ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 13, Issue, 07, pp. 63225-63227, July, 2023
https://doi.org/10.37118/ijdr.26931.07.2023

RESEARCH ARTICLE **OPEN ACCESS**

SPERM DNA BRIDGES VERSUS GENETIC VARIABILITY: AN EDITORIAL

Sanjay Mishra* and Pankaj Gupta

Department of Biotechnology, SR Institute of Management & Technology, Bakshi ka Talab, Sitapur Road, NH-24, Lucknow 226 201, U.P., India

ARTICLE INFO

Article History:
Received 27th April, 2023
Received in revised form
03rd May, 2023
Accepted 20th June, 2023
Published online 28th July, 2023

KeyWords:

Apoptosis, ICSI, Male infertility, Sperm DNA.

****Corresponding author: Sanjay Mishra,***

ABSTRACT

Sperm DNA fragmentation is recognized to compromise male fertility. The data entail that sperm DNA damage can be competently treated with oral antioxidant administration during a comparatively short time period. It is an understanding that the 2 types of DNA appear to be different and autonomously packaged molecules; though, research has demonstrated the interdependent nature of these conformations in contributing to male infertility. Data must endure to be congregated to establish strong associations between traditional semen analysis parameters and sperm DNA integrity; this information remnants controversial and useless in clinical practice until novel techniques for the diagnosis and treatment of sperm DNA can be established. More modern technology must be employed to correlate such information into valuable clinical awareness. This editorial is the collation of reports relating to research on sperm DNA biochemistry and molecular biology to establish an opinion revealing sperm DNA integrity likely to be both tremendously fragile and remarkably significant for male fertility.

Citation: ***Sanjay Mishra and Pankaj Gupta. 2023.*** "Sperm dna bridges versus genetic variability: an editorial". *International Journal of Development Research*, 13, (07), 63225-63227.

INTRODUCTION

Sperm DNA fragmentation is recognized to compromise male fertility. Sperm DNA damage can be capably treated with oral antioxidant administration throughout a comparatively short time period [1]. Infertility is a rising problem among couples trying to conceive; in the past the female partner was singled out as the key reason for being incompetent to bear a child. Current research now exposes that male infertility may contribute limiting to two thirds of all couples looking for infertility treatment. For several years a conventional semen analysis (concentration, motility, and morphology) has perceived as adequate to diagnose male infertility; though, scientific investigation must now take into account 2 different kinds of DNA, which have been confirmed to support this diagnosis. Nuclear DNA (nDNA), confined in the head of the sperm, is accountable for packaging entirely the paternal genetic material likely to be required for the fertilized egg. nDNA can be impaired or conceded through 4 interconnected courses, namely, defective chromatin packaging, apoptosis, oxidative stress, and genetic lesions. Mitochondrial DNA (mtDNA) is sited in the midpiece of the sperm; when coupled with the tail, it is liable to mobilize the sperm towards egg fertilization. Infertility is classically defined as a state in which a couple desiring a child is unable to conceive following 12 months of unprotected intercourse [1]. In infertile couples, accountability for the lack of conception is usually divided into thirds, with one third because of male factors, one third due to female factors, and the final third due to overlapping factors from both partners. The functioning and major outcomes of sperm and DNA bridges in context to genetic variability can be explained as follows:

Nutraceuticals have been encouraged as a mode of potentiating sperm production and quality in the subfertile male. In a recent study, the administration of folic acid and zinc sulfate to subfertile males was shown to result in a significant improvement in sperm concentration compared to placebo. Treatment lasted 25 weeks and the daily dose of folic acid and zinc were 5 mg and 66 mg, respectively [2]. Although the beneficial effect on fertility remains to be established, this finding opens new avenues of future fertility research and treatment through administration of arginine, vitamin B12, methylcobalamin and ginseng [3] One of the main reasons studies looking at the efficacy of antioxidant therapy in the treatment of male infertility have not yet been conclusive may be due to inadequate patient selection. Not all infertile males have an increase in oxidative stress in their testis and semen. Consequently, in principle, only those men who have a measureable proliferation in oxidative stress should benefit from antioxidant therapy. Probably the best marker to recognize these males would be reactive oxygen species (ROS) levels in semen [3]. The foundation of the evaluation of the man remains semen analysis. Though it gives some quantitative and qualitative information about the sperm sample, current insight into the molecular biology and genetics of the sperm cell have validated that morphology and

