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RESEARCH HIGHLIGHT

Infertility treatment, a matter of a lovely sperm?

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Nowadays, the efficiency of the infertility treatment is relatively low. One of the cues to counteract this problem relies on the optimum selection of spermatozoa. We developed a new method (sperm selection assay (SSA)) based on the chemical attraction of spermatozoa that are at the best functional state. Additionally, the SSA leads spermatozoa to complete and/or acquire the competence to fertilize the egg. These effects are equally observed either in normal or subfertile semen samples. Those capabilities of SSA may improve the success of current infertility treatment.

INFERTILITY, A SOCIALLY SENSITIVE DISEASE

Infertility is increasing and affects more than 70 million couples worldwide. Assisted reproduction technologies (ARTs) have facilitated the birth of babies that would be impossible under natural circumstances. However, the current efficiency of infertility treatment is around 30%, while the unsuccessful couples undergo the expensive and emotionally disturbing treatment even more than once.[1] What are the reasons for this low performance? One explanation may rely on sperm attributes since the commitment of the spermatozoon is not only to fertilize the egg but also to directly affect early embryo development and implantation.[2] Therefore, the selection of a 'good' spermatozoon becomes essential, especially for intracytoplasmic sperm injection (ICSI) into the egg. This medical procedure, called ICSI, is the most popular ART nowadays.[1] In the majority of *in vitro* fertilization laboratories, the sperm selection for ICSI is based on sperm morphology and motility. However, these features do not predict how healthy a sperm is.[3] Ideally, a method for sperm selection must be as natural as possible, and should stand on the sperm competence even beyond fertilizing the egg.

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CAN A SPERMATOZOON AT OPTIMUM FUNCTIONAL STATE BE SELECTED?

Capacitation is a functional process that enables the spermatozoon to fertilize the oocyte. Interestingly, capacitated spermatozoa can be recruited by the chemical guidance of a gradually distributed attractant molecule. This phenomenon is called sperm chemotaxis, which may transport spermatozoa to the egg's vicinity.[4,5] Very low doses of progesterone (a steroid secreted by the cells surrounding the oocyte) attract capacitated human spermatozoa.[6,7] By combining the ability of chemotaxis to select good spermatozoa with the use of progesterone as an attractant molecule, a new sperm selection assay (SSA) was recently developed.[8]

CAPACITATED SPERM AND MORE

The SSA is efficient in recruiting capacitated sperm, which is potentiated after successive SSA. Oxidative stress is a well-known stimulus for DNA fragmentation, which is one of the causes of failure of fertilization, embryo development and implantation.[2] After SSA, the level of oxidative stress and DNA fragmentation is significantly reduced, while sperm motility and viability are kept constant and high. Thus, the SSA supplies an elite subpopulation composed of spermatozoa that are capacitated, with intact DNA, low oxidative stress and high levels of motility and viability.

GRADUAL SUPPLY OF PROGESTERONE ENHANCES SPERM FITNESS

For running the SSA, sperm are previously incubated under capacitating conditions, thus promoting the acquisition of a subpopulation of capacitated sperm, which is the one that follows the chemical attraction of progesterone. Surprisingly, exposure to progesterone gradients stimulates the preparation of spermatozoa for fertilization. This is particularly notable in samples that are unsuccessful in getting the expected level of capacitated spermatozoa on their own. How can a gradient of such tiny amounts of progesterone (picomolar!) stimulate sperm capacitation? The molecular bases of this intriguing fact need to be further investigated.

UNDER THE SSA UMBRELLA EVERYTHING IS OF THE SAME COLOR

In subfertile semen samples, the efficiency of SSA to select a subpopulation enriched with spermatozoa at the best functional state is essentially the same as that observed in normal ones. Even normal semen (and those with a history of unexplained sterility) is also benefited by SSA. In this context, the initial level of capacitated sperm seems to better mark the differences between semen samples, instead of the classical sperm parameters such as sperm concentration, motility and morphology. In other words, when semen is evaluated from a physiological point of view (like selection of capacitated sperm by chemotaxis), the traditional classification of semen is not longer supported.

IS TRANSLATIONAL MEDICINE ALSO POSSIBLE FOR SSA?

As mentioned above, SSA provides a subpopulation enriched in spermatozoa at the best functional state, and this may have several medical applications. The use of a subpopulation containing the best spermatozoa selected by a natural procedure would increase the chance to pick out the optimum spermatozoon for ICSI, or to fertilize the oocyte during co-incubation under *in vitro* conditions. Thus, the application of SSA in the treatment of infertility may enhance the probability of proceeding with a normal embryo development and child delivery. Additionally, SSA may be used to easily

diagnose the physiological state of a semen sample and to predict its performance under ART treatments. The main novelty of SSA is to help poor semen samples to naturally prepare spermatozoa for fertilization, which in times of transgenesis and sophisticated biotechnologies, makes SSA a simple, non-invasive cellular therapy for the infertile couple. As a whole, these capabilities of SSA may improve the low efficiency of current ART procedures.

NOT EVERYTHING THAT SHINES IS GOLD

Sperm samples are heterogeneous. At any given time, even a good sample has a small subpopulation of spermatozoa at an optimum functional state.[4] Depending on the initial level of capacitated sperm, SSA increases two to four times the amount of the best spermatozoa the sample has (in some extreme cases, it is raised up to 11 times). Despite this notable efficiency, SSA cannot provide a pure population of good spermatozoa. Further studies are needed to verify whether the enriched sperm subpopulation selected by SSA is sufficient to enhance infertility treatment, and if so, to what extent.

1 Nygren KG, Sullivan E, Zegers-Hochschild F, Mansour R, Ishihara O *et al*. International Committee for Monitoring Assisted Reproductive Technology (ICMART) world report: assisted reproductive technology 2003. *Fertil Steril* 2011; **95**: 72209–22.
2 Barroso G, Valdespin C, Vega E, Kershenovich R, Avila R *et al*. Developmental sperm contributions: fertilization and beyond. *Fertil Steril* 2009; **92**: 835–48.
3 Barratt CL, Mansell S, Beaton C, Tardif S, Oxenham SK. Diagnostic tools inmale infertility—the question of sperm dysfunction. *Asian J Androl* 2011; **13**: 53–8.
4 Eisenbach M, Giojalas LC. Sperm guidance in mammals—an unpaved road to the egg. *Nat Rev Mol Cell Biol* 2006; **7**: 276–85.
5 Guidobaldi HA, Teves ME, Uñates DR, Giojalas LC. Sperm transport and retention at the fertilization site is orchestrated by chemotaxis and oviduct movement. *Reproduction* 2012; **143**: 587–96.
6 Teves ME, Barbano F, Guidobaldi HA, Sanchez R, Miska W *et al*. Progesterone at the picomolar range is a chemoattractant for mammalian spermatozoa. *Fertil Steril* 2006; **86**: 745–9.
7 Teves ME, Guidobaldi HA, Uñates DR, Sanchez R, Miska W *et al*. Molecular mechanism for human sperm chemotaxis mediated by progesterone. *PLoS ONE* 2009; **4**: e8211.
8 Gatica LV, Guidobaldi HA, Montesinos MM, Teves ME, Moreno AI *et al*. Picomolar gradients of progesterone select functional human sperm even in subfertile samples. *Mol Hum Reprod*; e-pub ahead of print 10 June 2013; doi:10.1093/molehr/gat037.