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Review article

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EPIGENETICS OF REPRODUCTION

EPIGENETYKA ROZRODU

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Streszczenie. Badania epigenetyczne umożliwiają zrozumienie roli oddziaływań środowiskowych na genom, choroby i pozwalają na modulowanie tych interakcji w celu poprawy zdrowia ludzkiego. Znajomość zmian zarówno genetycznych, jaki i epigenetycznych w komórkach rozrodczych jest istotna w przypadku identyfikacji funkcjonalnych gamet i leczenia niepłodności. Przyszłe badania w obu modelach (zarówno ludzkim, jak i zwierzęcym) mogą pomóc lepiej zrozumieć mechanizmy leżące u podstaw związku pomiędzy zmienioną metylacją DNA plemnika a bezpłodnością. Obecnie nie jest jasne, czy wady metylacji znalezione w DNA plemników niepłodnych mężczyzn są wadami pierwotnymi czy wtórnymi zasadniczej bezpłodności. Zrozumienie podstaw zaburzeń metylacji DNA plemnika jest ważne dla rozwoju skutecznych terapii związanych z niepłodnością. Badania epigenetyczne niewątpliwie poszerzają nasza wiedzę ogólnogenetyczną. Są jednak przede wszystkim doceniane ze względu na nowatorskie i kompleksowe podejście do diagnostyki molekularnej i ukierunkowane zabiegi w zakresie klinicznym.

Key words: epigenetics, methylation, sperm.
Słowa kluczowe: epigenetyka, metylacja, plemnik.

INTRODUCTION

The most important epigenetic process taking place during spermiogenesis is compression of the sperm genome through replacement of histones with protamines (Marques et al. 2011). Certain histone variants are essential for normal spermatogenesis, primarily phosphorylated H2AX (gH2AX) and H3.3, which are involved in the MSCI (meiotic sex chromosome inactivation) mechanism, during which transcription in XY bodies becomes silenced. Specialized meiotic chromatin domains of mammalian spermatocytes form a specific nuclear territory where transcription and homologous recombination are limited during the pachytene of the meiotic prophase (Handel 2004; Marques et al. 2011; Sharma and Agrawal 2011). H2AX is an important part of the nucleosome of meiotic cells and undergoes phosphorylation in response to double-strand breaks (DSB) in DNA. During spermatogenesis H2AX is accumulated

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in the sex chromosome territory of spermatocytes in the leptotene and diplotene and enables efficient accumulation of DNA repair proteins. The introduction of H3.3 to the XY body is conducive to extensive chromatin remodelling and is of fundamental importance for gene silencing in X and Y chromosomes in the later stages of MSCI and in postmeiotic stages of spermatogenesis. Replacement of histones with protamines is associated with acetylation of core histones. Acetyl groups change the basic state of histones, decreasing their affinity for DNA and allowing protamines to interact with DNA. Following meiosis, the beginning of spermiogenesis is characterized by a wave of transcription activity which leads to activation of a number of significant postmeiotic genes in early haploid cells (Marques et al. 2011).

EPIGENETIC REGULATION OF SPERMATOGENESIS AND EMBRYONIC DEVELOPMENT

During differentiation of male gametes, the genome undergoes fundamental changes which not only affect DNA sequences, genetic information and homologous recombination, but also change their atomic structure and epigenetic information. It is important to understand how the specific chromatin structure of the sperm nucleus transmits epigenetic information and how it controls early embryonic development (Dada et al. 2012). Protamines P1 and P2 are essential for sperm function, and haploinsufficiency of either of them results in a reduction in the protein (Cho et al. 2001). Protamine phosphorylation is also very important. Mutation of calmodulin-dependent protein kinase IV (Camk4), which phosphorylates protamine P2, causes defective spermiogenesis and infertility. The P1/P2 ratio in fertile males ranges from 0.8 to 1.2. Disturbance of this ratio in either direction is characteristic of low-quality semen with DNA damage and reduced fertilization capacity (Wiland et al. 2006).

