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Commentary

Characterization of fertility related antisperm antibodies—a step towards causal treatment of immunological infertility and immuno-contraception

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Antisperm antibodies (ASA) occur in men and women and may significantly impair fertility. The identification of functionally relevant antigens of ASA is important for establishing causal treatment options on the one hand and may, on the other hand, enhance the development of tools for immunocontraception. One candidate protein is addressed in an article of Wang *et al.* [1] published in *Asian Journal of Andrology*.

The authors report results of animal experiments where that antibodies against nuclear autoantigenic sperm protein (NASP), a histone-binding protein, were investigated for their antifertility effect. Mice were immunized with a recombinant mouse NASP and a synthetic human NASP. It has been demonstrated that immunization with both NASP-variants can inhibit sperm-egg binding as well as *in vitro* fertilization (IVF). Moreover, this antibody interferes with the fertility of immunized animals as shown by a reduced litter size.

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The testis is an immunologically privileged site where germ cell antigens are protected from autoimmune attack [2, 3]. However, due to disruption of the blood-testis barrier occurring from testicular injury, or as a consequence of trauma to the epididymis or vas deferens many testicular isoenzymes and other proteins get autoantigenic during immunological challenges resulting in the formation of ASA in the blood serum, seminal plasma or located on the sperm membrane. ASA have also been reported to be associated with inflammation, cryptorchidism, varicocele and surgical intervention in the genital organs [4]. ASA may interfere with different sperm functions essential for the fertilization process. However, the problem is to detect whether or not ASA of an individual man are of functional relevance, i.e. whether the ASA binding to a sperm surface antigen also influences sperm function and which one. In previous studies several antibody-binding proteins have been characterized in isolated sperm surface membranes and several proteins have been described whose ASA could be associated with agglutinations [5], motility [6], cervix mucus penetration [7], acrosome reaction [8], zona binding [9] and penetration and oolemma binding [10]. NASP has been found to be important for the pronucleus formation to which most vasectomized men develop autoantibodies [11]. In the present study several important results regarding NASP have been obtained:

1. Sperm-egg binding and IVF of mouse oocytes with capacitated mouse spermatozoa were inhibited in the presence of antisera against NASP.

2. Anti-NASP did not change sperm motility.

3. Sera from infertile men containing antisperm antibodies reacted with anti-NASP.

4. After immunization of fertile female mice with NASP the pregnancy rate was significantly reduced and the reduction in litter size correlated with the antibody-titer.

Depending on the immunogen used (recombinant mouse NASP) or a synthetic peptide (human NASP),

the immunized mice regained fertility at rates comparable to those of the control mice after the antibody titer had declined or the animals remained infertile (immunized with mouse NASP). With regard to the mechanism by which fertility is disturbed—inhibition of sperm-egg binding and IVF—it is speculated that the antibody effect must be associated with the cell surface and not with the cytoplasm or nucleus. This is a little bit in contrast to the fact that NASP has been shown to be located mainly over the nucleus and only partly in the acrosome [12]: here the authors discuss that some part of the NASP may be exposed for a short time when it is carried into the ovum with the sperm nucleus at fertilization. This question can be answered after performing intra cytoplasmic sperm injection (ICSI), which will be the next step in a further study announced by the authors in order to investigate the direct effects of the anti-NASP antibodies on embryo development and implantation. As ICSI is suggested as the appropriate treatment to overcome antisperm antibodies`action on the one hand, and—according to my own experience—fertilization and pregnancy rates are lower in couples with male immunological infertility compared to couples without antisperm antibodies in the male, even when ICSI is applied, it will be very interesting to see what these future studies will reveal. They will probably show that it is not an antibody against a single sperm antigen that causes a significant reduction of fertility, but is more likely multiple ASAs that contribute to an individual fertility problem. Future results will increase our understanding of the specific mechanisms that elicit the autoimmune response and of the active profile of ASA that leads to an antibody-mediated infertility. Thus, specific therapies based on the use of monoclonal antibodies as well as new approaches to male immune contraception may be developed.

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