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Epigenetics of reproductive infertility

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1. ABSTRACT

Infertility is a complex pathophysiological condition. It may caused by specific or multiple physical and physiological factors, including abnormalities in homeostasis, hormonal imbalances and genetic alterations. In recent times various studies implicated that, aberrant epigenetic mechanisms are associated with reproductive infertility. There might be transgenerational effects associated with epigenetic modifications of gametes and studies suggest the importance of alterations in epigenetic modification at early and late stages of gametogenesis. To determine the causes of infertility it is necessary to understand the altered epigenetic modifications of associated gene and mechanisms involved therein. This review is devoted to elucidate the recent mechanistic advances in regulation of genes by epigenetic modification and emphasizes their possible role related to reproductive infertility. It includes environmental, nutritional, hormonal and physiological factors and influence of internal structural architecture of chromatin nucleosomes affecting DNA and histone modifications in both male and female gametes, early embryogenesis and offspring. Finally, we would like to emphasize that research on human infertility by gene knock out of epigenetic modifiers genes must be relied upon animal models.

2. INTRODUCTION

Infertility is described as inability to conceive after 12 months of regular sexual intercourse by

developmentally mature couple without use of any contraception. In human, either or both of the couple may acquire the infertility phenotype. It has an impact on one's mental state, lifestyle and medical conditions (1). According to different studies approximately 20–30% of infertility cases are due to male, 20–35% due to female, 25–40% due to combined problems in both parts and in 10–20% of cases, no causes are found. The highly occurrence of infertility in human population might be associated with individuals age, environment, lifestyle and health condition. Association of the causes of infertility that govern regulation of gene expression with genetic factors and altered epigenetic mechanisms can help in better understanding of this complex and chronic physiological conditions (2–4). Sequence analysis of human genome provide a brief molecular genetics of complex disorders and elucidates physical structure of DNA, in addition to significant details of the major part of the non-coding human genome (5). Discovery of the significant role of various molecular mechanisms intricate in the expression of coding and noncoding part of human genome at different time points of cell cycle in tissue specific manner during development and in normal or pathological condition may further help in understanding the complexity of diseases like infertility. This is because complete human genome is transcribed at some point of cell cycle. (6–9). Molecular mechanisms involved in regulation of genomic and chromosomal variations associated with infertility phenotype, with consecutive pregnancy losses or recurrent miscarriage and idiopathic cases are still to be reported (10, 11). To understand the molecular mechanisms involved in regulation of the expression of genes affecting infertility, the role of one's genotype, environment, health, nutrition and age with changes in one's epigenotype should be considered first, that would help to find out the unknown causes of the disease, like reproductive infertility. Genetic code refers stable outline of information determining the phenotype, while epigenetic code provides dynamic outline to fine-tune the phenotype according to various signalling, environmental factors, and microenvironment that surrounds the gametes and later the zygote. We will focus new insights analysing various studies of therapy based on epigenetics would be possible as epigenetic modifications are reversible (12–15).

2.1. Epigenetics

Epigenetics refers to molecular modifications in the chromatin affecting gene expression and genome stability without altering DNA sequence. Alternatively, epigenetics refers to changes in the phenotype caused by mechanisms other than changes in DNA sequences. Epigenetic modifications can switch genes on or off and determine which genes will be transcribed. Molecular modifications of DNA (without change of nucleotide sequence) or histones, which are closely associated with DNA is regarded as epigenetic changes. It is due to epigenetic control of gene expression, why a cell of skin issue differs from a cell of liver, lung, brain or muscle tissue. All of those tissues cells contain the same genome but genes are expressed differently (turned "on" or "off"), which creates the different phenotypes of cell. DNA methylation mediated epigenetic silencing is one way to turn off genes, and it contributes to differential expression. Silencing might also explain, in part, why genetic twins are not phenotypically identical. Thus, the significance of turning genes off via epigenetic changes can be easily perceived (16, 17). Most of the epigenetic changes that occur in sperm and egg cells are removed when two combine to form a fertilized egg, in a process called "reprogramming." This reprogramming allows the cells of the foetus to "start from scratch" and make their own epigenetic changes (18, 19). However, some of the epigenetic changes in parents' sperm and egg cells may escape from the process of reprogramming and can pass it to the next generation (20). This type of events that epigenetic marks (for examples, DNA methylation, histone methylation etc., see below) can be acquired on the chromatin of one generation and stably passed on through the gametes (i.e., sperm and eggs) to the next generation is defined as transgenerational epigenetic inheritance.

2.2. Epigenetic mechanisms modulating gene expression

Existence of special and new patterns of epigenetic mark(s) can be considered as heritable change in somatic cells, and cells keep it as cellular memory without any change in the nucleotide sequence(s) of DNA strand encoding gene(s) (20). Epigenetic mechanisms regulate gene expression via reversible modifications of chromatin either in DNA or histones and in some cases both DNA and histones. Under the influence of physiological factors, epigenetic modifications take a crucial role in packaging and interpreting the genome. Within the cell, important molecular and biochemical events/processes those interact with each other to silence genes are DNA methylation, histone modifications, RNA-associated silencing and rearrangement of nucleosome positioning (21).

2.2.1. DNA Methylation

DNA methylation is post replicative covalent attachment of a methyl ($-CH_3$) group to DNA bases and methylation of cytosine at fifth carbon is well-characterised epigenetic modification which represents less than 5% of all cytosines in the human genome (21, 22). The methylation reaction of cytosine-5-carbon in DNA (hereafter, DNA methylation) is