Research increasingly confirms the hypothesis that DNA is not uniformly packaged with protamines in mature mammalian sperm. Certain histones are preserved throughout spermiogenesis, and their presence is an important genetic code of the sperm cell and is not the result of abnormal protamination. This is a normal physiological condition. Histone replacement by protamines takes place at the spermatid elongation stage in spermatogenesis, after completion of meiosis. Spermatid elongation is also accompanied by other processes associated with its maturation which affect the motility and fertilization capacity of the sperm cell. The relationship between abnormal replacement of histones by protamines and overall poor semen quality may be due to a defect in the unique system of temporary uncoupling of transcription and translation during spermatogenesis (Sharma and Agrawal 2011; Dada et al. 2012).

The epigenetics of the sperm cell and its transcriptome may be a subject of particular interest for andrologists, geneticists, and especially patients with impaired protamine expression. Errors in the protamination process may affect the transcription of other genes. In mice, for example, deregulation of protamines causes premature chromatin condensation, arrest of transcription and failed spermatogenesis. The nuclei of human sperm, which retain 10–15% of the original content of histones, distribute them heterogeneously in the genome. Various studies have found that retained histones bind to specific regions in order to transmit epigenetic information to the early embryo. If so, this has profound and obvious consequences for sperm with abnormal histone replacement and for the use of this semen, or any immature semen, for intracytoplasmic sperm injection (ICSI). Research increasingly

often characterizes the role of retained histones in the entire genome of sperm cells in mature semen from fertile males and in individuals with chromatin structure disorders (Sharma and Agrawal 2011; Dada et al. 2012).

Gonadal sex determination and testicular development take place during embryonic development. These processes are initiated by differentiation of pre-Sertoli cells (PGCs) and in response to the testis-determining factor SRY (the sex determination region on the Y chromosome) (Michalczak-Janitz et al. 1995). Aggregation of pre-Sertoli cells and migrating mesonephric cells are regulated by testosterone (Piprek 2007; Masłowska et al. 2011). The testes of the foetus contain steroid receptors and are a target for endocrine hormones. Androgen receptor (AR) and oestrogen receptor b (ERb) are present in Sertoli cells. Although the testes do not produce steroids at this stage of development, oestrogens and androgens can influence the early functioning of testicular cells. Treatment with hormones that disturb endocrine system function – vinclozolin and methoxychlor – at the critical moment of gonadal sex determination may reduce the activity of spermatogenesis in adult individuals and in consequence cause infertility. Extrinsic factors may epigenetically induce a transgenerational phenotype. It is not clear whether steroidal factors malfunctioning during gonadal sex determination reprogram the germline epigenetically (altered DNA methylation) or genetically (Dada et al. 2012).

Numerous epigenetic modifiers, including DNA methyltransferases, histone-modifying enzymes and their regulatory proteins, play a key role in the development of reproductive cells. Some of them undergo characteristic expression in reproductive cells, while others are expressed more generally. Studies have confirmed the most important roles of tissue-specific genes of reproductive cells (Dnmt3L and Prdm9). There are many patterns of DNA methylation in the sperm cell, which can contribute to phenotypic differences in the next generation. The sperm cells of males with oligospermia often exhibit impaired DNA methylation in imprinted loci (Aslam and Fishel 1998; Dada et al. 2012).

The epigenetic mechanism regulates DNA accessibility throughout the life of the organism via a specific set of genes which is active at each stage of development. Each type of cell has its own epigenetic profile reflecting the history of its development and the effect of the environment, and ultimately the phenotype of the cell and the organism as well. At the moment of fertilization the paternal genome is packaged by protamines. The maternal genome, arrested in metaphase 2, is packaged by histones. After fertilization, protamines are rapidly replaced by histones and the oocyte completes the second metaphase, releasing a polar body. Histones H3 and H4, associated with paternal chromatin, acetylate more than those present in maternal chromatin (Wiland 2010).

