Prolistem®

AZOOSPERMIA TO HAPPINESS

A Breakthrough Approach Targeting Non-Classical Signaling in Sertoli Cells for Azoospermia

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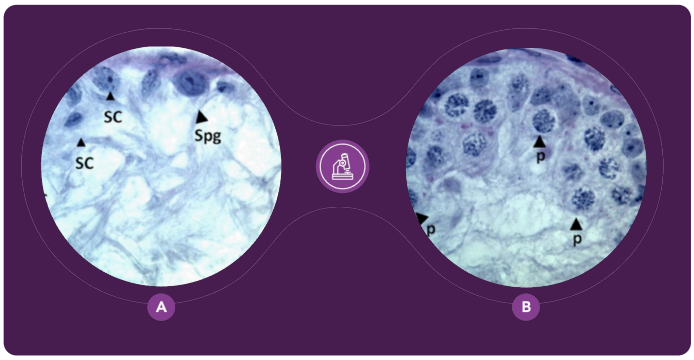
PROLISTEM®

Prolistem® is a novel solution for men dealing with non-obstructive azoospermia. It works in two phases to boost the chances of having a sperm.

Think of it like fixing a phone by restarting it, Prolistem® does something similar by temporarily lowering testosterone levels. We call it "Spermatogenesis Restarting Process" This process jumpstarts sperm production.



(A) Atrophic tubules that contained only Sertoli cells but some contained a few spermatogonia.

(B) Hormone suppression induced recovery of spermatogenesis in nearly all tubules (No sperm formation because of the low level of Testosterone)

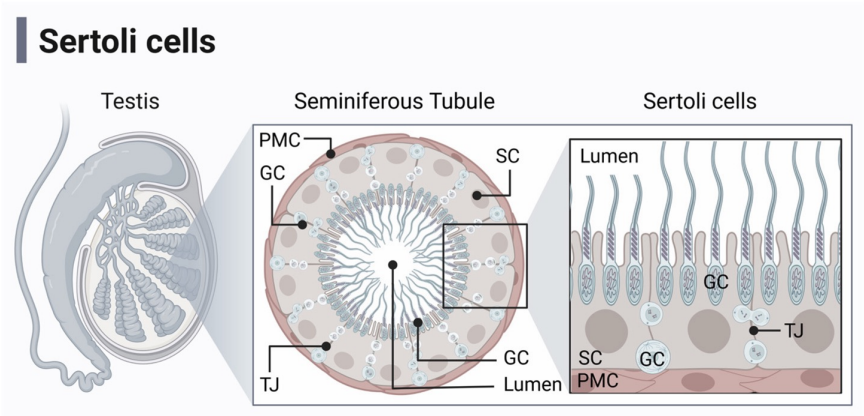
In our research and other studies, we discovered two important things. First, in men with azoospermia because of primary testicular failure, we found stem cells in the testis. These cells can divide and grow outside the testis. This shows that the testicular environment is really important.

Second, we noticed a link between testosterone levels inside the testis and the environment we mentioned earlier. When we lowered testosterone inside the cells, the stem cells grew more. This suggests that changing testosterone levels could be a way to help sperm production by adjusting the environment.

Sertoli Cells: The Environment Maker

Sertoli cells, residing in the testicular tubules, play vital roles in supporting sperm development. Acting as caretakers, these cells provide essential nutrients for the maturation of sperm cells. Additionally, they form a protective barrier, shielding developing sperm from the body's immune system.

Sertoli cells also respond to signals from testosterone, a key hormone, ensuring optimal conditions for healthy sperm growth. In essence, these cells act as custodians, orchestrating a nurturing environment essential for the successful development of sperm in the testicles.



