Epigenetics, infertility, and cancer: future directions

Emma James, B.S. and Timothy G. Jenkins, Ph.D.

Andrology and IVF Laboratories, Department of Surgery, University of Utah School of Medicine, Salt Lake City, Utah

Although direct correlates between cancer and infertile epigenetic profiles are rare, the general similarities between the two disease processes offer insights into the study of both abnormalities. Foremost among them is the nature of these pathologies, where one disease (cancer) is categorized by an inability to control or inhibit cellular proliferation, and the other (male infertility) is caused by an inability to maintain the normally efficient extreme proliferation of the male germ cell. Based on this similarity alone, the study of epigenetics in both male fertility and cancer has the potential to offer intriguing insights in both fields. The creative application of harmonious studies of both infertility and cancer is likely to yield useful and informative data that may aid in both the understanding and treatment of both pathologies. (Fertil Steril® 2018;109:27–32. ©2017 by American Society for Reproductive Medicine.)

Key Words: Cancer, epigenetics, DNA methylation, infertility

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/22368-25019

Large-scale epidemiologic work has revealed an interesting link between fertility and cancer. A recent study showed that infertile men have an increased risk of developing any form of cancer (1). Other, more targeted studies have shown correlations between infertile men and the risk of developing high-grade prostate cancers and, perhaps more intuitively, developing germ cell tumors (2–4). However, to date we have yet to elucidate these interesting links. It is important to consider all of the potential mechanisms that may describe this etiology. In cases where genetics have been ruled out, a very important potential candidate to explain the links between fertility and cancer are epigenetic alterations.

Epigenetic marks are known to be important and heritable regulators of gene expression in virtually every tissue in the body, in the developing embryo, and in various disease states including cancer. The basic mechanisms of epigenetic regulation include DNA methylation, histone modifications, and RNA transcripts.

DNA methylation occurs on cytosine residues at cytosine-phosphate-guanine (CpG) dinucleotides and is a powerful regulator of gene transcription. Cytosine methylation is mediated by the DNA methyltransferase (DNMT) family of proteins which both establishes and maintains methylation patterns in cells (5). The most fundamental regulatory function of DNA methylation occurs at CpG-rich promoter regions where the presence of methylation at cytosine residues effectively inhibits gene transcription by limiting access of transcriptional machinery.

In addition, various histone proteins, including H2A, H2B, H3, and H4, as well as associated tail modifications, such as methylation, acetylation, or ubiquitination to lysine (K) and serine (S) residues, also play important roles in transcriptional regulation. This is mediated largely through the facilitation of a more open or condensed chromatin structure at particular genomic regions as well as through modifying and maintaining chromatin architecture, which in turn is essential in driving either gene activation or silencing (6, 7).

Finally, the role of various RNA species (particularly, noncoding RNAs), although distinct from classically defined epigenetic mechanisms, has been implicated as a potential epigenetic mechanism of inheritance. These are particularly important regulators of cellular activity in somatic cells, but the function of these molecules is less intuitive in the quiescent sperm cell. Despite this, low quantities of small and noncoding RNAs have been found in male gametes, and these sperm-borne RNAs have even been detected in zygotes. Small RNAs are often implicated in regulatory functions, including gene silencing, so their presence in gametes confers a possible paternal contribution of post-fertilization epigenetic regulation in the developing embryo (8).

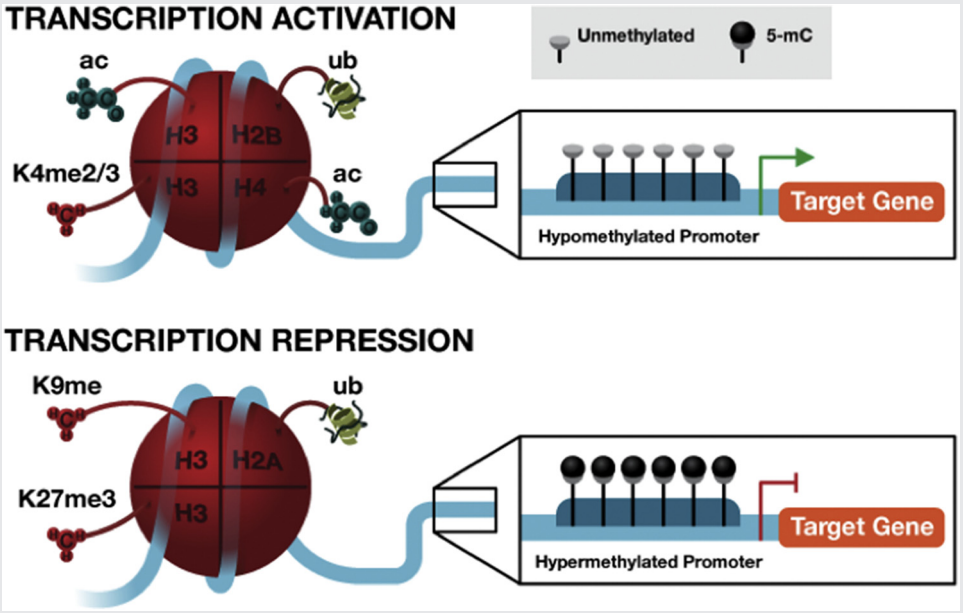
The role that these important marks play in gene regulation is clear, and a high-level depiction of these activating and repression is outlined in Figure 1.

