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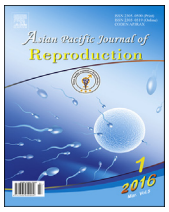

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# Change of epigenetic modification and human reproduction

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ABSTRACT

In recent years, it has become consumedly clear that changing of epigenetic modification is essential during both early and late oogenesis and spermatogenesis. Also epigenetic modifications are involved in some cases such as embryo development and growth, diseases and responsible for X-chromosome inactivation and genomic imprinting. Epigenetic reprogramming can be explained as any mitotic or meiotic changing which does not result any alteration in DNA sequence but will have important effect on the normal embryonic development. Germline epigenetic reprogramming in addition to requiring epigenetic modification to compose the germline, the primordial germ cells uniquely undergo striking wave of epigenetic reprogramming that most other lineage do not undergo. Epigenetic modification is affected by both internal factors and environmental factors during pre- and post-natal development. Because all of the epigenetic modification steps are not clear, by means of understanding epigenetic modification, misreprogramming of these steps can be modified with the aid of drugs and nutrients. Moreover, epigenetic regulation is essential to obtain the biological intricacy of multicellular organisms, cloning and producing of offspring by assisted reproductive technology (ART).

The objective of this review is to provide comprehensive summary of the current knowledge in the field of epigenetic modification in relation to male and female germline development and reproduction.

## 1. Introduction

Epigenetic modification such as DNA methylation, histon modification and non-coding RNA (ncRNA), plays important roles in the regulation of chromatic structure and gene expression [1,2]. Epigenetic is the study of transmittable alterations in gene expression that occur without changing the DNA sequence [3]. Each cell in the human body has the same genomes. Although each cell has one of many epigenomes, unique collection of epigenetic instructions for founding and protecting lineage-specific expression profiles [4].

In spite of the genetic information that is exceedingly stable, epigenetic occurrences are reversible and responsible to internal and external stimuli by changing the properties of proteins [5]. Epigenetic steps are involved in development, health, disease, aging, and responsible to phenomena such as X-chromosome inactivation and genomic imprinting [6]. Genomic imprinting is an epigenetic mechanism which uses suppressive modifications to reticence one parental allele, while activating modifications on the other parental allele enable expression [7].

Some imprinted genes show paternal expression while others show maternal expression. The best specified known mark of gene imprinting is DNA methylation and unmethylation [8].

## 2. Epigenetic modification process

### 2.1. DNA methylation

DNA methylation is accomplished by DNA methyltransferases enzyme (DNMTs), which adds methyl groups from S-adenosyl-methionine as a methyl donor to the 5-prime carbon of a cytosine residues of CpG dinucleotides [9]. DNA methyltransferase-1 (DNMT1) is the main human DNA methylating enzyme liable for the renovation of hemi-methylated sites to full methylation, termed maintenance methylation that

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occurs after DNA replication. DNMT3A and DNMT3B are principally involved in the methylation of new sites, known as de novo methylation [10].

Methylation of DNA plays an important role in the epigenetic control mechanism as genomic imprinting, suppression of retrotransposons that threaten genome integrity, the maintenance of genome stability, X-chromosome inactivation, and also gene expression regulation [11,12]. In 98% of the genome, CpGs are present around once per 80 dinucleotides. By comparison, CpG islands that comprise 1–2% of the genome, are around 200 base pairs (bp) to several kb in length and have a frequency of CpGs around five times larger than the genome as a whole [13].

### 2.2. Histone modification

Histone modification is an epigenetic determinant of chromatin structure and this mechanism plays an important role in epigenetic regulation of gene expression, DNA replication, recombination, repairs and genome integrity. Furthermore, they contribute in the formation of either condensed heterochromatic states or open euchromatic states [14,15].

