



## The Adipose Tissue: The New Positive Controller of Male Fertility?

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### Editorial

Along with people living horizontal increases continuously, obesity has become a global health problem that has reached its epidemic level not only in the Western countries, but also in developing countries. Accumulated evidence point out a negative impact of obesity on male reproduction. Obesity negatively affects male reproductive potential not only by reducing sperm quality, but in particular it alters the physical and molecular structure of germ cells in the testes, increases oxidative stress inside seminiferous tubules and ultimately affects the maturity and function of sperm cells. Interestingly, adipose tissue also exerts a positive effect on male reproduction. Appropriate lipid distribution appears to be indispensable for production of mature, functional sperm, according to a very new study in human and genetically engineering mice.

Type 2 Berardinelli-Seip congenital lipodystrophy (BSCL2), also known as congenital generalized lipodystrophy, is a rare autosomal recessive disease, characterized by a near total absence of adipose tissue from birth. BSCL2 is caused by mutations in BSCL2-encoding seipin. Seipin is highly expressed in human brain, testis, and adipose tissue. Lack of seipin is a hallmark of severe lipodystrophy. Moreover, loss of seipin in the brain has been linked to motor neuropathy. Interestingly, Cui X et al. unexpectedly made the surprising observation that seipin-deficient mice not only model BSCL2 with marked lipodystrophy but also exhibit complete male infertility, revealing a potential pivotal role of seipin during mammalian spermatogenesis. In continuance to this, they studied a male patient from a family affected by lipodystrophy, hoping to establish a relationship between lipodystrophy and male fertility. The patient exhibited an extremely muscular and acromegaloïd appearance, umbilical hernia and acanthosis nigricans over the axillae. As for the reproductive system, his sperm displayed several hallmarks of severe teratozoospermia syndrome, including abnormal head morphology and the presence of bundled sperm with large ectopic lipid droplets (LDs) appearing in their heads. Further Sequencing assay showed a 19-bp deletion from nucleotide 358 to 376 in exon 2, and a G to T mutation at nucleotide 757 (codon 253) in exon 5 of BSCL2 gene occurring in the patient. These data clearly provide an important clue to the possible involvement of Seipin in the germ cell development.

To examine the testicular function of Seipin more closely, Jiang et al. first examined the expression pattern of Seipin protein in testis using immunohistochemistry. In humans, seipin was present in the cytoplasm of late spermatocytes to spermatids but absent from mature sperm, while in mouse, seipin appeared at later phases of spermatogenesis and was detectable in steps 7-16 spermatids before

incorporation into the residual body, suggesting a distinct role of Seipin in different species [1].

Further evidence for a direct role of Seipin in the modulation of sperm formation is provided by using a knockout mouse model with the specific loss of seipin in germ cells (gS-KO). Interestingly, abnormal clustering of late spermatids of seminiferous tubules at stages VII and VIII were observed in the seminiferous epithelial cycle of mutant mice. gS-KO tubule sections near completion of spermiogenesis contained massive accumulations of spermatids in bundle-like structures, suggestive of defects during spermatid individualization, which defines the final stage of normal spermiogenesis. Similar to the ectopic lipid spheres observed in sperm from human patient, gS-KO mice contained large ectopic LDs in the perinuclear region of round to elongated spermatids. The author, therefore, performed lipidomic analysis of fatty acid compositions by liquid chromatography-tandem MS of whole testes. The results showed elevated levels of phosphatidic acid (PA) and altered phospholipid (PL) homeostasis in gS-KO testes, concomitant with the appearance of large ectopic LDs in sperm. Taken together, defects associated with the loss of seipin emphasize a central role of appropriate lipid metabolism and distribution during spermiogenesis.

Compelling evidence indicates that common regulatory signals are implicated in the integrated control of energy balance and reproduction. For example, ghrelin, the endogenous ligand of the growth hormone (GH) secretagogue receptor (GHS-R), has been proved to cooperate with other regulatory signals, such as the adipocyte-derived hormone leptin, in the integrated control of energy balance and reproduction. Similarly, another novel adipocytokine, namely resistin, directly participates in the control of testicular testosterone secretion under the precise control of an array of hormones and mediators that include gonadotropins, PPAR $\gamma$  transcription factor, leptin and the nutritional status. Of note, all the signals mentioned above originate from adipose tissue. Thus, a proper distribution of adipose tissue may be essential for the completion of normal spermatogenesis. The identification of Seipin as a regulator of spermiogenesis represents a step change in our understanding of the homeostatic mechanisms that are responsible for regulation of germ cell differentiation in the testis. The study may therefore pave the way for treatments for male infertility in obese patients.

### References

1. Jiang M, Gao M, Wu C, He H, Guo X, et al. (2014) Lack of testicular seipin causes teratozoospermia syndrome in men. *Proc Natl Acad Sci*: 111(19): 7054-7059.