Received September 15, 2017; revised October 28, 2017; accepted November 7, 2017.
E.J. has nothing to disclose. T.G.J. has nothing to disclose.
Reprint requests: Timothy G. Jenkins, Ph.D., 675 Arapeen Dr., Suite 201, Salt Lake City, Utah, 84108 (E-mail: tim.jenkins@hsc.utah.edu).

Fertility and Sterility® Vol. 109, No. 1, January 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2017.11.006

FIGURE 1



Some of the most common epigenetic marks that are associated with gene activation or repression. DNA methylation at promoters at cytosine-phosphate-guanine (CpG) dinucleotides can regulate the activation or silencing of gene transcription. Similarly, histone modifications including ubiquitination (ub), monomethylation (me), dimethylation (me2), trimethylation (me3), and acetylation (ac) at various histones (H3, H2A, H4, H2B, etc.) can drive gene regulation. These histone modifications typically occur at histone tails on lysine residues (K4, K9, K27, etc.).

James. Epigenetics, infertility, and cancer. Fertil Steril 2017.

EPIGENETICS OF SPERM AND MALE INFERTILITY

When considering the heritability of epigenetic marks, it is important to assess the specific marks found in gametes. Sperm cells in particular possess a highly unique epigenetic landscape that is strikingly distinct from that of somatic cells and that likely reflects modification and transitions that occur throughout spermatogenesis. These epigenetic marks have potential implications downstream relating to fertility, fertilization, and embryogenesis (9). These epigenetic signatures in sperm include a unique nuclear protein composition, DNA methylation, and the presence of spermatozoal RNAs (8).

Throughout the process of spermatogenesis in human sperm, protamine proteins, P1 and P2, replace 90%–95% of histones. Protamines aid in the formation of the tight toroid structures necessary for the extremely tight chromatin compaction, which in turn facilitates motility and protection of sperm DNA. The 5%–10% of histones that are retained in sperm are thought to be retained at deliberate locations throughout the genome to provide an additional mechanism of epigenetic regulation through both their placement and the presence/retention of histone tail modifications (9). These histones and associated tail modifications, though not as widespread as in somatic cells, appear to play a key role in embryo development and normal cell function.

DNA methylation also is readily observed in sperm cells and appears to be a key driver for regulation in the developing gamete and may potentially affect events beyond fertilization. Despite the fact that a majority of paternal methylation marks are actively removed during the epigenetic reprogramming events that follow fertilization, some regions (including paternally imprinted regions) escape this reprogramming and are able to pass methylation signatures to the developing embryo (10). Such a transmission of information from one generation to the next that is modifiable by exposures seen throughout the preconception life of the father is a remarkable potential mechanism capable of affecting embryogenesis and even offspring phenotype.

Spermatozoal RNAs are a relatively recent discovery, and the implications of these small and noncoding RNAs are still unclear (11, 12). However, it has been hypothesized that they may play a role in protamination and histone retention owing to their location in the nuclear envelope (13). In addition, it is thought that they may remain stable in the embryo and have a role in regulating gene expression (14), which provides an additional level at which the sperm epigenetic landscape may be informative to embryogenesis. Recent studies have implicated spermatozoal microRNAs as a potential epigenetic mechanism of expression that may be inherited transgenerationally (15).

To further illustrate the essential nature of these epigenetic marks, it has been demonstrated that epigenetic marks in sperm have a clear relationship to male infertility. In fact, improper processing of protamine transcripts and abnormal P1-P2 ratios have been implicated as a possible cause of subfertility and poor semen parameters (16, 17) likely owing to the alteration in the localization or density of histone marks and associated tail modifications. In addition, differential