Invited Commentary

Prospects for clinically relevant epigenetic tests in the andrology laboratory

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The review published by Kläver and Gromoll is a timely reminder of the ever-changing landscape of the clinical andrology laboratory as well as the limitations of current approaches to properly diagnose and treat male infertility.¹ In a variety of disciplines, the clinical relevance of epigenetic status is becoming increasingly apparent. In this paper, the authors review the various studies that have evaluated the epigenetics (primarily DNA methylation) of sperm in the context of infertility, and they discuss the potential value of sperm epigenetic analysis in the workup of idiopathic male infertility.

Epigenetics refers to heritable modifications to the genome that do not alter the nucleotide sequence. Epigenetic modifications include DNA methylation or hydroxymethylation, histone modifications, microRNAs and sRNAs. These epigenetic modifications modulate gene expression, and are largely responsible for phenotypic and functional differences between cell types and tissues in an organism. Our understanding of the role of aberrant epigenetic status in the development of various disease states has incrementally increased over the past decade, but is still generally in its infancy.

Sperm epigenetics represents a particularly interesting, and potentially clinically important field of study. As the authors highlight, there are strong data to support the involvement of aberrant sperm DNA methylation associated with oligozoospermia, and some evidence that abnormal methylation is related to motility and morphology defects. Additionally, aberrant methylation has been found to be more common in patients with abnormal chromatin packaging. The implication is that aberrant epigenetic status may explain some proportion of idiopathic male infertility cases and if so, sperm epigenetic analysis might be a valuable addition to the limited repertoire of clinically relevant tests available in the andrology lab. Additionally, the unique epigenetic marks found in sperm for genes associated with embryonic development, bivalent histone marks and DNA demethylation (trivalency)², and the demonstration of defects in this pattern in some patients with abnormal embryogenesis, is suggestive that sperm epigenetic marks may be involved in regulation of embryogenesis.
In addition to its potential relevance in reproductive medicine, the methylation status of the male gametes might have clinically relevant implications in offspring health. Increasing evidence suggests that epigenetic alterations to the paternal germline may confer risk to offspring. For example, children of men who smoked prior to conception had increased incidence of leukemia\textsuperscript{3}, and offspring of older fathers are more likely to develop autism, schizophrenia, and other neuropsychiatric disorders.\textsuperscript{4} While an epigenetic link for these phenomena has not been established, it seems plausible that altered epigenetic status of sperm might play a role.

The implementation of sperm epigenetic testing in the andrology laboratory holds great promise, however the field is in its infancy. Two recent studies have attempted to characterize normal sperm methylation patterns using gene-specific \textsuperscript{5} and genome-wide approaches.\textsuperscript{6} Additional systematic studies will be critical in defining the normal sperm epigenome. In addition, studies to assess the degree of epigenetic heterogeneity in sperm from a single collection are critical, as essentially all studies to date report average methylation for the entire sperm population. Lastly, characterization of the persistence of altered sperm epigenetic marks following fertilization is critical in order to predict the potential impact of altered sperm DNA methylation on offspring health.

Analysis of the epigenetic status of sperm may well prove to be a valuable diagnostic tool for male infertility, and it will certainly lend new insights into the mechanisms for transgenerational epigenetic inheritance, but in order for the field to reach its full potential careful and thoughtful studies are needed to fully characterize the normal sperm epigenome, then assays to predict epigenetic abnormalities in sperm must be preceded by large-scale, repeatable validation studies. Until such studies are completed, the clinical utility of sperm epigenetic assays remains a hypothesis.

**Competing interests**  
The authors declare no competing interests associated with the content of this manuscript.

**References**