motility alone are not the only grounds upon which sperm should be assessed. Generally overlooked is the fact that sperm carry 2 different categories of DNA. The nDNA, commonly called the genome, is located in the head of the sperm. The second DNA type is called the mtDNA and is accountable for delivering the sperm to the egg by providing ATP for cellular acceleration. Both types of DNA work toward the common goal of fertilization, but each is susceptible to a myriad of factors that could derail the fertilization process. Flawlessness in both types of DNA contributes equally to the problem at hand. This article hopes to elucidate male factor infertility as contributed by both kinds of DNA. Origins of nDNA Damage nDNA in somatic cell nuclei is packaged into structures called nucleosomes. These structures consist of a protein core formed by an octamer of histones with 2 loops of wrapped DNA. The nucleosomes are then further coiled into regular helixes called solenoids, which increase the volume of the chromatin [4]. Sperm nuclei, however, need to be packaged much differently and more compactly to assure proper delivery of the nDNA. There are believed to be 4 levels of organization for packaging spermatozoon nDNA [4]. One level consists of anchoring the chromosomes to the nuclear annulus. In another, DNA loop domains are created as the DNA attaches itself to the newly added nuclear matrix. The arrangement of these loop domains ensures that the DNA can be delivered to the egg in a form that is both physically and chemically accessible to the growing embryo. Chromosome repositioning and organization within the matrix of the sperm head is another level. Condensation of nDNA into tiny, supercoiled dough- nuts called toroids by replacing the nuclear histones with structures called protamines completes the levels of chromosomal organization. Human sperm contain 2 types of protamines that are about half the size of typical histones; throughout evolution, they have increased the number of positively charged residues, allowing formation of a highly condensed complex with the negatively charged paternal genomic DNA. Besides, the addition of cysteine residues allows the creation of disulfide bonds between adjacent protamine molecules, thus strongly stabilizing the nucleo-protamine complex [5].

Many factors (both endogenous and exogenous) can influence this, contributing to male infertility [6,7]. Scientists agree on 4 distinct methods, although there may be others, by which nDNA can be compromised or damaged: defective sperm chromatin packaging, apoptosis, oxidative stress, and genetic lesions [8]. The effects of these damaging methods are often found to be interrelated. It is thought that these nicks exist naturally and serve to relieve torsional stress. The presence of these nicks is greatest during transition from round to elongated spermatids in the testis and occurs before complete protamination within the sperm. Topoisomerase II is the enzyme that creates an ligates the nicks within nDNA during this process. Also involved in sperm chromatin packaging is the replacement of histones with protamines. Protamines are major DNA-binding proteins essential for chromatin condensation [9]. During epididymal transport, histones are replaced by transition proteins, only to be replaced by protamines [6]; both intermolecular and intramolecular disulfide cross-linking among the cysteine-rich protamines compresses the DNA into one sixth the volume occupied by somatic cell nDNA. Human sperm contain 2 different types of protamines, which are believed to be present in equal amounts in fertile men: P1 and P2 [10]. Experiments have shown that the ratio of P1 to P2 is critical to male fertility, more specifically to the sperm's fertilization ability [11]. Besides, recent testing has demonstrated that P2 precursors (pre-P2) are vital in maintaining the delicate P1:P2 ratio. Translation of pre-P2 mRNA appears to cause abnormal head morphogenesis, reduced sperm motility, and male infertility. Also, a low pre- P2: P2 ratio suggests a link between deficient protamine processing and decreased nDNA integrity [12]. In infertile men, ejaculated spermatozoa often possess partially degraded nDNA, usually considered to be indicative of the apoptosis pathway; this ''escaping'' of the apoptosis signal is referred to as ''abortive apoptosis'' [13]. Another well-known inducer of the apoptotic pathway is telomere shortening. Telomeres are capping structures at chromosome ends that protect against rearrangements, preventing ends from being recognized as nDNA breaks [8]. They are usually composed of tandem TTAGGG sequence repeats that are bound to a complex array of proteins. In the absence of telomerase, telomeric sequences are lost after each round of replication, eventually creating a shifted sequence that could be recognized as an nDNA double-stranded break; this would then be recognized by a genomic surveillance mechanism that appears in the elongating spermatid [8]. This recognition is another way to induce an apoptotic response, possibly contributing to the ''abortive apoptosis'' theory. Abortive apoptosis is a theory that still requires much scientific evidence to be considered valid. Because of naturally occurring processes within the spermatozoa that mimic somatic cell apoptosis, many believe that this theory requires additional evidence.