The epigenetic profile of reproductive cells changes dynamically during development. In post-implantation mammalian embryos, pluripotent cells in the epiblast lead to the formation of primordial germ cells (PGCs). Reproductive cells undergo several changes in their epigenetic profile during various stages of meiosis. For example, pre-meiotic PGCs and spermatogonia display unique patterns of histone modification, such as a low level of H3K9me2, but in male embryonic cells these patterns are dynamically transformed during the initiation of meiosis. Changes in composition and modification of histones can contribute to chromatin modifications necessary for proper meiosis and further development of gametes. Both male and female

reproductive cells undergo final changes after meiosis. In haploid round spermatids a complete reorganization of the nucleus occurs, although certain histone marks such as H3K9me2 are retained in the inactive X chromosome. A tissue-specific coupler of H1T2 histone variants appears at this stage and plays a key role in chromatin condensation during spermiogenesis. Later the coupler of HIIs1 histone variants (spermatid-specific histone variant) (Wiland 2010) is expressed in elongated spermatids. During replacement of histones by protamines, nuclear histones undergo hyperacetylation during spermiogenesis and shortly afterwards are disassembled and replaced by transitional proteins (TP1 and TP2). In the final stage, transitional proteins are removed and replaced by protamines. Incorporation of protamines in the sperm chromatin causes DNA condensation, which is important for the emergence of the sperm cell and to ensure a safe environment for the genome. Somatic-like chromatin present in the sperm nucleus can transmit epigenetic information to offspring. The methylation pattern of the entire genome changes slightly during spermiogenesis, after the pachytene spermatocyte stage. Methylation of histones in spermatogenesis is carried out by methyltransferases H3K4 and H3K9 (Oakes et al. 2007).

Hyperacetylation of histone H4 is associated with histone replacement in haploid spermatids. The double bromodomain-containing protein BRDT (sequences recognizing acetylated lysine) binds hyperacetylated H4 histones before they accumulate in condensed chromatin, and aids in organization of the sperm genome by mediating in histone acetylation inducing chromatin condensation and the maintenance of acetylation of other histones from specific regions (Govin et al. 2006; Winnicki 2009).

BORIS, a regulatory protein of gene imprinting sites, is expressed in male gonads and is directly involved in removing methylation markers during differentiation of male gametes (Olszewska and Kurpisz 2010). Research has shown that BORIS is also associated with methylase mediating de novo methylation, as well as with demethylation mediating the removal of imprinting marks (Zaid et al. 2010; Gryzińska et al. 2012).

Both genetic and epigenetic disorders can contribute to idiopathic infertility in men, which can affect the results of in vitro fertilization. Advanced age in the mother is one of the obvious factors contributing to poor fertility, but little is known of the effect of the age of the father. We know that advanced age in the father is associated with reduced semen volume, sperm morphology defects and reduced motility, but this does not significantly reduce sperm concentration. Many studies have documented age-dependent changes in the testes (Mitchell et al. 2005; Kobayashi et al. 2007; Oakes et al. 2007, 2009; Marquez et al. 2011; Sharma and Agarwal 2011).

One of the main problems in defining the effect of DNA modification on fertilization is the lack of reliable techniques enabling easy and repeatable analysis of the level of modification in each gamete. The simple, basic Sperm Chromatin Dispersion (SCD) test, which offers stable results, can be used to analyse the quantity of methylated DNA remaining and the level of DNA damage in each sperm cell (Benchaib et al. 2003; Wyrobek et al. 2006).

