Male infertility joins the translational medicine revolution. Sperm DNA: from basic science to clinical reality

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This issue of MHR contains six papers outlining and discussing the current state of our knowledge about male germ-cell DNA including the packaging of DNA during spermatogenesis and its unpacking in the oocyte, assessment of DNA damage in the male germ line and the consequences of this damage upon early embryo development and the subsequent generations. As is the nature of New Research Horizons review papers, the authors have been encouraged to be speculative, thought provoking, challenging whereas at the same time outlining future directions of travel. These reviews were invited as a result of an ESHRE Workshop (the meeting took place in the Karolinska Institute, Stockholm, Sweden, 21–22 May 2009) on ‘Sperm DNA: organisation, protection and vulnerability—from basic science to clinical application’. They represent an important benchmark for male reproductive health and will provide a platform for a clear and rapid improvement in our understanding of DNA in the male germ line and the effective translation of this knowledge into clinical practice.

The assessment, origin, dynamics and consequences of damage to the paternal genome are receiving ever increasing attention. The importance of assessing DNA damage was highlighted following the demonstration of higher levels of chromatin damage in men with severe semen defects (Sun et al., 1997) and the potential negative impact of high levels of sperm DNA damage on both natural (Spanò et al., 2000) and ART conception (Larson et al., 2000). Subsequently, the field has seen a rapid expansion. In animals, where experiments can be performed to induce DNA damage to the paternal germ line, there have been clear and very strong associations between damage to the paternal genome, adverse affected embryo development and importantly subsequent negative effect on the newborn and subsequent generation (Fernandez-Gonzalez et al., 2008). It is not the purpose of this editorial to reiterate what the individual authors discuss but three key themes are outlined below.

Male infertility requires more robust diagnostic tools: DNA damage assays are likely to be the answer

Clinical andrology, more specifically the assessment of semen, has a chequered history with a number of false dawns. For example, the assessment of sperm function has failed to make a significant impact on the clinical management of couples. The reasons for this (e.g. lack of standardised protocols) have been rehearsed elsewhere (Lefèvre et al., 2007) but in reality the considerable progress that has been made in understanding of the basic science around how a cell prepares for fertilization has not (yet) been translated into routine clinical practice.

The diagnostic and predictive value of traditional semen parameters has been debated for over 80 years yet the debate rumbles on. There is no doubt that, at least at the lower ends of the spectrum, e.g. low concentrations of spermatozoa, there are significantly higher chances of subfertility but, except in rare cases, e.g. globozoospermia (Kilani et al., 2004), basic semen assessment using the three main parameters of sperm concentration, motility and morphology has limited clinical value. This of course has been known for many years. In a series of outstanding papers on very large groups of men (~1000 in each group) published almost 60 years ago, MacLeod and Gold (1951) concluded that ‘The greatest difference between the two groups [infertile an fertile] is seen at the count levels under 20 million/cc. Only 5 per cent of fertile men compared with 16 per cent of the “infertile” group fall into this category’. The greater difference between the two groups [infertile an fertile] is seen at the count levels under 20 million/cc. Only 5 per cent of fertile men compared with 16 per cent of the ‘infertile’ group fall into this category. A plethora of subsequent studies has repeated these experiments in various guises and, not surprisingly, come to the similar conclusions. Therefore, there is an urgent need to develop new assessments of male reproductive potential and testing of DNA and its packaging in the human spermatozoon is
likely to be a very important tool in the armamentarium. Importantly, there are already considerable data to support the clinical use of DNA damage assays. However, if these assays are to be routinely used in clinical practice, there must be (i) robust methods for the detection of DNA damage and (ii) a rigorous examination of their application using standardized procedures as is necessary for tests in other disciplines (Glud and Glud, 2005). Additionally, there needs to be a critical determination of where these assays fit within the patient pathway. For example, diagnostic tests can be used as replacement, triage or add-on with their usefulness being dependent on a large number of factors (Bossuyt et al., 2006). To date, DNA damage assays have not yet been evaluated in this critical manner and, quite simply, they need to be.

**The basic science research continues to expand rapidly**

Although fundamental questions remain, our understanding and basic science knowledgebase of DNA in the male germ line are dramatically increasing. One rapidly expanding area is the packaging of the DNA during spermiogenesis and it is unraveling during the early events of fertilization. The recent discovery of a potential epigenetic imprint arising from histone modifications in the human spermatozoon (Hammoud et al., 2009) has exciting research and potential clinical applications. We do not yet know if key genes responsible for early development carry a specific epigenetic mark in the male but preliminary data are suggestive. Additionally, it is clear that in cases of ICSI, although the ‘best’ spermatozoon is selected, cells with damage DNA and/or poor packaging are routinely injected into the oocyte. How the oocyte recognizes these defects and the degree to which it can repair damage to the spermatozoon are fundamental yet unresolved questions, although we do know that defects in the embryo repair pathway can have negative consequences for embryo development. One particular area of focus is that of environmental, occupational and lifestyle influences that contribute to the integrity of the paternal genome. We are becoming increasingly aware of the negative impact of these factors, and although more detailed studies are required, we are now obtaining answers to commonly asked clinical questions such as what is the effect of chemotherapy/radiotherapy of the paternal genome and the subsequent progeny? Without question the quality of our basic science base is growing and we are now in a position logically to examine new versions of old treatment regimens, e.g. use of antioxidant therapy for men with high levels of oxidative stress in their spermatozoa (Kessopoulou et al., 1995). Basic research is yielding new areas for translation into clinical practice.

**Animal experiments have a fundamental role to play**

Although there is considerable data on human ART, a number of experiments to address fundamental mechanisms are not feasible in humans but some data provide clear warnings of the potential impact of our clinical work for the next and subsequent generations.

With the long-term follow-up data on children born as a result of ART still in its infancy, it is essential that we translate findings from animals to the human field to understand the implications of the clinical work of injecting and using spermatozoon with highly damaged DNA. ART is not always known for its careful, thoughtful and progressive assessments of new developments. In this area, clear warnings are presented and judicious use of genetically compromised gametes is warranted.

Overall, these six reviews provide the reader with a comprehensive state of the art analysis of the field. Encouragingly, it is an optimistic picture. Male infertility has traditionally suffered from a lack of basic science research to support the development of new diagnostic tests and a non-ART-based treatment. Our increasing understanding of the make up of paternal DNA is likely to provide answers to both these previously intractable questions along with a number of others. Now is the time for male infertility to join the translational medicine revolution with justified confidence of success.

**References**


