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Human Reproductive Cell DNA Damage and Repair

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Abstract

The primary underlying paradigm of sexual reproduction is the development of sufficiently genetically distinct and high-quality male and female gametes that, after syngamy, result in embryos with genomic potential for future adaptive change and the ability to respond to selective pressure. Isogamy is defined as the fusion of distinct gametes that results in the production of a normal and viable embryo, and it occurs in tandem with precise structural, physiological, and molecular control of gamete function for species survival. The goal of this review is to highlight gamete genome organization, differences in gamete production chronology between males and females, inherent DNA protective mechanisms in these reproductive cells, the etiology of DNA damage in germ cells, and the remarkable DNA repair mechanisms that function to maintain genome integrity, both pre and post-syngamy.

***Keywords:** Isogamy; Gametes; Embryo; Genome; Germ cells; DNA repair*

Introduction

The occurrence of isogamy, or the fusing of different gametes, plays a function in sexual reproduction imparting the potential for adaptive changes in a population. Isogamy, which produces a normal zygote, offers the phenotypic variance on which natural selection can act, and hence is the foundation of evolutionary potential. Between eight and fourteen cell divisions after conception, Primordial Germ Cells (PGCs) emerge from the epiblast in humans. PGCs begin to proliferate after differentiation, but the timing and conclusion of this process differ depending on gender.

PGCs expand to produce a pool of spermatogonial stem cells in the male embryo, which remain in mitotic and meiotic arrest until adolescence. Some of these spermatogonial stem cells enter the spermatogenic cycle when they reach puberty, eventually maturing into adult spermatozoa, while others remain stem cells throughout the male's life. Mitotic proliferation (spermatocytogenesis) results in the production of large numbers of spermatocytes [1], meiotic recombination, and chromosome segregation produces genetically diverse haploid spermatids, and spermatid cytodifferentiation (spermatogenesis) involves complex morphological and genome remodeling that radically transforms the round spermatid into highly specialized and species-specific spermatids. Although the quality and amount of sperm produced by a healthy male may vary after puberty, most males can generate spermatozoa far into their senior years. The average male is predicted to create about 525 billion sperm in his lifetime.

Female gamete production differs significantly; PGCs move into the embryonic gonad and proliferate to create a resident population of primary oocytes that stay in prophase 1 meiotic arrest until adolescence. Oocytes are periodically released from the follicular pool after the start of her first menstrual cycle, and under the appropriate endocrine control, a proportion of them are recruited, and then selected, until one becomes dominant and meiosis 1 resumes. Following that, ovulation and fertilization with the male gamete occur, and meiosis 2 is completed. Although the human ovary produces

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roughly 1-2 million oocytes at birth, this number drops to 300,000 by adolescence, 25,000 by the age of 37, and 0 by menopause by the time a woman reaches menopause. Thus, during a female's reproductive lifetime, roughly 500 mature oocytes are ovulated, with the vast majority of gametes suffering from atresia.

Awareness of the sensitivity of male and female gametes to DNA damage, as well as the DNA repair mechanisms inherent in the spermatozoon and oocyte, requires an understanding of this fundamental variation in gamete formation. The focus of this review will be on irreversible and repairable DNA damage in human reproductive cells, as well as the implications for infertility. Additionally, DNA damage response mechanisms in the spermatozoon, oocyte, and zygote to preserve genome integrity will be examined. The male gamete is the only cell in mammals that are biologically equipped for autonomous subsistence before conception, whereas the female gamete is a "quasi-sedentary" gamete. The female soma, which consists of the cumulus oophorous, granulosa cells, and the ovarian environment, protects the oocyte and helps to manage and regulate the maturation process. Nonetheless, there is a significant variation in chromatin arrangement between the spermatozoon and the oocyte. While the oocyte's DNA is packaged into histone-like somatic cell proteins, the spermatozoon's nucleus undergoes a dramatic reorganization in the last stages of spermatogenesis, with Transition Nuclear Proteins (TNP) and protamine’s replacing about 80% of the original histones [2-4]. The oocyte's susceptibility to DNA damage is less well documented than that of the spermatozoon, possibly due to the difficulties of acquiring oocytes for research. However, it is well acknowledged that the oocyte is more sensitive to external stimuli at certain times and that there is a larger chance of DNA damage as a result. When oocytes are dividing, they are more vulnerable to DNA damage. As a result, this happens during the fetal stage before they have been arrested in prophase I, and later in adulthood when they resume meiosis during the pre-ovulatory stage of the menstrual cycle [5-7].

Conclusion

In the zygote stage, the oocyte's ability to repair sperm DNA damage is also determined by the type of sperm DNA damage. Because the oocyte has the BER pathway, SSBs and a basic site leftover from partial SSB repair in mature spermatozoa can be easily fixed. However, it's worth noting that the oocyte's expression of the OGG1 enzyme is likewise relatively low at this time. Some researchers believe that the coincidental complementarity of the sperm and oocyte is a sophisticated system that checks the compatibility of the oocyte and fertilizing spermatozoa since both must participate in the repair of oxidative DNA damage. Unlike SSB repair, DSB repair in the zygote is accomplished through the use of NHEJ and HR. During the cell cycle, these routes are not equally significant. The balance of DSB repair pathways varies by cell type and developmental stage, with HR being more critical in the early phases of development. This is because HR prefers to repair DSBs caused by replication stalling. The NHEJ pathway, on the other hand, plays a crucial role in sperm DSB repair during the zygotic stage.

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