

## The follicle-stimulating hormone receptor (FSHR) is expressed in human sperm and it may be considered as molecular marker of the detrimental effects related to the physiopathology of testicular varicocele

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Localization of the follicle-stimulating hormone receptor (FSHR), has been always closely related to the testis and ovary. FSH/FSHR role in Sertoli cell, has been known, however, the sites of FSH action within the male reproductive system are not resolved yet. Few studies have raised the intriguing possibility that germ cells may exhibit FSHR, all the reports point to Sertoli cells as the exclusive FSH target cells in testis. Besides, the attention has been always paid on the FSHR several polymorphisms which affect receptor sensitivity and expression. The presence of FSHR in germinal cells from spermatogonia to spermatocytes, including round spermatids is controversial or excluded. The mechanisms by which testicular varicocele affects fertility remain undetermined. Recently, our studies showed that the disease causes damage in sperm at the molecular level opening a new chapter in the already multifaceted physiopathology of varicocele. Samples used in this study were from normozoospermic and from diagnosed varicocele of grade III on the left testis patients. To date four FSHR isoforms were discovered, FSHR1, FSHR2, FSHR3 and FSHR4. The activity of FSHR1 is mediated by G proteins, which activate adenylate cyclase. FSHR2 and FSHR3 also bind FSH, but this does not result in activation of adenylate cyclase. FSHR4 does not bind FSH. By western blot analysis, we showed that healthy sperm express FSHR1, FSHR2 and FSHR3 while FSHR4 is almost absent. Varicocele does not express FSHR2. Immunofluorescence assay evidences FSHR localization prevalently at the midpiece level, which was strongly reduced in varicocele sperm. Responses to different FSH concentrations on motility and survival were significantly reduced in varicocele respect to the normal sperm, probably due to the lower FSHR1 expression and FSHR2 absence. The FSHR significance in human male gamete also emerged from the acrosome reaction histochemical studies, during FSH treatment which significantly induced the process. Our data showed for the first time that human sperm express the FSHR and constrain the need of further studies on the molecular anatomy of human male gamete both in healthy and in pathological conditions related to the male genital apparatus, considering the high couple infertility linked to the male. The translation of these new researches in the clinic surgery of testicular varicocele needs to be taken into account since molecular alterations in sperm imply a decline in the acquisition of fertilizing ability, and to date controversies exist on the opportunity to intervene surgically.

### Keywords

FSHR, human sperm, testicular varicocele