catalysed by DNA methyltransferases (DNMTs). This family of enzymes transfers the methyl group from S-Adenosylmethionine (SAM) to cytosine-5-carbon in DNA. There are five DNMTs; DNMT1, DNMT3A, DNMT3B, DNMT3C and one cofactor DNMT3L. They actively regulate three different processes, that is, maintenance methylation, *de novo* methylation, and protection from retrotransposons activities (23). DNMT1 is the main enzyme of all human DNMTs responsible for the renovation of hemi-methylated sites of DNA to fully methylated as per parental DNA strand and is termed as maintenance DNA methylation occurs during replication. DNMT3A and DNMT3B are principally involved in *de novo* methylation, as they take part in the methylation of new CpG sites (24, 25). DNMT3C is responsible for silencing evolutionarily young retrotransposons in the male germ line by methylating their promoters and this specialized activity is required for mouse fertility (26). DNMT3L, fifth member in the DNMT3 family is considered to be required for the establishment of maternal imprints in oocytes and express during spermatogenesis (21, 27, 28). DNMT2 is another member in this family, incapable of DNA methylation though is associated with embryonic stem cells and actively takes part in RNA methylation (29). In mammals, generally transcription initiated at promoter regions rich in CG sequences, where cytosine is present next to a guanine and linked by a phosphate group called a CpG site. Such CpG-dense site(s) in DNA is known as CpG islands (18). Maintenance of repressive chromatin state and gene silencing can orchestrate by DNMTs, along with other enzymes. Proteins having methyl-binding domain, like MeCP2, MBD1, MBD2, and MBD4 remain bind to the methylated DNA strand and inhibits binding of transcription factors to DNA, which leads to stop the gene expression (30, 31) . Conversion of methyl-cytosine into cytosine during DNA demethylation is either active or a passive process. The active demethylation is replication-independent, which uses ten-eleven translocation (TET) enzyme family (TET1, TET2, and TET3) to catalyse hydroxylation of 5mC followed by activation-induced cytidine deamination, and by DNA break and repair mechanisms. Whereas, passive mechanism is replication-dependent, and occurs due to failure of maintenance methylation as a result of, (i) non availability of methyl donor SAM, (ii) loss of DNMT1 function by mutation, or (iii) as shown by an *in vitro* demonstration: in presence of unusually high Ca^{2+}ions in a reducing environment and DNMTs demethylate DNA (32–36). DNA hypermethylation of promoter region causes gene silencing and demethylation results in gene expression (36–42).

2.2.2. Histone modification

Nuclear histones have positively charged amino acids (aas) in their N-terminus projecting towards outer surface of the core histone octamer and referred as “histone tail”. Histone tails contain 15–38 aas in numbers and influences nucleosome assembly into higher order chromatin structures. Amino-terminal tails of the four core histones are subject to enzyme-catalysed post-translational modifications (PTMs) of selected amino acids, and has the ability to accumulate or decode information. (43, 44). Nucleosome consist of 147 base pairs of DNA wrapping 1.7 times an octamer assembly of histone proteins (two each of H2A, H2B, H3, and H4) is known as the individual units of chromatin (45, 46). PTMs of histones regulate gene expression and dynamics of DNA-histones (octamer) interactions by the process of methylation, phosphorylation, acetylation, deamination, ADP ribosylation, tail clipping, proline isomerization, ubiquitylation and sumoylation. In most of the species, histone H3 acetylation occurs at lysine (K) 9, 14, 18, 23, and 56; methylation occurs at arginine (R) 2 and K 4, 9, 27, 36, and 79; and phosphorylation occurs at serine (S)10, 28, threonine (T)3, and 11. Similarly, in case of histone H4 acetylation occurs at K 5, 8, 12 and 16; methylation occurs at R 3 and K 20; and phosphorylation at S 1 (47, 48). Histone modification plays an important role in determination of chromatin structure which contribute in regulation of gene expression, DNA replication, recombination, repairs and genome integrity, inaddition to the formation of either heterochromatin (condensed) or euchromatin (open) (49–52). Higher levels of acetylation, including H3K9 and trimethylation at H3K4, H3K36, and H3K79 are the characteristics of euchromatin, whereas heterochromatin is characterised by lower levels of acetylation and higher levels of methylated H3K9, H3K27, and H4K20 (53, 54). Histone modifications are actively added or removed by various histone-modifying enzymes, which are referred as writers or erasers respectively. To organize transcriptional regulation, histone-modifying enzymes catalyse modification of specific amino acids with particular modifying groups in a site-specific manner. Histone modifications play a significant role in structural organization of chromatin by altering the electrostatic charge, which is provided by substituted group and facilitate to recognise sites for different adaptor proteins (45, 50, 55, 56). Determination of DNA accessibility to transcription factor complexes at promoter region and contact between octamer core and DNA is regulated by histone modifications (50). Thus, quantitative detection of different histone modifications may contribute important information to understand epigenetic regulation of pathophysiological processes and development of histone modifying enzyme-targeted drugs for therapy (56, 57).

2.2.3. Non-coding RNAs (ncRNAs)

RNA without the ability to encode a protein owing to lack of distinct open reading frame is commonly termed as non-coding RNA (ncRNA). However, ncRNAs regulate the expression of other genes in cis-

and trans-, inaddition to their involvement in important functions like genomic imprinting, X-chromosome inactivation, transposon, virus silencing, developmental designing and differentiation (58, 59). In general, function of ncRNAs are the transcriptional and post-transcriptional regulation of gene expression (60). ncRNAs regulate the expression of one or more genes on the same chromosome when form the cis, whereas, when form trans regulate the expression of one or more genes on the different chromosomes or regulate mature RNAs in the cytoplasm (61–63). Generally, ncRNAs are classified based on their length or function. ncRNAs associated with epigenetics are reported to play a role in heterochromatin formation, histone modification, DNA methylation targeting, and gene silencing. ncRNAs can be classified into (i) short ncRNAs (<30 nts)-microRNAs (miRNAs), short interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs) (ii) long ncRNAs (>200 nts) (64). Most of the non-coding RNA belongs to the lncRNAs group. miRNAs bind to a specific target mRNA to induce cleavage or degradation or block translation, that might happen in context of a feedback mechanism associated with DNA methylation (65–67). *Similarly, like miRNAs, siRNAs* mediate post-transcriptional gene silencing (PTGS) by mRNA degradation. *In addition, siRNAs are reported to* induce heterochromatin formation via mRNA-induced transcriptional silencing (RITS) complex, which promotes H3K9 methylation and chromatin condensation when attached to siRNA (68, 69). *piRNAs are named so as they interact with* PIWI *family of proteins and play a role in* chromatin regulation, in addition to suppression of transposon activity in germline and somatic cells. *piRNAs work in a peculiar way, form* complexes with PIWI-proteins*, which* target and cleave transposon, as piRNAs are antisense to expressed transposons. The cleavage produces additional piRNAs, which target and cleave another transposon. Thus, the cycle continues to release a number of piRNAs and potentiate transposon silencing (70, 71). lncRNAs play a role in chromatin remodelling by forming a complex with chromatin-modifying enzymes and utilize their catalytic activity to specific sites in the genome, ultimately modify chromatin organization and gene expression. In addition, lncRNAs function in transcriptional and post-transcriptional regulation and are precursor for siRNAs (72–75).

Transcriptional machineries and regulators gain access of chromatin to extract genetic information by specific arrangement of nucleosome locations in the genome (76). Therefore, particular location of nucleosome changes dynamically and exact position of nucleosome with respect to the particular sequence of genomic DNA is simply referred to as nucleosome positioning. However, at a particular time sequencing-based mapping approaches can identify the positions of individual nucleosome (77). Nucleosome positioning affects DNA packaging in chromosomes and in recent time there is involvement of multiple RNAs. The correct position of nucleosomes at transcription start sites has an essential degree of control over the initiation of transcription (78). DNA methylation linked with specific histone modifications play significant role in nucleosome remodelling (50, 79).