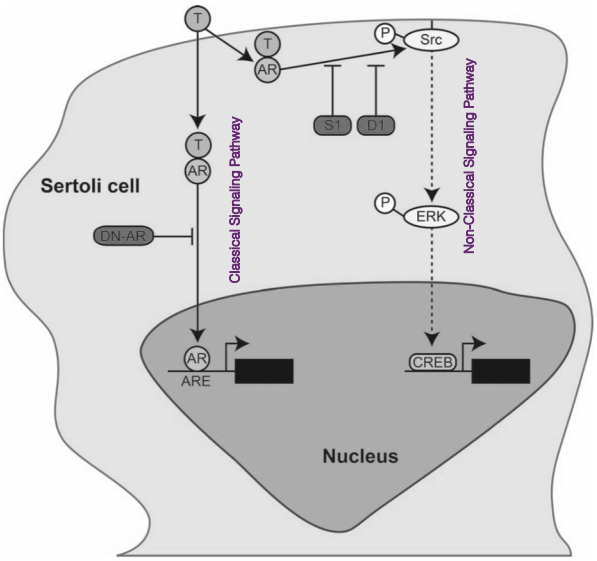
Seminiferous tubule anatomy. Sertoli cells (SC) and germ cells (GC) are located in the seminiferous tubules of the testis, which are surrounded by peritubular myoid cells (PMC). SC function to nurture spermatogenesis and protect GC from immune responses. They make up the blood–testis barrier by forming tight junctions (TJ) with adjacent SC.
Figure created with BioRender accessed on 1 December 2022.
Ref: https://www.mdpi.com/1422-0067/24/4/3371

UNDERSTANDING THE TESTOSTERONE'S ROLE

To grasp how Prolistem works, let's delve into the science behind testosterone's role in sperm production. Testosterone, a key regulator of spermatogenesis, is produced by special cells in the testicles in response to signals from the brain's luteinizing hormone (LH). This hormone exerts its effects by binding to the androgen receptor (AR), a transcription factor also known as NR3C4.

The Androgen Receptor acts as a crucial switch in cellular activities in response to testosterone, primarily located in somatic cells, including Sertoli cells but not in germ cells, playing an essential role in postmeiotic germ cell development and influencing the overall progression of spermatogenesis.

Sertoli cells, specialized within the seminiferous tubules, provide vital support for germ cells through nourishment, barrier creation, and hormonal regulation, with their successful development dependent on testosterone signaling through AR.



This well-established and extremely well-studied pathway, which can take hours to show a response, has become known as the Classical Signaling Pathway.

However, we discovered that testosterone can also act in Sertoli cells in a fast (<1 min) pathway, so-called Non-Classical Signaling Pathway.

Classical Pathway

The classical pathway is the slower and more traditional pathway. Here's how it works:

1. Testosterone binds to the androgen receptor (AR) in the cytoplasm of the Sertoli cell.
2. The AR-testosterone complex undergoes a conformational change, allowing it to detach from heat shock proteins.
3. The AR-testosterone complex then translocates to the nucleus of the Sertoli cell.
4. In the nucleus, the AR binds to specific DNA sequences called androgen response elements (AREs).
5. AR binding to AREs triggers the transcription of genes involved in spermatogenesis.

This process can take hours or even days to complete

Non-Classical Pathway

The non-classical pathway is a faster-acting pathway. Here's a breakdown of the process:

1. Testosterone binds to the AR in the cytoplasm of the Sertoli cell, similar to the classical pathway.
2. However, instead of translocating to the nucleus, the AR-testosterone complex interacts with proteins on the inner face of the cell membrane.
3. This interaction activates various signaling molecules, such as Src and ERK kinases.
4. These activated kinases trigger cellular processes essential for spermatogenesis, including cell proliferation, differentiation, and metabolism.

The non-classical pathway's effects are evident within seconds to minutes

The classical pathway provides long-term regulation of gene expression, while the non-classical pathway mediates rapid cellular responses. Disruption of either pathway can lead to infertility

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PROLISTEM® WORK THROUGH THE NON-CLASSICAL PATHWAY

Reducing testosterone levels with Prolistem® can activate the non-classical pathway. This shift in testosterone regulation induces a survival mode in spermatogenesis, prioritizing the non-classical pathway. This heightened emphasis on the non-classical pathway enhances the stem cell environment, initiating and promoting sperm production.