Epigenetic modification at the N-terminal tail of histones can be post-translationally modified by methylation, acetylation, phosphorylation sumoylation and ubiquitinylation at lysine, arginine, serine and threonine amino acids. Such a modification plays significant roles in both structural and functional states of the chromatin [16]. These modifications are completed by a range of enzymes including histone methyltransferases, acetyltransferases, kinases and ubiquitylases. Histone demethylases, deacetylases, phosphatases and deubiquitylases are able to eliminate the mark from the histone tail and subsequently proteins can distinguish and bind to these specific modifications and utilize an effect on gene activity [17].

Altogether about 40 histone residues can be modified. Each modification seems to have unique influence on the transcriptional activity of the associated gene as acetylation of lysine residues is connected with the relaxation of chromatin, permitting access to the transcription factors and active transcription, deacetylation leads to contraction of the chromatin, inhibiting access of transcription factors and silencing the loci. Similarly, methylation or phosphorylation can be connected to gene activation or gene silencing depending on the position of the amino acid modified [18].

### 2.3. Non-coding RNAs (ncRNAs)

Sections of mammalian genome which transcribed mainly consist of non-coding (nc) RNAs. ncRNAs are classified according to their function or length [19]. ncRNAs are transcripts without a clean open reading frame; so they do not code proteins, but regulate the expression of other genes in cis and trans. These ncRNAs are involved in essential functions such as genomic imprinting, X-chromosome inactivation, transposon, virus silencing, developmental designing and differentiation [20,21]. When ncRNAs act to form the cis, they are able to regulate the expression of one or more genes on the same chromosome. On the other side, when ncRNAs act to form the trans, they are able to regulate the expression of one or more genes on the different chromosomes or regulate mature RNAs in the cytoplasm [22].

## 3. Epigenetic in germline

Epigenetic programming in the germline such as DNA methylation, histon modification and chromatin remodeling occurs during the primordial germ cell specification, gametogenesis and pre-implantation development [23].

During development, germ cells undergo a series of specific events that allow them to distinct from other cell types. Major alterations in cellular specification must occur through differentiation and reprogramming events. Overall this stage epigenetic modification, undergo extensive changes [24]. After fertilization in mammals, the genomes inherited from both sperm and oocytes combine and the first of two major reprogramming events during the life cycle occurs, which leads to the production of a totipotent zygote [25]. First, comprehensive alterations in DNA methylation and chromatin remodeling occurs in developing germ cells and in the pre-implantation embryo, rendering these “embryonic cells” especially susceptible to environmentally induced epigenetic modifications. Second, the accurate timing of de novo DNA methylation during gametogenesis is poorly understood [26].

In the case of imprinted genes, the timing of de novo DNA methylation varies between the male and female germlines [27]. DNA methylation plays an essential role in embryonic development such as in regulating gene expression. A differential pattern of DNA methylation not merely is present on paternal and maternal genomes, but also helps distinguish germ cells and somatic cells. The differential DNA methylation pattern of imprinting genes is determined in male and female germ cells during gametogenesis [28,29].

## 4. Epigenetics and environmental effects

Existence evidence suggests that the environmental factors during pre- and post-natal development can increase the risk of chronic diseases such as cancer, diabetes, cardiovascular disease, obesity and behavioral disorders like schizophrenia by altering epigenetic programming [1]. Furthermore other environmental factors like chemical pollutants, tobacco smoke, alcohol, radiation, dietary components, temperature changes and other external stresses can indeed have effects on development, metabolism and health, sometimes even in subsequent generations [30]. These environmental factors could interrupt DNA methylation and DNA fragmentation like infertile men which is found to have greater DNA fragmentation and higher reactive oxygen species levels than fertile men. These results indicate that DNA damage caused by oxidative stress may facilitate aberrant global DNA methylation [31].

Several studies accomplished in relation to effect of environmental factors and change of epigenetic modification such an assessment performed by Oakes *et al*. showed that 5-aza-20-deoxycytidine, an anticancer agent, causes a decrease in global DNA methylation that leads to altered sperm morphology, decreased sperm motility, decreased fertilization capacity and decreased embryo survival [32].