3. EPIGENETIC REGULATION OF GERM CELL DEVELOPMENT

In developing testes and ovaries, specialised cells that produce sperm or eggs (oocytes) in male and female respectively are referred as germ cells. Differentiation of germ cells into gametes (gametogenesis) and reunion of gametes (fertilization) to form embryos is associated with dramatic cellular differentiation accompanied by vigorous changes in gene expression, regulated by epigenetic mechanisms (80). In normal cells, epigenetic modifications are reversible and allow change of gene activity when necessary. This occurs extensively in developing germ cells in which epigenetic information is re-set to instrument the sperm and egg with appropriate epigenetic information for directing embryonic and post-natal development in the offspring (81). Central event in the formation of gametes is meiosis, which involve histone modifications when homologous chromosomes pair and recombine and chromatin is repressed by meiotic silencing at unpaired regions. Further, male and female germ cells are differentially marked by parental imprints, which provide genomic imprinting in mammals (82). During development, epigenetic profile of germ cells changes dynamically and remains involved in accession of the capacity to support zygote to embryo development (83). Primordial germ cells (PGCs) are founder cells of the germ line and may be the embryonic precursors of gametes. During relocation to the developing gonads, PGCs experience genome-wide reprogramming which is a crucial event to reunite parent-specific epigenetic information and is important for organization of sex-specific germ line development and identity (84–86). However, epigenetic programming is susceptible to alteration by various factors. Altered epigenetic states can be transmitted to the next generation and may affect health and development of offspring, may contribute in the developmental origins of health and disease (DOHaD) (87–89).

3.1. Spermatogenesis

Spermatogenesis is a three-step process consisting of spermatogonial proliferation, spermatocytic meiosis and spermiogenesis. During spermatogenesis highly compacted paternal DNA (that remain in the sperm head) passes through extensive remodelling to form inactive heterochromatin and those heterochromatins gradually aggregate to reach

a highly condensed form in the sperm head (90–93). The genome of spermatids compacted in the sperm genome owing to substitution of histones by non-histone proteins, during which histones are first replaced by transition proteins (TNP1 and TNP2) and eventually by protamines (P1 and P2). This is the reason why sperm genome is transcriptionally inert, since protamine-bound structure is 6 to 20 times more compact than histone-bound structure. Additionally, human sperm carries various types of RNA molecules, including more than 100 types of miRNAs (94–96). Thus, disturbance at any step in the epigenetically highly regulated process of spermatogenesis may lead to male infertility. In addition to packaging of DNA into the spermatid nucleus various epigenetically driven processes linked to spermatogenesis are chromosome condensation, XY body formation and retrotransposons silencing (97, 98). Before spermatogenesis, within the PGCs and prospermatogonia silencing of transposable elements (TEs) takes place which are pieces of mobile DNA and include DNA transposons, long terminal repeat (LTR) retrotransposons, long interspersed nuclear elements (LINEs) and short interspersed nuclear elements (SINES). TEs comprise 45% of human DNA and unless silenced via methylation facilitated by DNMT3L, their movement may be mutagenic and may cause chromosome breakage, improper recombination and genome rearrangement (91, 99–102). In male germ cells, paternally imprinted genes subjected to monoallelic expression are silenced via methylation and express only from the allele inherited from maternal source, proving that genomic imprinting is an epigenetic phenomenon. Therefore, certain genes are expressed in a parent-of-origin-specific manner (21, 103). During spermatogenesis, an epigenetic mechanism termed meiotic sex chromosome inactivation (MSCI) occurs which is distinct from X inactivation in female somatic cells and leads to inactivation of most genes on the X and Y chromosomes. Furthermore, piRNAs has been identified to be exclusively expressed during spermatogenesis (104–106).

3.2. Oogenesis

Oogenesis is the maturation of female gametes by meiotic division. During oogenesis DNA incorporated with histones having PTMs (those modifications were achieved during oocyte growth) that arrest it *in* metaphase of *meiosis II* (82). Oocytes nuclei lack of H1 linker histones and compensated with a specific H1 variant whose role in embryogenesis is yet to decipher (107). It is reported that epigenetic modifications are necessary for post implantation development, which takes place during a specific phase of oocyte growth (108). Chromosome segregation and kinetochore function is regulated by histone deacetylase 2 (HDAC2) via H4K16 deacetylation and occurs during oocyte maturation (109). Chromatin organization, histone methylation and expression of certain genes play significant roles during follicle maturation that require development of oocyte (110). Methylation of H3K9me1 and H3K9me2 for early oocyte meiotic progression is mediated by euchromatin histone-lysine N methyltransferase 2 (EHMT2) (111). Ubiquitination of histone H2A is coupled with transcriptional silencing of large chromatin areas during meiotic oocyte (112). Genomic imprinting in the oocytes occurs after birth which is stopped at the diplotene stage of prophase I and completed in the fully-grown oocyte stage by *de novo* methylation process (83, 113). Thus, production of gametes requires orderly and extensive epigenetic reprogramming in premigratory and migratory germ cells with an appropriate epigenotype to support subsequent normal development (114). However, for epigenetic regulation of oogenesis, whether it occurs via cytosine methylation or not, has wide range of effects on subsequent success of pregnancy and the intrinsic health of offspring. Any aberration in epigenetic regulation is reported to be associated with disease states in adult offspring including type II diabetes, hypertension, cancers and infertility (87, 115).

4. REPRODUCTIVE INFERTILITY

Infertility is one of the major public health concerns. It has significant social and psychological impact and to overcome those it brings economic burden. Almost equal numbers of male and female are infertile. Occurrences and progression of reproductive infertility is reported to be caused by various genetic and epigenetic factors. (10). Any disorder in the regulating mechanisms of gene expression during diseased condition is not clearly understood till date. Various studies have been reported the impact of individual's environment rather than genetic makeup is responsible to initiate reproductive infertility.

4.1. Epigenetic regulation of reproductive infertility

Various histone modifying enzymes like histone de/acetylases and demethylases are recognised to take part in the regulation of chromatin organization and their association and function in diseased condition is really interesting to understand, particularly relating to reproductive infertility. Gene expression is tightly regulated by histone chaperones and methyltransferases via post translational modifications of histone tails (50, 116). The structure of chromatin organisation changes continuously to provide a portion of the DNA strand as active or inactive genome owing to its dynamic and plasticity nature (117, 118). The dynamic structure of chromatin renders a particular part of genome (euchromatin) highly accessible to transcription machinery, which is identified by DNA hypomethylation, RNA Pol II, and histone modifications (23, 119) . Therefore, in the current scenario of epigenetic research (106, 120)

it is important to finding the factors associated with alteration of chromatin organization and their involvement in normal as well as pathophysiological conditions, like reproductive infertility. It will enhance the understanding of molecular mechanisms involved in both normal and diseased states.

