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Review Article

ANTI-SPERM CONTRACEPTIVE VACCINES: A HYPOTHESIS TO DEVISE A NEW, INNOVATIVE CONTRACEPTIVE AGAINST SPERMS INSIDE A WOMAN'S UTERUS

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ABSTRACT

This article states a hypothesis of devising a new, immune-contraceptive vaccine against sperms. Experimental research has already been carried out in this area, using antigens from the sperm head. This poses several problems like acrosomal interference and variations caused due to capacitation of the sperm. We have suggested that the SPAG6 antigen on the sperm tail be used for the same purpose, which will overcome all such troubles and maintain a uniformity of interaction in the recipient female. This vaccine, when formulated, can be used to immunize females who use a convenient and non-invasive birth control method.

Keywords: Sperm, Immune-contraceptive, Vaccine, Birth control, SPAG6, Infertility.

INTRODUCTION

The fast population growth in many countries has been a major problem; therefore, the family planning program needs to be implemented widely and effectively. The human population continues to grow and is estimated to rise to 10.1 billion by the end of the century[1]. There is a need for safe and highly effective contraceptive options for both men and women. Until recently, male contraception was always associated with the problems of low efficiency, irreversibility and unwanted side effects.[2] Development of tools or materials for contraception is still underway; one of them is the immune-contraception method.[3,4] The aim of this hypothesis was to design an immune –contraceptive vaccine using SPAG 6 protein.

Anti-sperm antibodies (ASA) are a reason of infertility in some males. ASA impair both sperm function and fertilization. These auto antibodies may affect pre as well as post-fertilization stages of the reproductive process [5]. Mutations in the *SPAG6* gene could be one cause for male infertility.[6] Sperm-associated antigen six is a protein that is encoded by the *SPAG6* gene in human males. This protein is present in the tail of permeabilized human sperm and is involved in flagellar motility and maintenance of the structural integrity. The protein is recognized by ASA from an infertile man. The correlation of ASA with cases of unexplained infertility implicates a role for these antibodies in blocking fertilization [7].Working along these lines; we can develop antibodies against human sperm *in vitro*. We have hypothesized that monoclonal antibodies (MoAb) against human ejaculated sperm can be developed from mice immunized with sperm membrane preparations. The tissue and species specificity of MoAb against *SPAG6* can be evaluated using antibody preparations with heterologous sperm and seminal plasma. Vaccination with these sperm antigens will cause a reversible contraceptive effect in females and males, by inducing a systemic and local antisperm antibody response. Infertility after anti-sperm antibody binding can be caused by auto agglutination, sperm cyto-toxicity, blockage of sperm-ovum interaction, and inadequate motility. The efficacy can be enhanced by combination vaccination, including peptides based on various sperm antigens, like using multi-epitope vaccines combining sperm proteins involved in various steps of the fertilization cascade [8].

Contraceptives

In the present day, birth control and family planning are of major concern. However, the contraceptive options available to men are limited to vasectomy, condoms, and early withdrawal, all of which present certain problems. The former is considered to be a permanent method of birth control, considering that the surgery to reverse infertility has only a limited success rate. The latter two methods have failure rates even under perfect use. They are between 80 and 90% successful under actual use. Therefore, it is necessary to develop new male contraceptives that are safe, reversible, and more effective than current offerings. Contraceptive vaccines may be an attractive addition to the currently available range of family planning methods, offering several potential advantages [9]. Several antigens of gametogenic origin have already been identified and successfully applied to induce infertility in experimental animals.

Contraceptive Vaccines

An examination of the literature covering, the last decade has shown that there are a diverse number of immuno- contraceptive vaccines (CV) that are still under research and development. Current Contraceptive vaccines target g*amete production* [luteinizing hormone-releasing hormone (LHRH /GnRH), follicle stimulating hormone (FSH)], *gamete function* [sperm antigens and oocyte zona pellucida (ZP)] and *gamete outcome* [human chorionic gonadotropin (HCG)]. Vaccines targeting gamete production affect hormone production. Vaccines inhibiting gamete function are the preferred target. Although CV targeting ZP has a high contraceptive efficacy, they cause oophoritis, affecting sex hormones. For human applicability, the current research is focused on isolating infertility-related epitopes (B-cell epitopes) and modulation of immunogenicity by various carriers and adjuvants. The HCG vaccine, which targets gamete outcome is the first CV that has undergone Phase I and Phase II clinical trials in humans [8].

