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Editorial

New approaches to male infertility: Forum introduction

Maciej K Kurpisz*

Address: Forum coordinator, Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland

Email: Maciej K Kurpisz* - kurpimac@man.poznan.pl

* Corresponding author

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It has been shown that reproductive potential of human population has a tendency to diminish. Approximately, 20% couples can be threatened by infertility out of those, male partners can be suspected for a leading reason of this disorder accounting for 40–60% cases. At the same time, modern techniques of assisted reproduction (ART) although quite aggressive, cannot exceed 1/3 part of couples who wish to be succesful in procedures of *in vitro* fertilization. An increased sensitivity of males to spermatogenetic disorders became one of the hot issues, intensively studied throughout the world. Therefore, it has been of great interest to look at intragonadal germ cells differentiation, looking at the network of molecular signaling in order to better understand spermatogenic disturbances that may even arise in pre-puberty [1]. It has been shown that several factors may put into question the fertilization potential of prepubertal boys. There can be procedures due to malignant diseases provoking chemo- and radiotherapy with severe consequences for the future fertility status. On the other hand, abnormalities in the male reproductive tract (uni- or bilateral cryptorchidism, testicular torsion, inguinal hernia, physical injuries of testis) may induce anti-sperm antibodies with severe consequences that can be visible only at reproductive age. Once developed antisperm antibodies may be sustained and enhanced through bacterial or viral infections and subsequently may stop or severely alter spermatogenesis [2]. On the other hand, inflammatory process in the testis may be perpetuated to that level (by pro-inflammatory cytokines) that may completely inhibit spermatogenesis in sexually mature individuals through enhanced oxygen metabolism (ROS – reactive oxygen species) which in turn may mediate germ cells apoptosis. The first paper of our Forum (by J. Lysiak) is addressing this problem describing different pathways of apoptotic mediation through IL-1, TNF-alpha and IL-18. In our recent studies, we have detected in the male gonad (on mRNA level) possibility-for IL-18 auto-regulation through IL-18 accessory protein in heterodimeric receptor for IL-18. It is question of intensity (or type) of inflammatory factor that may drive to one of the three-mediated apoptotic pathways directed through the mentioned cytokines.

Next two papers (by A. Suri; A. Domagała and M. Kurpisz) are dedicated to the problem of sperm surface antigens as well as to the naturally developed anti-sperm antibodies in humans. It has been almost thirty years when the first delineated sperm antigens inducing antisperm antibodies were reported. Since then, sophisticated methodology has been applied in order to indicate the most immunogenic sperm antigens which are mainly responsible for antisperm antibody triggering. Antisperm antibodies may either block sperm transport (or even to disturb spermatogenesis in vigorous inflammatory reaction) and agglutinate the cells within ejaculated sample as well as to inhibit their traversing through cervical mucus, uterus and Fallopian tubes, and finally to block sperm-oocyte interaction. They can be sometimes detrimental even for an early embryo development despite of the IVF application [3]. Sperm antigens have been dissected according to their topographical distribution and can be divided into a) plasma membrane antigens, b) outer acrosomal membrane, c) acrosomal matrix, d) inner acrosomal membrane, e) equatorial segment, f) nucleus, g) neck and h) tail. They have been identified by numerous techniques as: natural antibodies induced in infertile individuals (sera samples), polyclonal antibodies induced in experimental animals, monoclonal antibody technology, cDNA testicular library screening, and perhaps the most sophisticated, recently explored technology, of so called 'pro-

teomics' including application of two-dimensional electrophoresis and computerized protein identification [4]. Still, identified sperm antigens can be prospectively used in two directions: to create a contraceptive cocktail with aim to be specifically applied in females (with highly private specificities therefore without immunological side-effects). On the other hand, there can be also dissected according to their immunogenic (immunodominant) potential and synthesized peptides of the known antigenic determinants can be inserted to immunologically infertile individual successfully competing for antisperm antibody binding to sperm (novel way of treatment). Sperm proteomics and sperm antigen dissection, described in both enclosed in forum articles are excellent catalogues for such potential candidates.

The last article of the Forum (by D. Sanocka and M. Kurpisz) is dedicated to the ROS release and its effect on male infertility. It has been known for a long time that oxygen metabolism can be detrimental to the cells and tissues, adjacent to the inflammatory site. Unpaired electrons make the external orbit vulnerable and imitate the effect of ionizing radiation within the tissue affecting the lipids, proteins and DNA. DNA integrity as well as surface structures of sperm may be particularly threatened due to the necessity of their subtle interaction with an oocyte (receptor-ligand interaction) as well as for the quality of genetic material. It seems trivial but the infection agent is easily penetrating non-specific innate defense either in male reproductive tract as well as the cervical environment of female. In fact, both these compartments interact permanently with the outside world keeping inside natural bacterial flora. However, this delicate balance can be easily affected when virulent infecting agent penetrate the epithelium. Together with unprotected intercourse, bacteria mixed with spermatozoa provoke an immune response and infertility. But even without triggering the immune response bacteria induce so called oxidative stress that can be detrimental to sperm quality [5]. Bacteria attract leukocytes to the site of inflammation, those in turn produce cytokines that augment NADP(H) pump on the cell membrane for secretion of ROS. In this case a 'vicious circle' may be easily created since ROS themselves may influence transcription factors that in turn may produce even more cytokines (in consequence, more ROS). Thus, in the male reproductive tract, bacterial infection and oxidative stress may create a ground for sperm deterioration and transitory or persistent infertility. The latter phenomenon is strictly dependent upon the cell membrane damage and oocyte fertilization is negatively linked to peroxidation product on the cell (unpublished data) even when applying IVF intervention. Thus, oxidative stress has grown up to the point of molecular phenomenon responsible for 'male factor'. Interestingly, antioxidants seem to offer new ways of conservative therapy that is currently used in variety of diseases, including autoimmunity, cancer as well as infertility. The article inserted to our Forum is therefore important contribution to new approaches counteracting the male infertility.

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