Oxidative stress upon spermatozoa is induced by an increase in the amount of reactive oxygen species (ROS) that are present in the fluids filling the male genital tract [13]. Sperm are particularly susceptible to oxidative stress due to the high content of unsaturated fatty acids in their membranes, as well as their limited stores of antioxidant enzymes [15]. Their increased susceptibility is enhanced by defective chromatin packaging, causing further damage to the genome; individuals with varicoceles are predominantly susceptible to this type of damage [16]. ROS are created by metabolizing ground-state oxygen into the superoxide anion and H_2O_2 [17]. They play a pivotal physiologic role, controlling gene and protein activities vital to sperm proliferation, differentiation, and function [13]. ROS also promote tyrosine phosphorylation to support sperm capacitation. It is known that the main source of excess ROS generation in semen is leukocytes; genital tract infections are considered to be the most common cause. Three possible sources of excess ROS generation are from within the human sperm itself. The first is through leakage of electrons from the mitochondrial transport chain [17-19]. This was proposed because of tests performed on rat spermatozoa indicating increased translocation of mitochondrial free radicals into the sperm genome. However, further investigation has demonstrated that mitochondrial blockers do not have the same effects on human spermatozoa [13]. The second proposed source is through NADPH oxidase in sperm. This theoretic oxidase would serve to transfer electrons from NAD (P) Hto ground-state oxygen to create the superoxide anion. It is known that NAD (P) H in leukocytes helps to contribute to ROS production in rat spermatozoa, but it has yet to be demonstrated in humans [14-16,19]. The third proposed intracellular source of ROS production is through the generation of nitric oxide (NO) [18]. NO is a free radical created from the oxidation of L-arginine by 3 isoforms of nitric oxide synthase (NOS). NOS activity has been shown to be associated with the acrosome reaction and capacitation of mouse sperm, thus influencing their fertilizing potential.

Very recently, a novel sperm selection assay has been proposed to select viable sperm free of chromosomal anomalies for use with ICSI. Sperm hyaluronic acid (HA) binding has demonstrated the ability to isolate mature, viable sperm with unreacted acrosomal status, without damaging the specimen [7,14,20]. One principle of this assay lies in the expression of the chaperone protein HspA2; in spite of its key role in meiosis, HspA2 levels have become indicative of sperm maturation [21]. Low levels of HspA2 expression are associated with diminished sperm maturity, increased frequency of chromosomal aneuploidies, presence of apoptotic processes, and fragmented nDNA. The second principle involved takes into account remodeling of the cytoplasmic and membrane-specific biochemical markers, facilitating the formation of sperm binding sites for the zona pellucida of oocytes and for the binding sites of HA. Immature sperm that fail to undergo membrane remodeling are unable to bind to immobilized HA and will not be selected in this assay [21]. Because of such promising results, a kit for this assay has become commercially available. The sperm-hyaluronan binding assay (HBA) has been marketed for routine testing of sperm motility and fertility [22] . Unfortunately, HBA results have fallen well short of expectations in predicting successful fertilization rates in IVF, demonstrating less significance than sperm morphology and limiting its clinical predictive value. Further research is needed to perfect techniques that will be employed to improve the

quality of spermatozoa that are selected for use in all ART techniques to improve outcomes.

Conclusion and Future Perspectives: Conclusively this editorial is a briefing of studies on sperm DNA biochemistry and molecular biology, providing new insights to explore a strong platform to establishing a hypothesis that sperm DNA integrity is both extremely fragile and exceedingly important for male fertility concomitant with nutritional/nutraceutical measures to achieve this genetic pattern.

Acknowledgements: Authors are grateful to Mr. Pawan Singh Chauhan, Chairman, SR Institute of Management & Technology, Bakshi Ka Talab, Lucknow- 226201, U.P., India for his generous support and throughout inspiration for accomplishment of this study. Besides, authors are thankful to members of Board of Directors, SR Institute of Management & Technology, Bakshi Ka Talab, Lucknow-226201, U.P., India for providing necessary facilities and time-to-time encouragement for exploring the R&D in the area of Biotechnology.

Conflict of interest: Authors declare no conflict of interest.

REFERENCES

Agarwal, A. and R.A. Saleh, 2002. Role of oxidants in male infertility: Rationale, significance, and treatment. *Urol. Clin. North Am.,* 29: 817–827.

Agarwal, A. and T.M. Said, 2003. Role of sperm chromatin abnormalities and DNA damage in male infertility. *Hum. Reprod. Update,* 9: 331–345. PMID: 12926527

Aoki, V.W., L. Liu, K.P. Jones, H.H. Hatasaka, M. Gibson, C.M. Peterson and D.T. Carrell, 2006. Sperm protamine1/protamine 2 ratios are related to *in vitro* fertilization pregnancy rates and predictive of fertilization ability. *Fertility Sterility*, 86: 1408–1415. PMID: 17011555

Baker, M.A. and R.J. Aitken, 2005. Reactive oxygen species in spermatozoa: Methods for monitoring and significance for the origins of genetic disease and infertility. *Reprod. Biol. Endocrinol.,* 3: 67–75.