4.1.1. DNA methylation and reproductive infertility

Imbalances in DNA methylation of the genome results in human diseases, including reproductive infertility and equal proportion of males and females contribute in the onset of reproductive infertility in human (121, 122). Male infertility owing to DNA methylation seems to be ubiquitous in the sperm genome, including changes in imprinted and non-imprinted genes (123). Impaired spermatogenesis is reported to be associated with incorrect imprinting (124). Epigenetic modifications serve as a crucial role in male infertility by regulating germ cell development and maintenance, for which abnormal imprinting due to dysregulation of DNA methylation is associated with male infertility (125). The sperm with aberrant DNA methylation patterns in imprinted genes generate imprinting abnormalities in the offspring when used in Assisted Reproductive Technologies (ART) (126). Alteration of DNA methylation in the promoter region of *Mthfr* (methylenetetrahydrofolate reductase), hypomethylation in the regions of imprinted IGF2-H19 locus, hypermethylation in the imprinted *Mest*, *Lit1* (Protein LIT-1), *Snrpn* (small nuclear ribonucleoprotein N), *Peg3*(paternally expressed 3) and *Zac* (ADP-ribosylation factor GTPase-activating protein AGD12), as well as altered DNA methylation in various imprinted and non-imprinted genes like *H-Ras*, *Nt3* (3'-nucleotidase), *Mt1a* (metallothionein 1A), *Pax8* (paired box 8), *Diras3* (DIRAS family, GTP-binding RAS-like 3), *Plagl1* (pleiomorphic adenoma gene-like 1), *Sfn* (stratifin) and *Sat2chrm1* (spermidine/spermine N1-acetyltransferase family member 2) are associated with reproductive infertility (122, 127). Paternally and maternally imprinted gene methylation abnormalities have been reported in male infertility phenotype. The association of low methylation or unmethylation pattern at H19 imprinted gene with hypermethylation at the MEST imprinted gene is observed in oligospermic phenotype (128, 129). Impaired DNA methylation observed in male with reproductive infertility might be due to failure of re-methylation in spermatogonia or alterations to methylation maintenance in spermatocytes. In addition, impaired activation of DNMTs results in abnormal DNA methylation patterns (97). Oligoasthenoteratozoospermia and oligozoospermia phenotypes are frequently observed with DNA methylation-mediated genomic imprinting (130). Furthermore, there is report that sperm DNA methylation patterns differ significantly and consistently between fertile vs. infertile and normozoospermic men and DNA methylation patterns may be predictive of embryo quality during IVF (131). Now it can be described as, if epigenetic modifications are key factor in sperm maturation, then any change in epigenetic patterns of men with infertility phenotype may provide a reasonable explanation for complications associated with ART (125, 128).

The chances of accumulating aberrant DNA methylation and propagation of mutations produced due to spontaneous deamination of 5hmC during the prolonged period of replication and cell division are much greater in males than in females (82). Most of the imprinted genes are believed to be epigenetically modified at the time of oogenesis. The expressions of imprinted genes like parental-origin-specific monoallelic genes are regulated by DNA methylation in the differentially methylated region (DMR), and epigenetic modification is independently imposed during oogenesis (103, 132). Imprinted DNA methylation is reported to be acquired during follicle growth from primary to the secondary stage, which correlates to oocyte size with gene-specific kinetics for imprint acquisition in females.

However, to facilitate fertilized oocytes to develop offspring with normal life, DNA methylation should be correctly imposed at imprinting control regions (ICR) of imprinted genes during oocyte growth and maturation. In addition DNA methylation maintenance factors such as Dnmt1, Stella, zinc finger protein 57 (Zfp57) and methyl-CpG binding protein 3 (Mbd3) should be expressed and stored properly. Otherwise, any aberration would results in reproductive infertility (133–135). The *de novo* Dnmt3a and the accessory protein Dnmt3L in mice are reported to be key regulators of DNA methylation that co-operate in *de novo* methylation of DNA in the germ line and recognize the target sequence based on nucleosome modification and CpG spacing. Female mice lacking either Dnmt3a or Dnmt3L are fertile but their heterozygous progeny lacks the maternal imprint and the mice die before mid-gestation. Whereas, male mice that lack Dnmt3a or Dnmt3Lare infertile and oligospermic (23, 136–138). Thoroughly studies are required to decipher how genomic imprinting acquisition in the oocyte changes under female reproductive infertility conditions, as imprints are acquired during oocyte growth. Hence, timely acquisition of correct imprinted DNA methylation patterns in oocytes and the maintenance of genomic imprinting after fertilization are both required for normal embryonic development (139, 140).

Thus, DNA methylation is found to be closely associated with reproductive infertility. Understanding the mechanisms underlying DNA methylation is important in order to develop therapeutic strategies for reproductive infertility owing to abnormal DNA methylation during spermatogenesis and oogenesis.

A number of problems like transgenerational inheritance of human epigenetic genes and the association between DNA methylation and other epigenetic factors are still to be finding out.

4.1.2. Histone modifications and reproductive infertility

PTM of histones play an important and active role in proper cell function. The N-termini of histone tails contain amino acid residues that are affected by methylation, acetylation, phosphorylation, ubiquitylation and sumoylation. The sum of these modifications and the information they communicate is referred to as the histone code which act to inhibit and/or enhance gene expression (50). Improper histone modification is reported to have a significant effect in reproductive infertility in both male and female.

