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Biomarkers of Testicular Injury and Dysfunction

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Commentary

The assessment of human testicular function and male gamete quality currently relies on hormone measurements and semen parameters (sperm counts, motility and morphology). Semen analyses are highly variable both within and between individuals, which demonstrates their lack of sensitivity. Meanwhile, hormone measurements are generally unreliable at detecting mild testicular injury, in order that only severe, potentially irreversible, injuries are often detected. A more sensitive approach is required that permits for translation of findings in preclinical species to humans and for monitoring of occupationally and environmentally induced testicular dysfunction at an early, reversible stage of injury.

Previous history

The human testis is extremely sensitive to toxicant-induced injury, yet the available tools for detecting the consequences of exposures are quite limited. The necessity for monitoring is illustrated by the 1977 exposure of workers to the nematocide 1,2-dibromo-3-chloropropane (DBCP) during a pesticide factory . An investigation revealed that a high proportion of workers exposed to DBCP were either azoospermic (13%) or oligospermic (33%); duration of exposure was associated with the severity of the testicular injury. A followup study of those workers 7 years later showed that permanent destruction of the germinal epithelium had occurred in most of the highly exposed men.

About 40% of testicular mRNAs are detected in sperm, indicating that the sperm transcriptome are often wont to monitor organic phenomenon during spermatogenesis. Various studies have investigated the association between altered testicular function and sperm mRNA transcript content, finding: i) significantly different motility-related sperm mRNA transcript abundance between normal and motility-impaired men, ii) altered sperm protamine mRNA levels in men with infertility and iii) higher sperm Bcl2 mRNA in infertile men. Sperm RNAs could also be passively retained or play a lively role in chromatin structure, imprinting, gene silencing and embryogenesis. These results have led to the proposal that 'As an entirely non-invasive proxy for the testis, this (sperm) RNA offers considerable potential as a marker for fertility status and therefore the genetic and environmental influences that would make all the difference between a fertile and infertile phenotype. 'Sperm DNA methylation marks offer an identical potential for insight into disrupted spermatogenesis. The germline DNA is demethylated early during embryonic development then remethylated during a sex-specific manner later in development and through spermatogenesis. Since DNA methylation remodeling is happening during spermatogenesis, various studies have investigated the association between altered testicular function and sperm DNA methylation marks, finding aberrant DNA methylation of both imprinted and nonimprinted genes. A recent study compared genome-wide DNA methylation profiles for men with poor in vitro fertilization-related embryogenesis and abnormal sperm chromatin compaction, finding a subset of men with genome-wide DNA methylation defects with imprinted genes more susceptible to being abnormal than the whole genome. Studies of altered sperm DNA methylation following toxicant exposure during adult animals have included extensive studies of the consequences of a chemotherapeutic regimen in a rat model, and therefore the effects of tamoxifen exposure of rats on sperm imprinted gene DNA methylation. In summary, sperm mRNA transcripts and DNA methylation marks are acquired during spermatogenesis and reflect the integrity of that process. Measuring these sperm molecular biomarkers can provide insight into the testicular response to environmental and occupational chemical exposures.

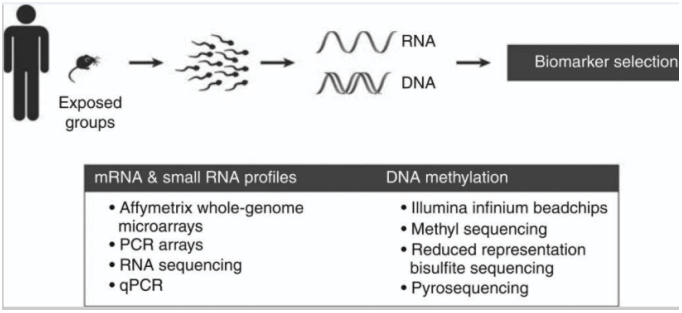

Figure 1. Technical approaches used in identifying sperm molecular biomarker from rodent toxicity studies and chemically exposed populations in humans.

Current research and new findings

Our animal-related work has made several unique contributions to the present field, including i) developing a sperm mRNA transcript panel to detect responses over a time course of testicular toxicant exposure during a rat model and can be extended to look at dose-dependent responses, ii) using the rat model to point out that a sperm mRNA transcript panel is more sensitive than standard histopathology in detecting toxicant-induced perturbations and iii) determining that sperm mRNA transcript patterns are toxicant specific. we've also published a study of human sperm CpG methylation profiles and mRNA alterations related to low sperm motility. during this publication, we showed that i) low motility sperm have genomewide DNA hypomethylation which will flow from to a failure of the sperm to finish chromatin compaction properly due to increased histone deacetylase 1 (HDAC1) presence; ii) low motility sperm have reduced mitochondrial NAD-dependent deacetylase sirtuin-3 (SIRT3) mRNA content which could be associated with increased subcellular reactive oxygen species during spermatogenesis resulting in the abnormal motility phenotype; and iii) this oxidative stress could also be impeding the power of DNA methyltransferase-3a (DNMT3A) to line the right methylation marks which might also contribute to the hypomethylated phenotype.

We have very strong evidence that a panel of sperm mRNA transcripts can detect and predict low level exposures to Sertoli cell toxicants in the rat. To develop our current 12-transcript PCR array panel, we exposed rats to the Sertoli cell toxicant 2,5-hexanedione (2,5-HD) and selected one time point (3 months) and one dose (0.33% within the drinking water) to study. Repeatedly testing this exposure condition, we performed whole-genome Affymetrix GeneChip arrays (128 significantly altered transcripts out of ~ 27,000) followed by a 29-transcript PCR array and a 12-transcript PCR array. Transcripts chosen for the PCR arrays were driven by exposure related fold-change, and known expression and function within the testis. With each refinement of the PCR array panel, we improved the yield of significantly altered transcripts among those measured (Figure 1).

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We then applied the 12-transcript PCR array panel to all 17 exposure groups tested to date, and found that each of the 12 transcripts is significantly altered in at least one exposure setting. This includes validation with a second Sertoli cell toxicant that yielded overlapping results, as well as exposure to a germ cell toxicant (DBCP) and multiple time points of both exposure and recovery from exposure. With a set of only 4 transcripts (Abi2, Clu, Ptgds and Sod3), we can detect at least one significantly altered sperm mRNA transcript in each of the 17 exposure models tested. We have begun to apply this same assay refinement strategy to DBCP, our model germ cell toxicant, to expand the PCR array panel to better include responses to germ cell injury.

In addition to mRNA transcript characterization, we are also interested in how these transcripts may correlate with decreased sperm performance. We are using in utero insemination with sperm from exposed rats (2,5-HD for 3 months) to determine i) if the sperm from exposed rats features a decreased ability to fertilize oocytes and ii) if this decreased function correlates with abundance of our candidate mRNA transcripts. This may compile much of the work we've accomplished in our animal models by integrating molecular indicators of testicular injury with functional relevance.

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