Review Article

Sperm–zona pellucida interaction and immunological infertility

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Immune reactions against gametes appear to be physiologically important for the maintenance of homeostasis in reproduction. In contrast, aberration of the immune homeostasis might give rise to ‘immunological infertility’. Antisperm antibodies cause infertility by blocking fertilization. The mechanism can be explained as inhibiting the acrosome reaction of sperm by their blocking effect on capacitation through inhibiting an increase of fluidity of the sperm membrane. Autoantibodies against zona pellucida also cause infertility by blocking sperm–zona pellucida interaction, though the definitive mechanism has not been elucidated.

Pretreatment of spermatozoa with D-mannose completely inhibited sperm penetration through, but not binding to, the zona pellucida. Furthermore, very rapid kinetics between sperm extracts and D-mannose by a BIAcore apparatus suggest that a D-mannose ligand of the sperm surface is easy to bind to and dissociate from a D-mannose residue in the sperm receptor site on the zona pellucida. Thus, D-mannose on the human zona pellucida might be an essential molecule acting as a second sperm receptor, through which sperm penetrate into the zona pellucida.

Because these antibodies appear to not cause any deleterious clinical symptoms, sperm and zona pellucida antigens are promising candidates in the development of an immunocontraceptive. (Reprod Med Biol 2006; 5: 95–104)

Key words: antisperm antibody, autoantibody to zona pellucida, immunocontraception, immunological infertility, mannose.

IMMUNOLOGICAL INFERTILITY

Nonspecific and specific immune reactions against gametes or embryos appear to be physiologically important for the maintenance of homeostasis in reproduction.1 For example, in the male and female reproductive tracts, activation of the complement system by immature and aged sperm can enhance their destruction and clearance during the selection of active motile sperm. This mechanism of sperm selection is physiologically important, whereby increasing the opportunity of sperm to fertilize the ova.2 Furthermore, the present study has shown that the occurrence of cellular and/or humoral immune reaction against sperm antigens expressed on the surface of embryos appears to augment their receptivity by the uterus.3

In contrast, aberration of the immune homeostasis might give rise to ‘immunological infertility’. The majority of subjects with asthenozoospermia and/or oligozoospermia have a higher incidence of low complement-inhibiting activity and a reduced level of complement regulatory proteins, such as membrane cofactor protein (MCP, CD46) and decay accelerating factor (DAF, CD55) in their seminal plasma. This can lead to non-specific activation of the alternative complement pathway, thus, inflicting injury to sperm.4

An immune reaction acting adversely against gametes or hormones is a mechanism that contributes to the development of ‘immunological infertility’. A previous study reported the first case of an endocrine disorder that was the result of the production of an autoantibody to testosterone.5 Autoantibodies against zona pellucida (ZP) might cause infertility by blocking sperm–zona pellucida interaction.6,7 These antibodies

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are found in approximately 6% of infertile women with indeterminate etiology, whereas the incidence of infertility with associated antisperm antibodies is higher (approximately 18%).

The presence of these antibodies in blood, follicular and uterine fluids, and cervical mucus can impair reproductive processes that are crucial for a successful pregnancy. Because these antibodies appear to not cause any deleterious clinical symptoms yet be associated with infertility, sperm and ZP antigens are promising candidates in the development of an immunocontraceptive. Thus, immunologically defined factors, especially associated with gametes, are important to shed light on the process of human fertilization and to develop a contraceptive vaccine.

ANTISPERM ANTIBODY

Sperm can elicit an immune response in women as an alloantigen and in men as an autoantigen. Antisperm antibodies might cause infertility by (i) impairing sperm motility; (ii) blocking penetration of cervical mucus by sperm; (iii) interfering with sperm–egg interaction; (iv) interfering with the implantation of blastocysts; and (v) inhibiting the growth and development of embryos.

To date, reports on the cytotoxic effects of antisperm antibodies on embryonic growth have been restricted to studies with experimental animals. In contrast, naturally occurring antisperm antibodies found in the sera of immunoologically infertile women do not appear to inhibit embryo growth or implantation of blastocysts. The clinical data clearly show that high implantation rate and subsequently high pregnancy rate are achieved by in vitro fertilization (IVF) and embryo transfer treatment of infertile women possessing sperm immobilizing antibodies in their circulation.3,8

The authors of the present study were the first to show that naturally occurring sperm immobilizing antibodies can block penetration of the sperm through the human ZP.5 This observation has been confirmed subsequently by many investigators10 and further substantiated by our clinical data.3,11 Although the definitive mechanism whereby antisperm antibodies block sperm–zona interaction has not been elucidated, the capacity of antisperm antibodies to inhibit the acrosome reaction of sperm, an indispensable process for successful fertilization, is well established.10,12 It is noteworthy that the inhibition is reversible. Sperm preincubated with antisperm antibody recover their ability to penetrate the ZP with subsequent washing in antibody-free medium (Fig. 1).1 Recovery from the blocking effect of antisperm antibodies on the acrosome reaction is also observed after incubation of the antibody-bound sperm in antibody-free medium.12 The inhibitory effects of the antibodies on the acrosome reaction might be explained by their blocking effects on capacitation13 through inhibiting an increase of fluidity of the sperm membrane.14

AUTOANTIBODY TO ZONA PELLUCIDA

From circumstantial evidence, the production of autoantibodies against ZP has been implicated in the development of immunological infertility in some women.6,7,15–27 Because the ZP plays an important role in such reproductive processes as expression of the sperm receptor site(s) and protection against polyspermy and zona shedding on implantation, the presence of antibodies impairing such functions could result in infertility.

However, there has been serious controversy over the actual existence of such antibodies because antizona activities have been detected in the sera of both infertile and fertile women and men, and these activities disappeared after thorough adsorption of the sera with porcine red blood cells.28,29 In many previous reports showing the presence of antizona activities, indirect immunofluorescence (IF) method using porcine ZP as the target instead of human ZP was used as a screening test, because the ZP from these two sources show antigenic cross-reactivity and the availability of human ZP is limited. However, IF test using intact porcine ZP was proven to have some methodological problems on account of binding of non-specific immunoglobulin and hetero-hemagglutinin against porcine red blood cells.

Figure 1 Time course results of zona penetration test using sperm exposed to serum containing sperm immobilizing antibody (cited from1). (■) Serum containing sperm immobilizing antibody; (□) control serum.