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Short Communication

Evidence on the Contribution of the Male Genome to Embryo Ploidy

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DESCRIPTION

It has been recognized for some time that the spermatozoon is more than simply responsible for delivering the male counterpart of the parental genomes. Indeed, the male gamete also triggers the pre-fertilization steps by activating the maternal genome, provides a scaffold for sperm aster development, and subsequently organizes the first mitotic spindle, responsible for triggering the first cleavage division of the zygote into two daughter cells. While these roles are far more modest than what was envisioned in the 18th century, these sperm functions are remarkable and instrumental for the evolution of a living conceptus [1].

It is difficult to pinpoint a pioneering study that established the relevance of the integrity of DNA carried by each spermatozoon. J. Michael Bedford comes to mind as being the first to recognize this in his comparative and evolutionary work on mammalian reproduction, describing the peculiar heterogeneity of human sperm cells [2]. This observation has led to the well-known work on Sperm Chromatin Structural Assay (SCSA) by Don Evenson, now acknowledged as a routine ancillary test to screen for male factor infertility [3]. Although several tests are available to measure sperm DNA integrity that vary in technique, reproducibility, cost, and objectivity, SCSA is now considered a gold standard [4-6]. The Comet assay is considered to be the most sensitive test, with its two variants, alkaline or neutral, the latter capable of detecting exclusively double-stranded DNA breaks. The most commonly used assays, however, are Terminal Deoxynucleotidyl Transferase dUTP Nick End Labeling (TUNEL) and Sperm Chromatin Dispersion (SCD) assays, which provide information on the Sperm Chromatin Fragmentation (SCF) by assessing the overall presence of nicks and breaks within the DNA in addition, they can screen an extremely low number of spermatozoa, such as in cases of severe oligozoospermia or surgically retrieved from the epididymis or testis.

Mechanism

Assessment of SCF has prompted several studies that have delineated the stealth male factor dysfunction to be responsible for a reduced ability to procreate despite normal semen parameters and a reproductively healthy female partner of an appropriate age. Elevated SCF has been linked to a suboptimal reproductive potential in natural conception, Programmed Intercourse (PI), and Intra-Uterine Insemination (IUI) [7-9]. This observation has been less straightforward pertaining to Assisted Reproductive Technology (ART), where the effect of compromised chromatin integrity of the male gamete inconsistently affects clinical outcome with standard *in vitro* insemination and rarely with Intra-Cytoplasmic Sperm Injection (ICSI) [10,11]. Elevated SCF minimally impairs the ability of a spermatozoon to fertilize, inconsistently reduces the ability to achieve and sustain a clinical pregnancy; however, most importantly, it induces a higher pregnancy loss. The reasons for this occurrence have been attributed to the limited ability of an oocyte to process and repair the male genome [12].

The sperm genome, described by Douglas Carrell, depicts characteristic supercoiling of DNA around the protamine core aimed at protecting the sperm genome from aggressors during the journeys, initially in the male genital tract and later in that of the female. At the same time, limited access to the sperm genome restricts assessment of its integrity to histone-bound DNA linker regions, the only sites reachable by the SCF assays [13].

With the exception of some scientists, who believe that SCF occurs at the site of the seminiferous tubules as a consequence of genetic or environmental factors that disrupt meiosis and proper spermatogenesis, most investigators seem to believe DNA disruption occurs post-spermatogenesis [14]. Indeed, DNA damage may occur within the seminal tract, particularly at the site of a dysfunctional epididymis, which may allow suboptimal sperm cells to leak into the ejaculate. This is corroborated by the identification of spermatozoa with higher chromatin integrity during testicular and epididymis biopsies [15].

Treatment

It is with this understanding that clinicians have proposed to utilize spermatozoa that are directly retrieved from the seminiferous tubules to treat subtle forms of male subfertility [16]. In a recent study, the proportion of spermatozoa retrieved from different sites of the male genital tract evidenced a lower SCF

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in the testis that progressively deteriorated distally, reaching the highest DNA fragmentation rate in the ejaculate [17].

Surgically retrieved spermatozoa are currently an accepted treatment strategy for couples with the male partner with high sperm DNA fragmentation. Obviously, this approach exposes affected individuals to surgical and anesthetic risks, not to mention the emotional and economic distress involved. Furthermore, it is important to consider the consequent scarring effect of an open testicular biopsy on functional and healthy testicles [18].

Investigation of the correlation between SCF and semen characteristics does not offer an obvious link to sperm parameters, which is why SCF assays have served the common purpose to be used as adjuvant tests to shed light on the hidden male factor, which is not immediately manifested by an assessment employing the World Health Organization (WHO) semen parameters [19].

In a relatively recent study by Palermo and later supported by other investigators, a clear inverse correlation was found between SCF and progressive motility, as measured by several assays. This intriguing finding explains the correlation between elevated SCF and reproductive outcome vis-à-vis natural conception, programmed intercourse, and intrauterine insemination, where the semen specimen is unprocessed or spermatozoa are minimally selected. Conversely, in ART, such as *in vitro* insemination and ICSI, sperm selection focuses on providing a cleaner sample with a higher proportion of motile spermatozoa to be presented to the oocyte.

The availability of microfluidic chips has allowed the isolation of spermatozoa with motility that can be as high as 100%. Utilization of the microfluidic-based technology has been proven to enhance clinical outcome in couples where the male partner presents with high SCF [20-21].

Impact on conceptus ploidy

These early results have been received with skepticism because the mechanism that links high SCF to poor clinical outcome remains unclear. It seems intuitive that a fragmented male genome may appear to be unhealthy for the conceptus, and some studies have investigated repair mechanisms exerted by oocytes, specifically those from young and healthy donors, to correct the damaged DNA contributed by the male gamete.

However, it remains difficult to explain the mechanistic principle linking sperm DNA fragmentation with inability to procreate. In the most severe cases of elevated SCF, even with a young female partner and the utilization of ICSI, pregnancy may still not reach term. The higher pregnancy loss observed in these cases may explain the metabolic dysfunction generated by the fragmented DNA, which may lead to gene mutations or transcriptomic defects. An intriguing observation has been made by some investigators who claim that not just SCF, but more specifically the double-stranded SCF is responsible for the poor clinical outcome by contributing to structural chromosomal abnormalities in the conceptus.

CONCLUSION

To address these questions, we identified couples in which the male partner presented with high SCF, undergoing ICSI with Preimplantation Genetic Testing for Aneuploidy (PGT-A). To ameliorate SCF, we used spermatozoa retrieved directly from the testicle or ejaculate processed by Micro-Fluidic Sperm Selection (MFSS). Compared to cycles in which spermatozoa were processed by standard density gradient, the utilization of surgically retrieved spermatozoa or ejaculate post-MFSS in a subsequent cycle led to an enhanced proportion of euploid embryos, achieving a robust pregnancy outcome by diminishing pregnancy loss.

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