Male human with reproductive infertility shows various aberrant histone modifications in the sperm DNA. Relaxation of chromatin occurs due to histone acetylation that makes it more available for transcription factors while decetylation brings about gene silencing (141). Increased H3K9 acetylation and H3K27 tri-methylation in exons of the *Brdt* gene (bromodomain, testis-specific) leads to reduction in its expression (142). Loss of de-methylation activity on H3K9 causes reduced expression of TNP1 (transition protein 1) and PRM1 (protamine 1) genes required for histone replacement during spermiogenesis (143). Reduced H4 acetylation in spermatids with either qualitatively normal or abnormal spermatogenesis results in infertile phenotype (144). Aberrant acetylation of histones like H4K12ac in promoters of developmentally significant genes leads to an insufficient sperm chromatin compaction, which persist in the zygote (94). HDAC inhibitor trichlorstane is reported to a cause a significant decrease in number of spermatids and severe male reproductive infertility (145, 146). Histone methyl transferases (HMT) or histone demethylase (HDM) catalyze methylation or demethylation of H3 or H4 lysine residues, which promote gene activation or repression respectively. Notably, H3K4 methylation is associated with gene expression, but H3K9 and H3K27 tri-methylation are linked to gene silencing and heterochromatin formation. Further, loss of LSD1/KDM1 an H3K4 HDM during meiosis gives rise to germ cell apoptosis and male infertility phenotype (143, 147). During meiosis, mono, di and trimethylation of H3K4, H3K9, and H3K27 becomes peak, but the removal of H3K9 by the end of meiosis is a must for onset of spermiogenesis, as establishment and removal of methylation markers is critical for spermatogenesis (97, 148). In mice, reduction of H3K4 methyl transferase is reported to cause decrease in number of spermatocytes by an apoptotic process and block development in differentiation of spermatocyte cycle (149). Disruption of JHDM2A causes complete loss of TNP1 and P1 expression along with defective chromatin condensation and reproductive infertility, as JHDM2A is a H3K9 HDM and possesses a targeted action during spermiogenesis in mice (150). Jmjd1a is a key epigenetic regulator expressed in the testis and demethylates mono- and di-methylated H3K9me1 and H3K9me2 but not H3K9me3. Jmjd1a is reported to induce transcriptional activation by lowering histone methylation and increasing histone acetylation, as well as Jmjd1a deficiency causes severe germ cell apoptosis and blocked spermatid elongation, resulting in reproductive infertility in male mice. This is because, recruitment of cAMP-response element modulator (Crem) to chromatin as well as expression of Crem coactivator and their target genes like Tnp1 (transition protein 1), Tnp2, Prm1 (protamine 1), and Prm2 essential for chromatin condensation in spermatids decreases significantly (151).

The crucial role of histone modification and chromatin homeostasis in transcriptional regulation and normal development has been reported in number of studies. During oocyte reprogramming the replacement of histone variant H3.3 has been marked as an essential maternal factor, as well as mouse oocyte-specific knock out Hira (the H3 variant H3.3. chaperone) has been developed to investigate histone turnover during oogenesis. Depletion of Hira in primordial oocytes causes extensive oocyte death and severe defect in development due to lack of continuous H3.3./H4 deposition and ultimately abnormal chromosomal structure. Such defects led to reduce dynamic range of gene expression, production of invalid transcripts and unsuccessful *de novo* DNA methylation highlighting the significant role of H3.3 in oocyte reprogramming (152, 153). During meiosis, histone is deacetylated globally at the meiosis I & II stages by HDAC activity in mammalian oocytes. Various studies reported that aneuploidy occurred in fertilized mouse oocytes which ultimately resulted in embryonic death in the uterus at an early stage of development, if meiotic histone deacetylation is inhibited (154, 155). Kdm3b is a key H3K9 demethylase essential for postnatal somatic growth and female reproductive function. Disruption of Kdm3b decreases IGFBP-3 expression and resulted in fast degradation of IGF-1. In addition, the loss of Kdm3b function also prolongs female oestrous cycle, decreases ovulation capacity, oocyte fertilization rate, embryo implantation, decidual response and embryo growth. All together, these defects in reproductive function result in a female infertility phenotype, owing to association of these defects with extensive alterations of H3K9me1, H3K9me2 and/or H3K9me3 levels in the ovarian and uterine cells where Kdm3 is highly expressed (156).

4.1.3. Non-coding RNAs and reproductive infertility

Non-coding RNAs (ncRNAs) play an important role in epigenetic regulation of gene expression in

addition to their roles at the transcriptional and post-transcriptional level, as well as they play crucial roles in almost all cellular processes in eukaryotes including reproductive infertility (157). Small noncoding RNAs (ncRNAs) play crucial roles in different physiological processes and recent studies shows miRNAs, endo-siRNAs, and piRNAs are expressed in the male germline and essential for spermatogenesis (158). Aberrant expression of small non-coding RNAs mainly including siRNAs, miRNAs and piRNAs is associated with dysfunction of male germlines, such as sperm arrest or apotosis, which further leads to male infertility (159). Furthermore, aberrant expression of specific miRNAs is associated with certain male reproductive dysfunctions like reproductive infertility for which determination of expression of miRNAs may serve as a suitable molecular biomarker for diagnosis of male infertility. Presence of a single nucleotide polymorphism (SNP) at the miRNAs binding site in its targeted mRNA reported to involve in idiopathic male infertility (160). It is evidenced that extracellular/circulating miRNAs are present in various biological fluids. Some of the recent studies reported miRNA profiles in seminal plasma of patients with morphologically abnormal/low motility sperm or Non-Obstructive Azoospermia (NOA) are significantly different from healthy donors. However, the function of aberrant miRNAs in sperm movement, structural integrity, and metabolism is yet to be deciphered. Therefore, miRNA signatures may be used as biomarkers for the diagnosis of male infertility (159). The current understanding of lncRNA regulations in spermatogenesis and male infertility is incomplete. The advancement of molecular biology, genomic technology, bioinformatics approaches and public lncRNA annotation resources allow rapid discovery of potential lncRNA candidates in reproductive infertility (161). Research on ncRNA has been greatly smoothed by advancements in genomic technologies and bioinformatic approaches, which leads to anticipate that more novel species of ncRNAs may be observed in male germ cells to contribute answering the remaining problems in the field of male reproductive infertility (162, 163). On the other hand, role of ncRNAs in female reproductive infertility is still not explored enough.

Nucleosome positioning in the protamine 1 gene has been analysed *in vivo* using rat as a model system and *in vitro* for identification of regulatory elements (164). Various *in vivo* studies reported that histone hyperacetylation occurs during spermiogenesis before the nucleosome disassembly and histone hyperacetylation as well as rapid turnover of acetyl groups and reversibly expose binding sites in chromatin for subsequent binding of chromosomal proteins. It has been shown that histone hyperacetylation facilitated nucleosome disassembly and histone displacement by protamines and hyperacetylated nucleosomes appear in a more relaxed structure (165). Further, sperm DNA is extensively complexed with TNPs in association with nucleosome disassembly (166). Impact of nucleosome position in light of female reproductive infertility still not explored enough.

