The future of sex

Human spermatozoa

The vulnerability of the Y chromosome will be a key factor in shaping the evolutionary future of our species.

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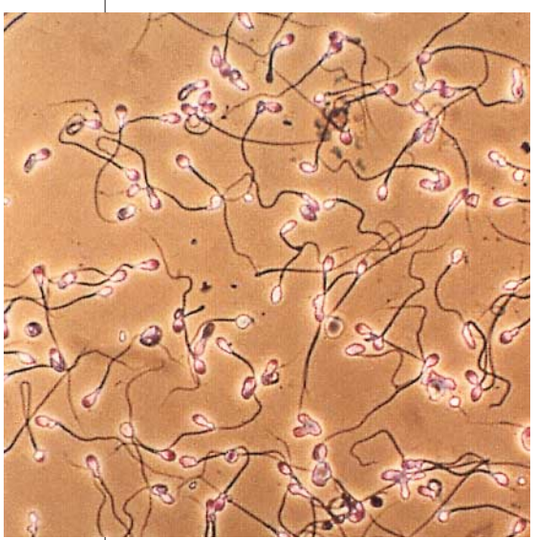
The desperate plight of the human spermatozoon is clearly reflected by the poor fecundity of our species. Human spermatozoa stand apart from the gametes of virtually all other mammals in the paucity of their phenotype, the inadequacy of their function, and the sensitivity to fragmentation of their mitochondrial and nuclear genomes. Roughly one in seven Western couples seek treatment for infertility, mostly because of problems with semen quality.

Even when a human spermatozoon achieves the fertilization of an oocyte, damage can crop up in the next generation. All dominant mutations in our species (such as those that cause achondroplasia, multiple endocrine neoplasia and Apert's syndrome) seem to arise in the male germ line. Spermatozoa are also important mediators of the environmental contribution to cancer in young adults and children; for example, heavy smoking in fathers is reported to confer a fourfold increase in cancer risk to their children.

The impact of environmental toxicants and the innate inadequacy of human spermatozoa are compounded by the advent of effective contraception and the introduction of assisted-conception technologies. This lifting of the selection pressure on fertility means that those endowed with genes for high fecundity have lost their advantage over those without. As a result, future generations are bound to experience a further decline in semen quality and, ultimately, human fertility.

What mechanisms are responsible for the poor fertilizing potential and genetic damage shown by human spermatozoa? Two main causes of germ-cell dysfunction have recently been discovered: gene deletions on the long arm of the male sex-determining Y chromosome, and oxidative stress. We believe that these aetiologies may be associated.



Swimming against the tide: sperm quality seems set to decline still further in future generations.

The Y chromosome is particularly vulnerable to gene deletions because it is not a matching partner for the X chromosome, so it cannot retrieve lost genetic information by homologous recombination. Over the past 300 million years, the mammalian Y chromosome has been reduced from a pairing partner to the X chromosome to a shadow of its former self, rescued only by a large addition from a non-sex-determining chromosome in 'placental' mammals. Many of the remaining genes have acquired functions essential for sex determination and spermatogenesis.

The original Y chromosome contained around 1,500 genes, but during the ensuing 300 million years all but about 50 were inactivated or lost. Overall, this gives an inactivation rate of five genes per million years. The presence of many genes that have lost their function (pseudogenes) on the Y chromosome indicates that this process of attrition is continuing, so that even these key genes will be lost. At the present rate of decay, the Y chromosome will self-destruct in around 10 million years. This has already occurred in the mole vole, in which the Y chromosome (together with all of its genes) has been completely lost from the genome.

Accelerated degeneration of the Y chromosome is found in the 5–15% of severely infertile men whose infertility is caused by wholesale deletions of parts of this chromosome. Because mutations that cause infertility cannot be inherited, the relative abundance of Y-chromosome deletions in male patients suggests an extremely high rate of spontaneous DNA damage. Even microdeletions on the Y chromosome destabilize its transmission, frequently causing it to be lost during gamete production.

One important mechanism by which DNA damage is induced in the male germ line is oxidative stress. Spermatozoa are particularly vulnerable to this because they generate reactive oxygen species and are rich in targets for oxidative attack. Moreover, because they are transcriptionally inactive and have little cytoplasm, spermatozoa are deficient in both antioxidants and DNA-repair systems. Oxidative stress is thus a major cause of male infertility, and contributes to the high rate of DNA fragmentation in spermatozoa.

Such DNA fragmentation probably predisposes the cell to mutagenic change, which would become fixed as a deletion in the embryo by aberrant recombination. The Y chromosome is susceptible to such recombination because of its high frequency of repetitive elements. Fragmentation induced by free radicals in the Y chromosome's DNA might also cause other post-fertilization genetic changes, such as insertions and amplifications. Because mutations that originate in this way precede the embryo's first cleavage division, they will enter the germ line and contribute to infertility and morbidity, including cancer, in the offspring.

At present, we have no idea what causes oxidative stress, DNA fragmentation and functional incompetence in human spermatozoa. But we do know for certain that such events put pressure on the vulnerable Y chromosome. In the long term, absolute selection against males with deletions that confer sex reversal or sterility will create strong pressure either to retain (and amplify) fertility genes, or for any fertile variant that replaces it. Could the present race of humans eventually be replaced by a new variant (or several independent variants that cannot cross-hybridize) with an alternative sex-determining/differentiation system? Such a new hominid race could differ from present humans in many other characteristics, depending on the gene pool of the new variant's handful of founders.

There is evidence of rapid 'selective sweeps' in the Y chromosome's evolution. These take place when a Y chromosome with an allele that confers a big selective advantage rapidly replaces other Y chromosomes in the population. As the Y chromosome is never broken up by recombination, whatever alleles lie at other genetic loci — even if they are deleterious — will 'hitch-hike' to fixation along with the advantageous variant. ■

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FURTHER READING

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