## 5. Epigenetics in assisted reproductive technologies (ART)

Several studies that accomplished in evaluating pregnancy outcomes following ART in humans are frequently challenged

by the confusing factors of increased maternal age and male/female infertility, each which of these are recognized independent risk factors associated with pregnancy loss, perinatal deaths, and subsequent complications [33]. In the epigenetics in assisted reproductive technologies, the DNA of spermatozoa is differentially methylated at several paternal and maternal imprinting regions in addition to shows unique globular methylation patterns. Reprogramming of the epigenome and imprinted loci during gametogenesis and pre-implantation periods is very essential for maintaining proper pattern of inheritance, particularly at imprinted loci [34].

Use of the assisted reproductive technologies such as intracyto-plasmic sperm injection (ICSI), round spermatid injection (ROSI) and IVF may increase the incidence of imprinting disorders and contrarily affect embryonic development by using immature spermatozoa that may not have proper imprints or global methylation established or using older oocytes which frequently remain acetylated during meiosis that suggesting that an age-related deficiency in the mechanisms regulating histone deacetylation contributes to the promote frequency of aneuploidy in older females. Absolutely it has been shown that some genes associated with chromatin organization and DNA methylation are downregulated in oocytes from aged mice. Although there is a slightly dispute association between ART and abnormal genomic imprinting in humans, now only three of nine recognized human imprinting syndromes have been implicated and their incidence is far low and this deregulation of imprinted genes lead to methylation defects at the DMRs of SNRPN (Angelman Syndrome), KCNQ1OT1 (Beckwith–Wiedemann Syndrome) and PEG1/MEST (Silver–Russell Syndrome) [35,36].

## 6. Conclusion

Epigenetic modification has an important role during embryo development, health, oogenesis and spermatogenesis. Restriction and specific epigenetic changing in the gene imprinting status and DNA methylation can be lead to specific human diseases. In addition to epigenetic modification changing with internal factors, it is affected by environmental factors and these epigenetic alterations may be inherited and passed onto next generation.

## Conflict of interest statement

We declare that we have no conflict of interest.