5. ENVIRONMENT INDUCING EPIGENETIC MODULATION OF REPRODUCTIVE INFERTILITY

The significant impact of epigenetic mechanisms for reproductive infertility is related by the fact that many environmental insults can induce epigenetic alterations. Various environmental and lifestyle factors (stress, physical activity, alcohol intake, smoke, and disrupted biological clock due to shift work) are known to affect male and female reproductive fertility; and in several cases they influence epigenetic modifications with implications for human diseases (167, 168). The significant effect on an individual infertile phenotype due to his/her genetic predisposition or his/her exposure to environment concluded that genetic factors do play a part in infertility. This develops the possibility of a connection between infertility and one's socioeconomic status and particularly the environment (169). In addition, a study concluded that the environment or genetic makeup of individual twins did not have a significant effect on any one twin having infertility, but that conditions and factors unique to individual twins could be associated with the reproductive disorder, although it did not rule out an indirect effect of one's environment on these factors (170). Thus, a link between epigenetic mechanisms specific to each individual and the onset of infertility phenotype is established, which suggest that epigenetic factors including DNA methylation and chromatin state, unique to each monozygotic twin could be attributed in part to their infertile state (171, 172). Different studies in animal models has been reported the presence of an environmental epigenetic inheritance through gametes, as well as food or physical activity can influence histone modifications and miRNA expression. Some foods (cruciferous vegetables) reported to inhibits HDAC activity in mononuclear cells of peripheral blood promoting H3 and H4 acetylation, cigarette smoke causes a down-regulation of mir-34b, mir-421, mir450-b, mir-466, and mir-469 (173–175). Alterations of DNA methylation due to environmental effects demonstrated to be induced in specific genome regions by toxic chemicals, high intake of alcohol and mother's diet, or smoking during intrauterine life (176, 177). The role played by paternal exposures to various pollutants and lifestyle-related conditions on the health status of the offspring and of the future generations.

Environmentally induced developmental defects associated with reproductive infertility are due to *in utero* exposure to phthalates, vinclozolin, bisphenol A (BPA) and diethyl stilbestrol which induce a variety of abnormalities in the reproductive tract of adult males

that resemble the pathophysiological features of Testis Dysgenesis Syndrome (178–181). Although, majority of case do not include assessment of epigenetic alteration, the persistence of effects throughout the life induced during development suggests involvement of epigenetic mechanisms. Further, environmentally induced epigenetic modifications associate with male infertility are exposure of adult male rats to different doses of butyl-paraben and exposure of adult male mice to methoxychlor which shown to alter DNA methylation in sperm (182–184). Exposure of neonates to bisphenol A (BPA) is reported to alter DNA methylation pattern of IGF2-H19 imprinting control region in sperm, as well as estrogen receptors alpha and beta in testis. Decreased spermatogenesis and sperm DNA methylation changes in imprinted genes owing to prenatal exposure of ethanol. (185–187). Besides, it is evidenced that an early developmental exposure to the fungicide vinclozolin increases spermatogenic cell apoptosis and alters sperm DNA methylation (122). Majority of environmentally induced epigenetic alterations associated with infertility are described in somatic cells supporting spermatogenesis, such as Sertoli and Leydig cells. Exposure to cadmium and either low or high doses of arsenic are reported in alteration of DNA methylation (188, 189).

The role of ionizing radiations in epigenetics of reproductive infertility has been recently invoked as a risk factor for alterations of DNA methylation. Radiations trigger a series of processes on the cells as genotoxic alterations, including intra- and inter-strand adduct formation leading to DNA breaks. However, the actual mechanism leading to a transgenerational effect is still to be elucidated. It has been reported that epigenetic mechanism of transmission of the radiation-exposure signal through sperm of irradiated mice involving altered DNA methylation and DNA repair processes, would introduce the persistence of instability in the germ line of unexposed offspring could be responsible of mosaicism in germ cells (190). A critical role in transgenerational radiation effects, like genomic and epigenomic instability could be played by piRNA pathway associated in maintenance of genomic stability by facilitating DNA methylation of transposable elements and also implicated in other epigenetic alterations, which affect a variety of cellular processes (191).

6. NUTRITIONAL FACTORS INDUCING EPIGENETIC REGULATION OF REPRODUCTIVE INFERTILITY

Nutritional factors play an important role in inducing epigenetic alteration in germ line and gonad development. Studies in mice have shown that dietary factors can change the epigenetic landscape in developing germ cells. However, the dietary factors do not directly lead to epigenetic changes but modulate the associated epigenetic enzymes (18). The expression of histone deacetylase, NAD-dependent protein deacetylase sirtuin 6 encoded by Sirt6 gene was significantly reduced in chronic high-fat diet and resulted in an increase of histone acetylation in elongating spermatids in mice (192, 193). During early phase of human spermatogenesis no role for TET enzymes has been suggested by the observation that 5-hydroxymethyl cytosine levels were low while 5-methyl cytosine levels remain constant. However, TET enzymes were successively expressed during late phase of human spermatogenesis, starting with TET2 in late pachytene spermatocytes and followed by TET1 and TET3 in step 1 and step 3 round spermatids respectively (194, 195). Further, paternal diet has a significant effect on germ line, observed from the influence played by paternal diet on gametogenesis. It has been evidenced that male mice fed with low-protein diet produce offspring with higher expression of genes involved in the synthesis of lipids and cholesterol suggesting cholesterol and lipid metabolism in an offspring can be strongly affected by paternal diet. However, sperm epigenome is not affected by diets and the changes in relatively few loci can have profound effects in the developing animal (196).

A recent study demonstrated that *in utero* undernourishment perturbs adult sperm methylome, suggesting alterations in gamete methylation could induce alterations in chromatin architecture, transcriptional networks differentiation, tissue structure and in turn is able to contribute in the intergenerational transmission of environmentally induced diseases (197). It has been evidenced that an association with chronic diseases (coronary heart disease, atherogenic lipid profile, obesity, raised levels of plasma fibrinogen, and decreased levels of factor VII), in adult life of the offspring strongly related to the timing in gestation of exposure to malnutrition (famine). Periconceptional exposure to malnutrition (famine) developed an under-methylation (likely related with low levels of methyl donor, SAM) in the DMR of the maternally imprinted *IGF2* gene, suggesting early under nutrition can cause epigenetic changes that persist throughout the life. On the other hand, there was no variation in *IGF2* methylation status in individuals exposed to malnutrition (famine) in later gestation (198–200). Recently, it has been reported that prenatal malnutrition-associated DMRs (P-DMRs) mostly occur in regulatory regions of genes showing differential expression during early development. (201). Limited availability of food during the father's pre-pubertal age was related to low cardiovascular disease mortality of the proband, while paternal grandfather exposure to a surfeit of food during the prepuberal age was related to increased diabetes mortality of the proband, suggesting an indirect impact of epigenetic inheritance in regulation of reproductive infertility (202, 203). Furthermore, nutrition during early development influence DNA methylation as one-carbon metabolism is dependent

on dietary methyl donors and on co-factors such as methionine, choline, folic acid and vitamin B-12 (204). Deficit in folate or its supplement caused epigenetic alterations due to decrease in DNMT1 activity (205, 206). Maternal behaviour although not directly regulated by nutrition, also programs the epigenetic DNA methylation and histone acetylation of the gluco-corticoid receptor gene in the hippocampus and determines the stress responses of the offspring (207, 208). Besides, alterations in the quantity of food consumed or the composition of the diet imposed solely during the preconception period affect oocyte maturity, blastocyst yield, prenatal survival and the number of offspring born alive as well quality of embryos and resultant offspring. Increasing evidence from a variety of species shows preconception nutrition can alter behaviour, cardiovascular function and reproductive function throughout post-natal life (209).