Here's what happens when Prolistem reduces intracellular testosterone:

non-classical pathway specifically triggered by reduced testosterone levels and aims to maintain spermatogenesis to some degree

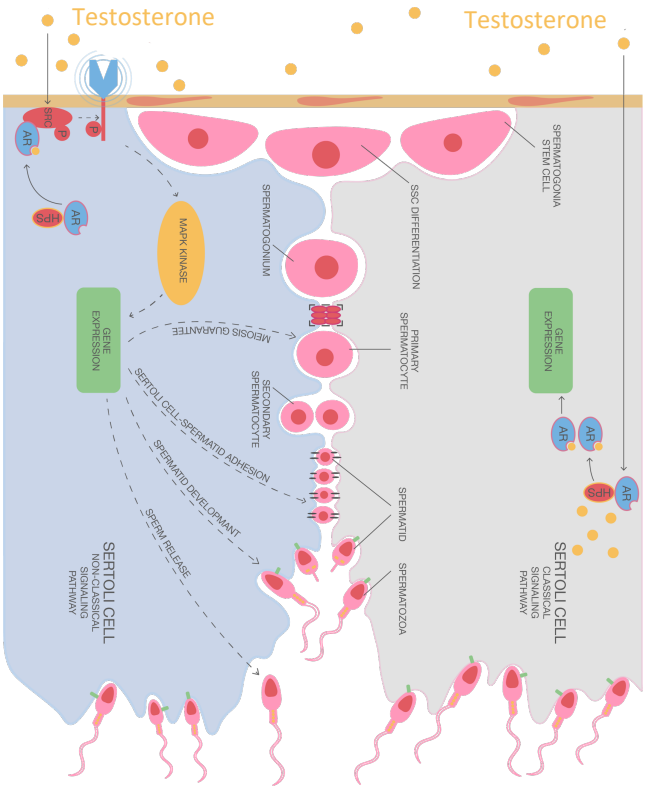
The non-classical pathway can be seen as an adaptive response to a changing environment (lower testosterone). It tries to maintain some level of function (spermatogenesis) in the face of a challenge.

This adaptation has limitations. It's a faster but potentially weaker response, and its effectiveness depends on the severity of the testosterone reduction

Overall, the non-classical pathway demonstrates the body's remarkable ability to adjust, but long-term function still relies heavily on the classical pathway

References:

- Molecular mechanisms of testosterone action in spermatogenesis William H. Walker. Steroids 74 (2009) 602–607
- Testosterone activates mitogen-activated protein kinase and the cAMP response element binding protein transcription factor in Sertoli cells. Charity Fix, Cynthia Jordan, Patricia Cano, and William H. Walker. PNAS July 27, 2004 vol. 101 no. 30 10919–10924
- Testosterone signaling and the regulation of spermatogenesis. william H. walker . 2011. Spermatogenesis 1:2, 116-120.
- Non-classical actions of testosterone and spermatogenesis. william H. walker. 2010. Phil. Trans. R. Soc. B (2010) 365, 1557–1569.
- Non-Classical Testosterone Signaling: A New Pathway Controlling Spermatogenesis? Lee B. Smith. 2016. biolreprod.115.137950.
- Nonclassical androgen and estrogen signaling is essential for normal spermatogenesis. Paul S. Cooke, William H. Walker. 2021. Seminars in Cell and Developmental Biology.
- Nonclassical Testosterone Signaling: A New Pathway Controlling Spermatogenesis?1 Lee B. Smith. 2016. BIOLOGY OF REPRODUCTION 94(2):43, 1–2
- Importance of the Androgen Receptor Signaling in Gene Transactivation and Transrepression for Pubertal Maturation of the Testis Nadia Y. Edelsztein, and Rodolfo A. Rey. 2019. Cells, 8, 861; doi:10.3390/cells8080861.
- What Does Androgen Receptor Signaling Pathway in Sertoli Cells During Normal Spermatogenesis Tell Us? Jia-Ming Wang, Zhen-Fang Li and Wan-Xi Yang. 2022. Frontiers in Endocrinology. Volume 13, Article 838858



Research is ongoing to understand how to potentially manipulate these pathways to improve sperm production in azoospermic men. There might be future therapeutic possibilities targeting these pathways to help with male infertility.

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