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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 multi-cellular 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 ubiquitylation 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

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