Histones are regarded as the best candidates for transmission of epigenetic information due to their modifying effect on chromatin structure, as well as their role in transcription. Methyltransferases facilitate silencing of genes via mono-, di- or trimethylation of lysine or arginine. The question remains as to whether modified histones play a key role in gene

expression during early embryogenesis or whether abnormal histone modifications in sperm are associated with impaired embryonic development. Changes in the methylation pattern can lead to biallelic expression or silencing of imprinted genes, causing various pathologies. Impaired spermatogenesis has been linked to abnormal H4 acetylation. H4 hyperacetylation has also been observed in infertile men with Sertoli cell-only syndrome (SCO – a syndrome characterized by a complete lack of germ cells in the seminiferous tubules) – Kusz et al. (2004). The semen of males with asthenozoospermia and teratozoospermia has a reduced DNA methylation level (Myers 2004; Mitchel et al. 2005; Chan and Trasler 2011; Pokrywka et al. 2014).

GENOMIC IMPRINTING AND IMPAIRMENT OF EPIGENETIC PROCESSES

Genomic imprinting is a phenomenon in which DNA methylation identifies differently methylated regions (DMRs), enabling monoallelic expression of parental genes in a specific manner. These markers, which are initiated in the germline, play an important role during embryonic growth and development (Chan and Trasler 2011). It is also defined as a mechanism of gene regulation, leading to expression of the genes of only one of the two parent chromosomes. Some imprinted genes are expressed from the copy from the mother, and others from the copy inherited from the father.

Monoallelic expression of imprinted genes depends on the epigenetic mark, which makes it possible to distinguish the two parent alleles. This imprinting mark must be hereditable and reversible, and must also be interpreted by a reading frame to cause expression or silencing of the gene. Although the nature of the entire complex remains elusive, the effect of DNA methylation and the allele-specific difference in chromatin structure have been described. Many imprinted genes contain one or more DMRs exhibiting an allele-specific DNA methylation pattern, which defines the state of gene expression (Delaval and Feil 2004; Edwards and Ferguson-Smith 2007; Marques et al. 2008, 2010, 2011).

Another intriguing question is how methylation of the maternal and paternal genome of imprinted genes can resist this active wave of DNA demethylation. One possible explanation is chromatin structure differing between the mother's and father's genome, because the former contains histones associated with DNA, while the paternal genome contains mainly protamines. Thus it would be useful to investigate whether methylated imprinted paternal genes retain histones during differentiation of sperm cells and whether they are thus resistant to DNA demethylation. In addition, a recent study presented evidence concerning a protein called Stella, which can protect imprinted genes and other genome sequences against methylation in the zygote. Stella is present in large quantities in the oocytes and relocates to both pronuclei after fertilization (Nakamura et al. 2007).

There is increasing evidence that spermatogenesis disorders leading to oligozoospermia are linked to semen with methylation defects in imprinted genes. Both hypomethylation on methylated paternal imprinted genes and hypermethylation on methylated imprinted maternal genes have been described in the sperm of individuals with a number of defects identified in the spermiogram, such as a reduced number or lack of sperm, abnormal morphology and/or motility, and abnormal replacement of histones by protamines (Marques et al. 2004; Kobayashi et al. 2007, 2009).

Marques et al. (2011) write that although the first report of analysis of methylation on an imprinted SNRPN gene (maternally methylated and paternally expressed) in the semen of patients with oligozoospermia did not describe any changes, this was due to the limitations of the MSP (methylation-specific PCR) technique used. The authors observed certain methylation disorders when they used a more sensitive technique (seminested PCR), but since methylation was also present in normal semen samples, it was concluded that somatic cell contamination was a likely cause. The first description of imprinting methylation defects in the semen of infertile men reported hypomethylation of H19 in individuals with oligozoospermia, while males with normal semen had complete methylation in this locus. Such hypomethylation affects one of the CTCF binding sites. The binding factor CTCF is an insulator protein that binds to the unmethylated maternal H19 DMR and prevents repeated imprinting of genes (Borghol et al. 1997; Marques et al. 2004, 2011; Manning et al. 2001).

