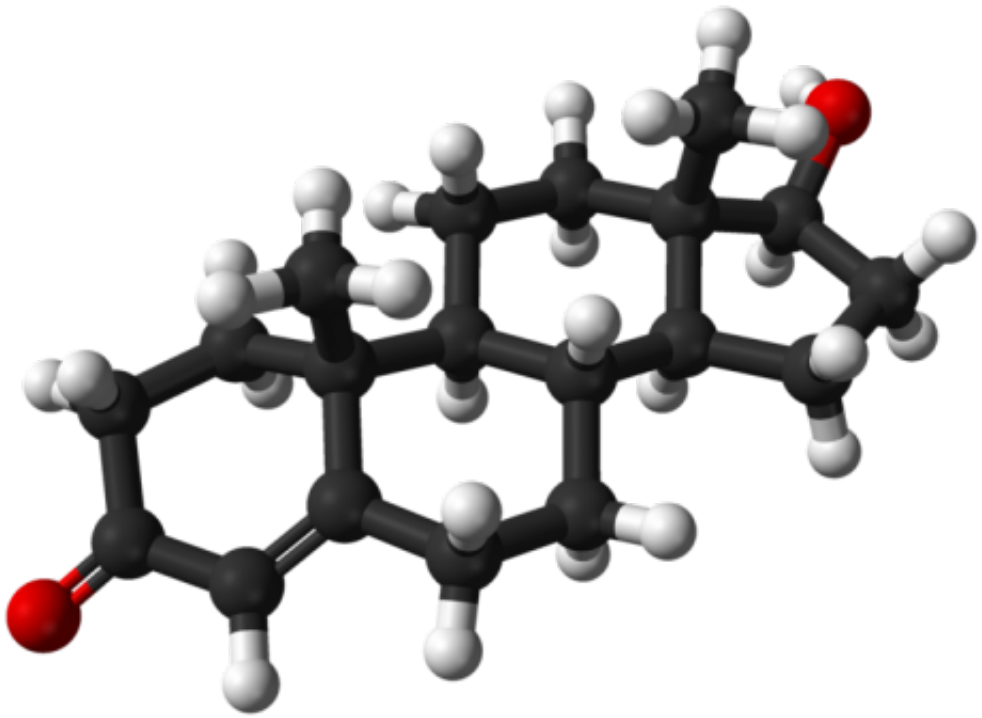

Ball-and-stick model of the testosterone molecule, $C_{19}H_{28}O_2$, as found in the crystal structure of testosterone monohydrate. Credit: Ben Mills/Wikipedia

Researchers led by teams at the Johns Hopkins Bloomberg School of Public Health and Wenzhou Medical University of China have discovered a way to keep adult stem cells that are destined to become testosterone-producing cells multiplying and on track to fulfill their fate,

a new study reports.

The findings could eventually help scientists develop transplantable cells that can churn out testosterone, avoiding the multitude of drawbacks associated with other ways to administer this quintessential male hormone. A report on the research is published online in the *Proceedings of the National Academy of Sciences*.

Scientists have long known that testosterone, produced by Leydig cells in the testicles, is necessary for the male reproductive system to develop in fetuses and to maintain male reproductive function later in life. More recent research has shown that testosterone performs a host of other critical jobs in the body, with deficiencies contributing to increased body fat, decreased muscle mass, increased fatigue, depressed mood, decreased cognitive function and reduced immune response. Low testosterone has also been linked to increased mortality risk in older men.

To combat these issues, and to synchronize secondary sexual characteristics with gender identity in transgendered men, doctors often prescribe testosterone supplements that can be administered a variety of ways, including injection or topically. But these methods have a number of side effects, including increased risk of heart attacks and strokes, prostate enlargement, breast enlargement and acne. These issues, says study leader Haolin Chen, Ph.D., senior scientist in the Department of Biochemistry and Molecular Biology at the Bloomberg School, stem from the dramatic peaks and valleys in blood concentrations of the hormone that result from artificial administration.

One way to avoid these issues would be to mimic the way the body naturally releases testosterone, with cells that release the hormone steadily over time. While Chen and his colleagues had been successful at isolating adult stem cells set to become Leydig cells, they were unsure

how to keep the cells multiplying, a process known as proliferation, and additionally to direct them to be testosterone producers, a process known as differentiation.

In the new study, the researchers used a method they'd previously developed to keep the stem cells alive, culturing them along isolated sections of the tubes that carry sperm in the testicles known as seminiferous tubules. For the next several weeks, the researchers fed these samples with various growth factors and other proteins that previous research had suggested might play a role in proliferation and differentiation.

They found a variety of factors that stimulated proliferation, including the proteins desert hedgehog (DHH), basic fibroblast growth factor, platelet-derived growth factor and activin. DHH and activin also stimulated differentiation. The research also showed that DHH played a vital role in transforming the stem cells into fully functioning, testosterone-producing Leydig cells.

Additionally, Chen and his colleagues determined that a protein called CD90, found on cell surfaces, could reliably distinguish the stem cells on the surfaces of seminiferous tubules that could be steered into Leydig cells.

Together, Chen says, these findings could be useful both for basic research as a model system for stem cells in general, and also to someday help researchers to create a population of testosterone-producing cells fit for transplant by isolating the right stem cells, prompting them to multiply and then to differentiate into Leydig cells.

"Our work could eventually offer a whole new therapy for individuals with low testosterone," Chen says.

"Regulation of seminiferous tubule-associated stem Leydig cells in adult rat testes" was written by Xiaoheng Li, Zhao Wang, Zhenming Jiang, Jingjing Guoa, Yuxi Zhang, Chenhao Li, Jinyong Chung, Janet Folmer, June Liu, Qingquan Lian, Renshan Ge, Barry R. Zirkin, and Haolin Chen.

More information: Xiaoheng Li et al. Regulation of seminiferous tubule-associated stem Leydig cells in adult rat testes, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1519395113