7. SIGNIFICANCE OF EPIGENETIC MODIFICATIONS FOR GAMETES

Epigenetic modifications are potentially reversible and alterations in DNA and histone methylation, histone acetylation and phosphorylations cause alteration of chromatin structure affecting gene expression culminating into changes in physiology, behaviour or phenotype. Some of the those modifications are heritable (210). Inheritance of persistent epigenetic modifications is referred to as epigenetic reprogramming (211). Gametogenesis is an important and crucial time, during which epigenetic reprogramming occurs and is essential for the imprinting mechanism that regulates the differential expression of paternally and maternally derived genes (212). After demethylation, which ensures genetic totipotency, CpG methylation of imprinted genes is re-established during gametogenesis through *de novo* methylation, in both eggs and sperms (213, 214). Established imprints are maintained in the embryo and further through all somatic cell divisions (103). Alterations of epigenetic modification takes place at each cell division and molecular blueprints are provided to the genome of germ cell for oocyte activation and embryonic development (215). Thus, alterations of epigenetic modulation status of gametes have an important role in normal development and diseases. Imprinted genes possess trans-generationally stable DNA methylation patterns indifferent to normal resetting which happened early in normal development (216). Imprinted genes possess molecular memory of their germ line, associated with a variety of allelic DNA methylation patterns affecting genotype. Imprinted epigenetic marks avoid normal epigenetic purging process, which occurs during gamete formation and transfers from parents to progeny through gametes. Epigenetic tags associated with a particular epigenetic profile avoid erasure during reprogramming for its passage to the next generation (87, 217).

7.1. Male gametes

Various epigenetic modifiers, including DNA methyltransferases, histone-modification enzymes and their regulatory proteins take active part in germ-cell development although some are specifically and others are more widely expressed in germ cells. Knockout studies have revealed critical role of some germ-cell-specific genes like Dnmt3L and Prdm9 (83). Different studies show the existence of a number of intra- and inter-individual differences in DNA methylation in human sperm samples that contribute to distinguish phenotypic character in the next generation (218). DNA methylation is a major mechanism by which epigenetic regulation occurs in gametes and embryos, and the maintenance of methylation patterns on DNA depends on different DNA methyltransferases. Several genetic diseases have been associated with DNA methylation defects, including ICF, RTT, X-linked dominant mental retardation, nonspecific X-linked mental retardation, and ATRX. Imprinting disorders can cause epigenetic alterations and may be due to gene defects (LIT 1, H19, IGF2, UBE3A, and RB1), deletions (15q-13), or UPD. (21, 219). The genome undergoes significant changes at the time of male gamete differentiation which affect DNA sequence and genetic information via homologous recombination as well as alter its nuclear structure and epigenetic information (103). Further, essential role of protamines 1 (P1) and 2 (P2) for sperm function shows haploinsufficiency of either one results in a reduced amount of the respective protein. The P1/P2 ratio in fertile men lies close to 1.0. and ranges from 0.8. to 1.2. Perturbation of this ratio, in either direction, is characterized by poor semen quality, increased DNA damage, and reproductive infertility (220). Knockouts of some imprinted genes mouse show significant neurologic defects ranging from abnormal maternal behavior (Peg3 and Peg1) and impaired memory (Grf1 and Gabrb3) to motor dysfunction with seizures (Ube3a) (221).

7.2. Female gametes

Significance of epigenetic modifications in female gametes is not yet well studied. However, some studies reported the effect of nutrition, environment and maternal socioeconomical status in epigenetics of female gametes which passes to the offspring. In females, random X-chromosome inactivation is started during gastrulation in the epiblast through the X-inactive specific transcript (Xist) gene, which encodes a long non-coding RNA that silences the X-chromosome transcribing it (222, 223). Epigenetic effects of periconceptional diet on DNA methylation shows altered nutritional status of mothers during seasonal changes, which results in epigenetic variation in three germ layers of offspring born during different seasons and these changes persist through adulthood (224). Smoking habit of mother can cause altered DNA

methylation and miRNA expression of gamete (225). Maternal psychological health also exerts a powerful influence over the epigenetic outcome in offspring. Domestic violence triggers stress in women. This type of stress resulted in epigenetic changes in the DNA of the cortisol receptor in offspring observed during adolescence (226).

8. EPIGENETICS AND EARLY EMBRYOGENESIS

Cell division and differentiation during embryogenesis follow highly regulated patterns and influenced by genetic and epigenetic mechanisms. Human genome undergo genomic reprogramming during embryogenesis involving global changes in DNA methylation which play an important role in developmental regulation of gene expression (227). During early embryogenesis, major part of the genome undergo demethylation and subsequent remethylation process, which contribute to chromatin decondensation and transcriptional activation of genes essential for embryo development (20). Two important epigenetic reprogramming that occur during embryo development, one at the formation of PGC and another in the early embryo soon after fertilization. Both events re-establish the epigenetic landscape to a ground state, from which differentiation of progressively more advanced lineages can takes place (228, 229). In both reprogramming events, there exist some similarity and intense changes are observed in a range of epigenetic properties which results in extremely different developmental outcomes (230). Isolated ICM cells or PGC are capable of becoming incorporated into all the tissues of the offspring's body if reintroduced into the early embryo (231). PGC-like cells can be formed from embryonic stem cells (ESC), which is originated from the ICM and when injected to the gonads readily differentiate into gametes, suggesting epigenetic ground state of PGC and ICM cells of early embryo are similar enough to allow same developmental outcomes if subjected to same environment (86, 232, 233). Gonadal pluripotent cells receive positional information and regulate alteration of epigenetic modification to induce cascade of differentiation, which leads to the formation of gametes. However, gonadal pluripotent cells receive different positional information if placed in the early embryo, which results in different epigenetic modification and their consequent differentiation along with a normal embryonic lineage (234). Thus, the cross talk between epigenetic landscape developed in a cell and their developmental fate, is regulated by environmental cues provided by their position within the space-time dimension of embryo development (235). Aberrant or incomplete epigenetic reprogramming at the preimplantation embryo stage or earlier may result in developmental delays and embryonic lethality. Lack of epigenetic erasure may not give rise to phenotype changes in the affected offspring but could be transmitted to the next generation, suggesting the impact of aberrant/error epigenetic modification during embryogenesis determine mortality and fertility ability of offspring (219).

