HUMAN SPERMATOZOA: FRUITS OF CREATION, SEEDS OF DOUBT

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Defective sperm function is the largest defined cause of human infertility, affecting one in twenty Australian males. Despite its prevalence, we are only just beginning to understand the underlying mechanisms. The past decade has seen two major advances in this field: *(1)* the discovery that Y chromosome deletions play a key role in the aetiology of non-obstructive azoospermia/oligozoospermia; and *(2)* recognition that oxidative stress can impact upon the functional competence of human spermatozoa through peroxidative damage to the sperm plasma membrane. Oxidative stress has also been found to disrupt the integrity of DNA in the male germ line and may represent an important mechanism by which environmental impacts on human health are mediated. Thus, paternal exposure to various toxicants (cigarette smoke, organic solvents, heavy metals) has been linked with oxidative DNA damage in spermatozoa and developmental defects, including cancer, in the F1 generation. The male germ line becomes particularly vulnerable to such factors during the post meiotic stages of differentiation. Pre-meiotic germ cells always have the option of undergoing apoptosis if DNA damage is severe. However, post meiotic germ cells have lost both the ability to mount an apoptotic response and the capacity for DNA repair. As a result, germ cells are particularly vulnerable to genotoxic agents during spermiogenesis and epididymal maturation. If the fertilizing capacity of the spermatozoa is retained following toxicant exposure, then DNA damage will be transferred to the zygote and must be repaired subsequently by the oocyte and/or early embryo. Aberrant DNA repair at this stage has the potential to create mutations that will compromise embryonic development and, ultimately, the normality of the offspring. Elucidating the causes of oxidative damage in spermatozoa should help resolve the aetiology of conditions such as male infertility, early pregnancy loss and childhood disease, including cancer.

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