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Commentary

In vitro Spermatogenesis Coupled with Intra-Cytoplasmic Sperm Injection

Azizbek Ashurmetov*

Central Clinical Hospital, Main Medical Department, Administration of the Republic of Uzbekistan, Tashkent, Uzbekistan

INTRODUCTION

This year marks the twentieth anniversary since Palermo et al. published their landmark paper on the use of intracytoplasmic sperm injection (ICSI) to achieve healthy human births for couples that could not otherwise conceive a child [1]. Now, two decades and over 10,000 births since that initial publication, ICSI is commonly used in fertility clinics in cases when the quantity or quality of spermatozoa are too low to generate embryos through traditional in vitro fertilization (IVF). While many questions linger as to the long-term outcome of ICSI from a genetic and epigenetic perspective, thus far no measurable abnormalities in offspring conceived by this technique have been observed [2]. Now just one spermatozoon is required for reproductive success. In cases where spermatozoa are not present in the ejaculate, testicular sperm extraction (TESE) is routinely performed to identify and recover elongated spermatids for injection into recipient oocytes. TESE complements ICSI, but is effective only when sperm are obtained. ICSI, therefore, is not a viable approach when only immature germ cells are present within seminiferous tubules. In these cases, the current options for parenthood are either to use donor sperm coupled with IVF or to adopt [3]. While both strategies make childrearing possible to otherwise infertile couples, for some the desire to biologically reproduce is sufficiently strong that these options are unsatisfactory. This scenario directly impacts three categories of males: adult men with non-obstructive azoospermia with only immature germ cells; adult men with cancer who did not cryopreserve their sperm prior to chemotherapeutic/radiation treatments and who subsequently have only immature germ cells, and prepubescent boys with cancer who do not yet make sperm and are receiving chemotherapeutic/radiation treatments. Implementing new reproductive strategies for these affected males through the translation of research findings from the laboratory to the clinic is a key challenge for this current decade [4].

A recent study of adult male infertility patients exhibiting spermatocyte maturation arrest, however, revealed that many of these patients also had fewer SSCs and differentiating spermatogonia, suggesting the possibility of a 'faulty niche' in these individuals [5]. Autologous SSC transplantation as a strategy for male fertility restoration, therefore, may not be a successful endeavor if the patients' testicular microenvironment is incapable of supporting sperm production.

For prepubescent boys diagnosed with certain types of cancer, cryopreserving their SSCs also raises the potential risk of collecting malignant cells interspersed within the sample, which could be reintroduced into the testis along with the SSCs during subsequent transplantation. This scenario warrants a stringent cell sorting protocol, one that filters out cancerous cells from the SSC population. They have described an innovative dual positive (CD90+) and negative (CD45-) selection strategy that uses fluorescence-activated cell sorting (FACS) to purify SSCs from a contaminated sample of non- human primate testis cells prior to transplantation. Their findings are promising, especially when compared to previous studies that report less successful results in filtering out malignant cells prior to cell transplantation into recipient mouse testes. In preparing a suitable filtering protocol for clinical applications, however, absolute certainty of removing all potential malignant cells prior to transplantation is unattainable, and the inherent risk such a procedure carries should be carefully considered. Additionally, a FACS-based selection of SSCs for transplantation would still not address the potential issue of a 'faulty niche' in the testes of some men that desire to reproduce. In vitro spermatogenesis is a potential solution, alleviating concerns of the quality of the recipient testis microenvironment as well as the possible contamination of SSC samples collected from cancer patients prior to transplantation. Following numerous reports over the past decade claiming to generate sperm in a dish, Sato in 2011 at last provided convincing evidence demonstrating the feasibility of this technique in mice. Utilizing a culture method that maintains cells at the liquid-gas interface, the authors cultured testicular tissue from neonatal mice for six weeks and produced sperm that successfully fertilized mouse oocytes by ICSI.

Correspondence to: Azizbek Ashurmetov, Central Clinical Hospital, Main Medical Department, Administration of the Republic of Uzbekistan, Tashkent, Uzbekistan, E-mail: ashuraz@mail.ru

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The resounding success of ICSI over the past twenty years has been truly remarkable. Many of the men whose sperm are not able to fertilize through conventional IVF may now have their reproductive objectives realized through this approach. For those remaining men and prepubescent boys for whom ICSI is currently not an option, the promise of in vitro spermatogenesis coupled with ICSI may soon close this 'fertility' gap in the not-too-distant future, providing an additional strategy to overcome male infertility. Further research combined with a receptive clinical community should promote the translation of this strategy from the bench to the bedside. With appropriate scrutiny and careful evaluation, in vitro spermatogenesis coupled with ICSI may bring us to the next frontier in assisted human reproduction.

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