9. ALTERATION OF EPIGENETIC MODIFICATIONS AFFECTING OFFSPRING

Offspring born with aberrant epigenetic modification may show anomaly character in reproduction at adult condition and ultimately results in infertile phenotype, since, germ cell development and early embryogenesis are critical stages when epigenetic patterns are initiated or maintained (169, 221, 236). Few genes in mammals termed imprinted are tagged with their parental origin that results in expression of only a single parental allele which depend on the epigenetic machinery for their initial designation of parental identity as well as establishment and maintenance of their parent-of-origin-specific gene expression. These monoallelically expressed, imprinted genes are reported to be significantly involved in fetal development, reproduction, and reproductive outcome (237, 238). Aberrant regulation of imprinted genes is associated with disturbed development and cause of various human disorders. The first report in humans occurred in Prader-Willi syndrome due to a paternal deletion of chromosome 15 or uniparental disomy 15 (both chromosome 15s from only one parent) and similar genetic disturbances were reported later in Angelman syndrome (239). Reprogramming of epigenome and imprinted loci during gametogenisis and preimplantation embryonic stage is essential for maintaining the pattern of proper inheritance, specifically at imprinted loci (219). It is evidenced that deregulation of imprinted loci has been associated with defective offspring in mice such as disruption of Igf2 imprinted region results in retarded offspring and loss of Igf2 imprinted region results in Beckwith-Wiedemann syndrome (240). Further, recent studies suggest that epigenetic mechanisms may be altered in aging oocytes, with age affect expression of DNA methyltransferases, which results in loss of DNA methylation patterns most notably for imprinted genes and is lethal to mouse embryos (241). One of the recent study has been reported that, obesity-related DNA methylation at imprinted genes in human sperm. According to Newborn Epigenetics Study (NEST), imprinted gene *IGF2* in children from obese father harbours decreased DNA methylation within its differentially methylated region (DMR). Abnormal DNA methylation has been reported in the DMRs of six out of 12 imprinted genes, such as hypomethylation at *MEG3*, *NDN*, *SNRPN* and *SGCE/PEG10* and hypermethylation at *MEG3-IG* and *H19* (242, 243). Long term cohort studies looking at the incidence of imprinting disorders and the use of ART have failed to draw a significant relation between the two, since,

gametes and embryo epigenetic reprogramming affect developmental outcome owing to use of assisted reproductive technologies (219, 244). Thus, remarkable mechanisms involved in regulation of imprinted loci may further help in identifying their role in proper parental inheritance of expression pattern of imprinted genes and their possible anxious state associated with the infertility phenotype (245).

10. CONCLUSION AND FUTURE PROSPECTS

Deciphering, interpreting and impact assessment of alteration of epigenetic modification in reproductive health is important to explore the cause of reproductive infertility in human. It is also important in case of livestock animals, especially, in goat farming. The basis of reproductive fitness seems to be shaped by different sets of consecutive epigenetic modifications. Exploring the epigenetic mechanisms responsible for infertile phenotype with increased pericentromeric blocks of heterochromatin on chromosomes 9 and Y, both locally or globally may further help to characterise the disorder at both genetic and epigenetic levels. The transmission of wrong information to the offspring is prevented by reprogramming events in reproduction, which ensure correct establishment and maintenance of epigenetic marks in germ cell development and early embryogenesis. Nutritional and metabolic factors reported to regulate cellular microenvironment during development and later stages in life owing to their crucial impact on epigenomic scenario. Identification of epigenetic markers in gametes together with detection of windows of exposures during germ cell development, which are sensitive to environmental factors, might hold great promise in predicting susceptibility to certain non-genetic diseases in offspring. Altogether, liability developed due to error/loss of critical steps in differentiation results in reproductive infertility and imprinting disorders. Still it is not reported the level upto which alteration of epigenetic modification can develop reproductive infertility, although studies using newer technologies are now able to finding and understand the potential mechanisms associated. The successful and widespread performance of ART to treat reproductive infertility suggests deep analysis and finding from epigenetic perspective, in addition to comprehensive strategy and planning to address nutrition, environmental factors, and in vitro embryo production.

Development of advanced methods to enhance the understanding of gene regulatory mechanisms affecting human reproductive infertility and outcome may support to improve rates of pregnancy using ART and provide better treatment options for phenotypes with reproductive infertility. Introduction of new or aberrant epigenetic marks at wrong site and undesired time during reproduction can adversely change normal development and growth, and hence, signifies importance of epigenetics in maintaining normal development and reproduction. Therefore, an individual might be susceptible to epigenetic reprogramming errors during the reestablishment of genome of gametes in zygotes, which differentiate into various types of tissue. Whereas, possibility of the activity of certain genes and pathways can be regulated by therapeutic approach owing to reversibility of epigenetic marks, which suggest to target epigenome for drug development. Finally, deciphering the whole epigenome associated with reproductive maturity and infertility would help us tremendously to tackle and treat the problems adopting easiest methods, rehabilitation to normal environment and adequate food supplement. Many dietary food component may help fix those aberrant epigenetic modifications into the normal state due to reversible nature of epigenetic modifications.

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Abbreviation: DNMTs: DNA methyltransferases; TET: ten-eleven translocation; SAM: S-adenosyl-L-methionine; PTMs: post-translational modifications; PGCs: Primordial germ cells; PTGS: post-transcriptional gene silencing; RITS: mRNA-induced transcriptional silencing; DOHaD: developmental origins of health and disease; TEs: transposable elements; LINEs: long interspersed nuclear elements; MSCI: meiotic sex chromosome inactivation; HDAC: histone deacetylase; EHMT: euchromatin histone-lysine N methyltransferase; ART: Assisted Reproductive Technologies; ICR: imprinting control regions; HMT: histone methyl transferases; HDM: histone demethylase; ECS: embryonic stem cells; NEST: Newborn Epigenetics Study

Key Words: Epigenetics, DNA methylation, histone modification, non-coding RNAs, DNMTs, Germ Cell, Spermatogenesis, Oogenesis, Reproductive Disorder, Infertility, Nutrition, Environment, Offspring, Review

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