Balercia, G., S. Moretti, A. Vignini, M. Magagnini and F. Mantero *et al*., 2004. Role of nitric oxide concentrations on human sperm motility. *J. Androl.,* 25: 245–249.

Carrell, D.T., B.R. Emery and S. Hammoud, 2007. Altered protamine expression and diminished spermatogenesis: what is the link? *Hum Reprod Update,* 13: 313-327.

Erenpreiss, J., M. Spano, J. Erenpreisa, M. Bungum and A. Giwercman, 2006. Sperm chromatin structure and male fertility: Biological and clinical aspects. *Asian J. Androl.,* 8: 11–29. PMID: 16372115

Huszar, G., S. Ozkavukcu, A. Jakab, C. Celik-Ozenci, G.L. Sati and S. Cayli, 2006. Hyaluronic acid binding ability of human sperm reflects cellular maturity and fertilizing potential: Selection of sperm for intracytoplasmic sperm injection. *Curr. Opin. Obstetrics Gynecol.,* 18: 260–267. PMID: 16735824

Jakab, A., D. Sakkas, E. Delpiano, S. Cayli and E. Kovanci *et al*., 2005. Intracytoplasmic sperm injection: A novel selection method for sperm with normal frequency of chromosomal aneuploidies. *Fertility Sterility*, 84: 1665–1673. PMID: 16359962

Mishra, S., P.R. Somanath, Z. Huang and S. Vijayraghavan, 2003. Binding and inactivation of the germ cell-specific protein phosphatase PP1γ2 by sds22 during epididymal sperm maturation. *Biol. Reprod.,* 69: 1572-1579.

Nanda, S., S. Mishra, V.P. Varshney and R.B. Singh, 2010 b. A biotechnological approach to apoptosis of somatic and germ cells in living organisms. *The Open Nutraceuticals J.,* 3: 81-93.

Nanda, S., V.P. Varshney and S. Mishra, 2010 a. Biochemical characterization of the mechanism of binding of a regulatory protein to the spermatozoa- specific protein phosphatase in Swiss albino rat. *J. Appl. Biosci.,* 27: 1715-1726.

Nasr-Esfahani, M.H., S. Razavi, A.A. Vahdati, F. Fathi and M. Tavalaee, 2008. Evaluation of sperm selection procedure based on hyaluronic acid binding ability on ICSI outcome. *J. Assist. Reprod. Genet.,* 25: 197-203. PMID: 18483762

Noegroho BS, Siregar S, Tampubolon KAG. (2022). Antioxidant Supplementation on Sperm DNA Fragmentation and Sperm Parameters: A Systematic Review and Meta-Analysis. *Turk J Urol.* 48 (5): 375-384.

Oliva, R., 2006. Protamines and male infertility. *Hum. Reprod. Update.,* 12:417–435.

Saleh, R.A., A. Agarwal, R.K. Sharma, T.M. Said, S.C. Sikka and A.J. Thomas, 2003. Evaluation of nuclear DNA damage in spermatozoa from infertile men with varicocele. *Fertil. Steril.,* 80: 1431–1436.

Shafik, A., A.A. Shafik, I. Shafik and O. El-Sibai, 2006. Sperm DNA fragmentation. *Syst. Biol. Reprod. Med.,* 52: 197–208.

Sharma, S., S. Kalim, M.K. Srivastava, S. Nanda and S. Mishra, 2009. Oxidative stress and coxsackievirus infections act as mediators of beta cell damage: a review. *Sci. Res. Essay*, 4(2): 42-58.

Tiwari, A,K,M , Abbas Ali Mahdi, A.A. , Mishra, S. , Parveen, H. and Fatima, G. (2020). Effect of iron and folate supplementation on Pb levels in pregnant anemic women: a prospective study, *Free Radical Research* 54(8-9): 662-669.

Torregrosa, N., D. Dominguez-Fandos, M.I. Camejo, C.R. Shirley and M.L. Meistrich *et al.*, 2006. Protamine 2 precursors, protamine 1/protamine 2 ratio, DNA integrity and other sperm parameters in infertile patients. *Hum. Reprod.,* 21: 2084–2089. PMID: 16632464

Vernet, P., N. Fulton, C. Wallace and R.J. Aitken, 2001. Analysis of reactive oxygen species generating systems in rat epididymal spermatozoa. *Biol. Reprod.,* 65: 1102–1113. PMID: 11566731

Vogt, P.H., 2004. Molecular genetics of human male infertility: From genes to new therapeutic perspectives. *Curr. Pharm. Design*, 10: 471–500. PMID: 14965334

****