Spermatozoa have drawn much attention for CV development. During the last two decades, significant progress has been made in the field of anti-sperm immune-contraception. Several sperm antigens have been delineated, cloned, and sequenced that have function in sperm physiology and fertilization. A series of monoclonal antibodies (MCAs) have been generated that inhibit fertility in various species of animals. A few of the sperm antigens recognized by these MCAs are sperm-specific and have been isolated and biochemically and immunologically characterized. Notable among these are lactate dehydrogenase (LDH)-C4, rabbit sperm auto antigens (RSAs), PH-20, SP-10, HSA-63, fertilization antigen-1(FA-1), FA-2 and cleavage signal-1 (CS-1) protein [10]. These are antigens present on the sperm head, and this approach is limited by the fact that the acrosomal membrane of the sperm head undergoes changes during maturation, or after ejaculation and just before fertilization.

Method to develop a contraceptive vaccine- A hypothetical approach

Sperms are motile structures that contain an outer membrane. The whole sperm cannot be used for the CV development as it has

several antigens that are likely to be shared with various somatic cells. Thus, only sperm-specific antigens must be used in the development of a successful CV [8]. Interaction between antibodies and some of the sperm membrane antigenic moieties is the main reason of immune infertility, because in live sperm cells ASA are not able to penetrate through the plasma lemma. Thus, we will mainly concentrate on the antigens present on the sperm surface, and not inside it. Since the sperm tail does not undergo any changes after ejaculation, unlike the acrosomal head, we will concentrate on the sperm tail antigen encoded by the *SPAG6* gene.

1. Isolation of SPAG6 protein from the sperm tail membrane

2. Production of antibodies against the SPAG6 antigen

A female mouse is injected with the SPAG6 protein. After a few weeks, the spleen is removed and spleen cells are fused to the mouse myeloma cell. The resulting hybridomas are grown under selective culture conditions. Secreted antibody class is determined using Ouchterlony double diffusion using class-specific anti-immunoglobulins. Culture supernatants are monitored for antibody activity, and characterization of antibody binding is carried out in a solid-phase radioimmunoassay (RIA) using washed human ejaculates as antigen. An enhanced chemiluminescence immunoblotting technique is used for analysis of sperm antigens recognized by the hybridoma antibodies [11].

The identification of human sperm antigens identified by antibodies of an animal model can often prove to be difficult. Thus, a combination of MoAb and testis c-DNA libraries can be used for direct identification of sperm-specific antigens [5].

3. Study of sperm-immune interactions

Human sperm proteins are separated by 2D gel electrophoresis, using IEF in the first dimension and SDS-PAGE in the second dimension. Interactions between these proteins and produced MoAbs can be studied by exposing the electropherogram to the antibodies, followed by western blotting [12].

4. Formulation of an immune-contraceptive vaccine

There are two methods:

a. Recombinant vaccine: There are several steps which includes primer design, sperm collection, sperm RNA isolation and C-DNA *SPAG6* production, construction of a SPAG6 gene recombinant vector. The construction of human sperm specific VDAC3 gene recombinant vector was established by Asmarinah et al [2]. In the future, this recombinant vaccine will be used to produce VDAC3 antibody for the development of contraceptive vaccines [2]. On the basis of his work, we have proposed the methodology for the design of new innovative recombinant vaccine using SPAG6 gene.

b. The immunogenic domain of the SPAG6 protein itself is isolated and used as a vaccine.

It is known that sperm antigens are poorly immunogenic. Adjuvants, as well as protein carriers often are important components of a vaccine formulation because they can enhance the immunogenicity of an antigen [13]. Thus, this r-DNA vaccine may be administered along with an appropriate adjuvant and protein carrier.

5. Testing the function of the vaccine

CONCLUSION

Our hypothesis has been supported by data and literature from already conducted research on human sperms and monoclonal antibodies. In the present paper, the production of MoAbs against a specific epitope (SPAG6 protein) associated with the human sperm tail has been described. The present study also suggests the feasibility of using these produced MoAbs to characterize sperm-surface antigens, which can then be used to formulate either traditional protein vaccines, or r-DNA vaccines. The identification of SPAG6 and other sperm antigens relevant to fertilization opens up opportunities for diagnosis, as well as treatment of immune infertility, other than providing a safe contraceptive method. Novel strategies such as using epitope-based vaccines can offer the advantage of directional immunity, leading to safer and more effective antigen-specific immune responses. Also, there may be a variability of immune response among individuals after this vaccination, as it is the case with any immunization procedure. This problem can be overcome by using passive immunization, employing preformed antibodies, as and when required.

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