## References


[1] Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. *Nat Rev Genet* 2007; **8**: 253-262.
[2] Ewka CM, Aafke PA, John CM, Johannes LH. Epigenetics and the placenta. *Hum Reprod Update* 2011; **17**(3): 397-417.
[3] Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. *Cell* 2007; **128**: 635-638.
[4] Jenuwein T. The epigenetic magic of histone lysine methylation. *FEBS J* 2006; **273**: 3121-3135.
[5] Gluckman PD, Hanson MA, Bateson P. Towards a new developmental synthesis: adaptive developmental plasticity and human disease. *Lancet* 2009; **373**: 1654-1657.
[6] Rodenhiser D, Mann M. Epigenetics and human disease: translating basic biology into clinical applications. *CMAJ* 2006; **174**: 341-348.
[7] Hirasawa R, Feil R. Genomic imprinting and human disease. *Essays Biochem* 2010; **48**: 187-200.
[8] Natasha M, Chong Suyinn, Moira K. Epigenetic regulation in male germ cells. *Reproduction* 2008; **136**: 131-146.
[9] Biermann K, Steger K. Epigenetics in male germ cells. *J Androl* 2007; **28**: 466-480.
[10] Theodore P. The epigenetics of early development: inferences from stem cells. *Mol Reprod Dev* 2014; **81**: 194-201.
[11] Anne G, Linda A, Claudine J. Developmental programming and epigenetics. *Am J Clin Nutr* 2011; **94**: 1943-1952.
[12] Daniel M. DNA methylation dynamics during epigenetic reprogramming in the germline and preimplantation embryos. *Gene Dev* 2014; **28**: 812-828.
[13] Koukoura O, Sifakis S, Spandidos DA. DNA methylation in the human placenta and fetal growth. *Mol Med Rep* 2012; **5**: 883-889.
[14] Hayashi-Takanaka1 Yoko, Yamagata Kazuo, Wakayama Teruhiko, Stasevich Timothy J, Kainuma Takashi, Tsurimoto Toshiki, et al. Tracking epigenetic histone modifications in single cells using Fab-based live endogenous modification labeling. *Nucleic Acids Res* 2011; **343**: 1-14.
[15] Bernstein BE, Meissner A, Lander ES. The mammalian epigenome. *Cell* 2007; **128**: 669-681.
[16] Angèle S, Maria-Elena TP. Epigenetic reprogramming in mammalian reproduction. *Epigenetics* 2009; **4**(2): 80-84.
[17] Niessen HE, Demmers JA, Voncken JW. Talking to chromatin: post-translational modulation of polycomb group function. *Epigenetics Chromatin* 2009; **2**: 10.
[18] Turner BM. Epigenetic responses to environmental change and their evolutionary implications. *Philos Trans R Soc Lond B Biol Sci* 2009; **364**: 3403-3418.
[19] Katayama S, Tomaru Y, Kasukawa T, Waki K, Nakanishi M, Nakamura M, et al. Antisense transcription in the mammalian transcriptome. *Science* 2005; **309**: 1564-1566.
[20] Brosnan CA, Voinnet O. The long and the short of noncoding RNAs. *Curr Opin Cell Biol* 2009; **21**: 416-425.
[21] Costa FF. Non-coding RNAs, epigenetics and complexity. *Gene* 2008; **410**: 9-17.
[22] Koerner MV, Pauler FM, Huang R, Barlow DP. The function of non-coding RNAs in genomic imprinting. *Development* 2009; **136**: 1771-1783.
[23] Reik W. Stability and flexibility of epigenetic gene regulation in mammalian development. *Nature* 2007; **447**(7143): 425-432.
[24] Davood S, Hans R. Reprogramming and the mammalian germline: the Weismann barrier revisited. *Curr Opin Cell Biol* 2012; **24**: 716-723.
[25] Allegrucci Cinzia, Thurston Alexandra, Lucas Emma, Young Lorraine. Epigenetics and the germline. *Reproduction* 2005; **129**: 137-149.
[26] Adam B, Maria EP. Epigenetic reprogramming and development: a unique heterochromatin organization in the preimplantation mouse embryo. *Brief Funct Genomics* 2010; **9**(6): 444-454.
[27] Lucifero D, Mann MR, Bartolomei MS, Trasler JM. Genespecific timing and epigenetic memory in oocyte imprinting. *Hum Mol Genet* 2004; **13**: 839-849.
[28] Sasaki H, Matsui Y. Epigenetic events in mammalian germ-cell development: reprogramming and beyond. *Nat Rev Genet* 2008; **9**: 129-140.
[29] Surani MA, Hayashi K, Hajkova P. Genetic and epigenetic regulators of pluripotency. *Cell* 2007; **128**: 747-762.
[30] Baccarelli A, Bollati V. Epigenetics and environmental chemicals. *Curr Opin Pediatr* 2009; **21**: 243-251.
[31] Tunc O, Tremellen K. Oxidative DNA damage impairs global sperm DNA methylation in infertile men. *J Assist Reprod Genet* 2009; **26**: 537-544.
[32] Oakes CC, Kelly TL, Robaire B, Trasler JM. Adverse effects of 5-aza-20 deox-ycytidine on spermatogenesis include reduced sperm function and selective inhibition of de novo DNA methylation. *J Pharmacol Expt Ther* 2007; **322**: 1171-1180.

[33] Sinclair KD. Assisted reproductive technologies and pregnancy outcomes: mechanistic insights from animal studies. *Semin Reprod Med* 2008; **26**: 153-161.

[34] Jacob SAJI, Moley KH. Gametes and embryo epigenetic reprogramming affect developmental outcome: implication for assisted reproductive technologies. *Pediatr Res* 2005; **58**: 437-446.

[35] Singh R, Kelsey A, Ashok A. Epigenetics, spermatogenesis and male infertility. *Mutat Res* 2011; **727**: 62-71.

[36] Amor DJ, Halliday J. A review of known imprinting syndromes and their association with assisted reproduction technologies. *Hum Reprod* 2008; **23**(12): 2826-2834.