Hypomethylation at CTCF binding sites may lead to deactivation of the parental copy of IGF2, causing biallelic repression in the embryo. Another study confirms these findings and added to the number of imprinted genes displaying methylation errors. The authors observed increased frequency of imprinting errors in semen from males with oligozoospermia, in two methylated paternal (H19 and GTL2) and three methylated maternal (PEG1/MEST, ZAC and SNRPN) imprinted genes. The level of global sperm DNA methylation assessed on the LINE1 and Alu regions was normal, suggesting that these defects were limited to imprinted genes (Kerjean et al. 2000). Imprinting errors resulting from a complete lack of methylation in the H19 gene and in the MEST gene occurred in the semen of males with a very low sperm concentration in their ejaculate. Moreover, analysis of the methylation level of the LINE1 transposon showed that hypomethylation is limited to imprinted genes (Kobayashi et al. 2007; Marques et al. 2008, 2011).

Other analyses have revealed methylation errors in imprinted genes in the semen of individuals with oligozoospermia, but also those with abnormal histone replacement (altered P1 : P2 ratio). Interestingly, one study also found a strong link between loss of methylation in the sixth CTCF-binding site and reduced sperm count, as previously described (Sharma and Agarwal 2011). Research has also been conducted on semen isolated from the testes of individuals with azoospermia to evaluate their imprinting status. Imprinting errors such as a complete lack of methylation in H19 and CTCF binding at the sixth site have been confirmed in the sperm of males with secretory azoospermia (Marques et al. 2011).

Various types of imprinting errors have been noted in the sperm of infertile patients with abnormal spermiogram parameters, such as oligozoospermia. Appropriate imprinting during male and female gametogenesis is essential for normal expression of these genes in the embryo and later on. Imprinted genes play an important role in regulating growth and development, particularly regulation of embryonic growth and placental function (Arnaud and Feil 2005). There is no evidence of the existence of a mechanism that could repair imprinting errors transmitted by gametes, and thus it is likely that embryos produced from sperm with an abnormal imprint will not develop in a natural way. Therefore analysis of methylation of imprinted genes should be added to the spermiogram of males with fertility disorders, particularly in cases in which severe oligozoospermia has been detected (Rossignol et al. 2008).

CONCLUSIONS

The role of epigenetic modifications in normal and abnormal development of reproductive cells requires further investigation so that scientists can better understand this mechanism. Research on sequencing of the entire genome may help to determine which types of methylated sequences are most sensitive to the effect of intrinsic and extrinsic factors. Despite demethylation of the entire genome taking place in the germline, there is still concern that some epigenetic defects may be transmitted from generation to generation. Unfortunately, an increasing number of studies are beginning to confirm this unsettling hypothesis. Our still limited knowledge in this area requires better understanding of the interactions between various epigenetic modifications and enzymes taking part in the normal development of male gametes, as well as changes that may prove significant for embryonic development.

It is clear that scientists should devote increasing attention to the subject of epigenetics and its mechanisms and continue to conduct research in this area, investigating not only fertility in individuals but also the effect of all commonly occurring factors (chemical compounds or even the physical activity of the organism) on the genome of the individual. In view of the increase in the number of diseases affecting our civilization, it would appear essential to explore this important area of genetics, which despite being relatively young, may prove to have a surprisingly significant impact on our lives and the lives of our descendants.

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Abstract. Epigenetic research offers a significant opportunity to understand the role of environmental interactions on the genome and disease, while enabling modulation of these interactions in order to improve human health. Knowledge of both genetic and epigenetic changes is essential for identification of functional gametes and for fertility treatment. Future studies in both human and animal models may enable better understanding of the mechanisms underlying the relationship between altered DNA methylation in the sperm cell and infertility. It is currently unclear whether methylation defects found in the DNA of infertile sperm are primary or secondary defects. An understanding of what underlies DNA methylation disorders will be important for the development of successful fertility treatments. While epigenetic research will unquestionably expand our knowledge of general genetics, it is mainly valued for its innovative and comprehensive approach to molecular diagnostics and is directed towards clinical procedures.