Chapter

Epigenetics in Reproductive Aging: Involvement of Oxidative Stress

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Abstract

Epigenetic alterations are one of the distinctive characteristics of aging. Epigenetics changes throughout the reproductive life of humans. The major epigenetic parameters viz. DNA methylation, histone modification, and chromatin modeling are altered in the oocyte and sperm due to aging. Also, aging is accompanied by oxidative stress resulting in oocyte and sperm DNA damage. Oxidative stress occurs when the body's antioxidant defense mechanism is overwhelmed by free radicals or pro-oxidant molecules such as nitrogen and reactive oxygen species, which are generated during normal cellular metabolism. This phenomenon is accompanied by a decline in the cell repair machinery, resulting in a wide range of DNA damage and distortion in cellular epigenetics. Still more, free radicals can directly or indirectly interfere with some epigenetic processes of the cell. For example, free radicals can impart the genome methylation profile by forming oxidized DNA lesions. Given the deleterious impact of oxidative stress on aging and cellular epigenetic profile, the ingestion of external antioxidants is encouraged to circumvent its side effects. This chapter provides insight into the interconnection between epigenetic alterations (histone modification, chromatin remodeling, DNA methylation and miRNA), reproductive aging, and oxidative stress.

Keywords: epigenetics, aging, reproduction, oxidative stress, DNA methylation, histone modification

1. Introduction

God blessed them, and God said to them, 'Be fruitful and multiply, and fill the earth' (Gen. 1:28a). Reproduction, a vital characteristic of life is a biological process by which new organisms (offspring) are made from their parents. Simply put, organisms replicate themselves via reproduction either sexually or asexually. For sexual reproduction, a new individual is made by the combination (union) of two gametes or sex cells - sperm and eggs (or ova) while in asexual reproduction, organisms make genetically identical or similar copies of themselves without contributing any genetic resources from another organism. In humans, reproductive functions diminish with age. It stops abruptly in females at menopause while in males it gradually declines. Aging is therefore an unavoidable and unappeasable natural process markedly disproportional gender-based impressions on human fertility. Epigenetic alterations are one of the distinctive characteristics of aging, epigenetics changes throughout

the reproductive life in human. In human, oxidative stress (described when there is an imbalance between the antioxidant defense system and pro-oxidant molecules - nitrogen and reactive oxygen species) play a major role in both male and female reproduction. Oxidative stress has adverse effects on both female and male gametes and the developmental capacity of embryos [1] . For instance, sperm quality and functions in males (characterized by immature and morphologically abnormal spermatozoa as well as infected white blood cells in the seminal ejaculates) are adversely affected in conditions of oxidative stress while in females, oxidative stress is involved in a number of age-related reproductive diseases such as endometriosis, tubal and peritoneal factor infertility, polycystic ovary syndrome (PCOS), ovarian cancers, and unexplained infertility. Furthermore, complications from pregnancy such as recurrent pregnancy loss, spontaneous abortion/still birth, hydatidiform mole, and pre-eclampsia have been linked to oxidative stress in females [2, 3]. All these alterations (aging) in the reproduction characterized by a progressive loss in both physiological and cellular functions are possible because of the enforced aging caused by oxidation stress that may be induced by various social habits and environmental factors [2]. The role of epigenetics has been suggested as one of the molecular mechanisms linking stress and aging by manipulating genomic function and phenotypic composition, such as aging-related consequences. Moreover, epigenetic modifications (covalent modifications of DNA and key histones that modulate activity of gene without altering the sequence of DNA) and chromatins aggregation play a vital role in reproductive aging [4]. For instance, in male, epigenetic mechanisms involved in the regulation of oxidative stress in the male reproductive system are crucial in spermatogenesis to keep testicular homeostasis through the modulation of molecular pathways. Also in females, alterations in epigenetics and its associated enzymes such as alterations in the levels of DNA methyltransferase (DNMT), DNA methylation as well as histone acetylation and methylation patterns adversely affect the oocytes [5, 6]. Put together, epigenetic modifications could affect gametogenesis as well as the embryo development since they involve germ cells and can therefore be transmitted to the offspring [7]. Since aging has been linked with epigenetic and reproductive alterations as well as increase in oxidative stress, which results in profound biological consequences, this chapter shall discuss the interconnection among epigenetic alterations (histone modification, chromatin remodeling, DNA methylation and miRNA), reproductive aging, and oxidative stress.

2. Reproductive aging

Aging, an unavoidable and unappeasable natural process, has markedly disproportional gender-based impressions on human fertility. As human age, their reproductive functions diminish. Both male and female sex hormones diminish with age. While the male sex hormones (androgens) and their breakdown products diminish gradually over the age span 50–90, the female sex hormones (estrogens) fall significantly at menopause. Moreover, in both males and females, sexual activity is reduced progressively between the ages of 20 and 60 [8, 9].

In the practical sense, all males between the age of 20–45 have some level of sexual activity. However, the frequency of intercourse in males may fall from an average of four per week in 20-year-olds to one per week in 60-year-old. This means that there is loss of sexual activity in males in only about 5% of the ages between 45 and 60. Moreover, there are certain systematic studies with reports of sexual behavior in

individuals above 60 years of age even though at least some males remain sexually active at age 90 according to clinical reports. By comparison of sexual activity in both males and females, there are wide individual differences in the level of sexual state of being active and sexual behavior, which is greatly influenced by psychological and social factors than by the levels of sex hormones circulating in the blood. Notwithstanding, the use of male sex hormones has been known with males since time immemorial [10].

The reproductive functions in males (both spermatogenesis and testosterone production), diminish with age even though slowly and to a relatively small degree. Changes associated with aging in the reproductive system of males may include changes in production of sperm, erection, and testicular tissue, all of which are gradual [11]. In human, males do not experience a major, rapid (over several months) change in fertility as they age unlike like menopause in females. The changes in males are associated with a steady and gradual process regarded as andropause. The testes are the primary organ in the male reproductive system where the change in aging takes place. The testes are the organ saddled with the function of making the male sex hormones (testosterone), the level which decreases with aging during which erection problem may arise. This process is however, a typically slow rather than a sudden and complete lack of function [12]. With aging, the testes can actually continue to make sperm but at a much slower rate of producing viable sperm cells. Also, other accessory organs of male reproduction function at a reduced rate; the epididymis, seminal vesicles, and prostate gland will continue to produce the fluid for easy sperm movement even though they lose some of their surface cells with aging. When all these occur, a condition known as sclerosis sets in such that the tubes that carry sperm may become less elastic. While a fall in testosterone level may be associated with primary hypogonadism in some men, it may be linked with secondary hypogonadism, accompanied by illness in other men [11]. Basically, a fall in the production of testosterone is concomitant with certain consequences such as diminished sexual function, mood, energy, bone density, and muscle mass. Therefore, energy or cognitive function are not improved by increasing the serum testosterone of older men with low testosterone to that of young men even though bone density, sexual function, mood, walking, and ultimately sexual function are well improved [13, 14].

In females, they often experience sudden loss of fertility between 30 and 40 years of their age. Within this age, females have a significant increase in the chances of having chromosomal defects in offspring, preterm delivery, spontaneous abortions, and intrauterine growth restriction (IUGR). This is accompanied by the onset of menopause [15, 16]. Contrastingly, this is not the case in males where the impact of their aging has not received much attention like that of female yet have the more striking negative consequences on the process of aging [17].

Reproductive aging in females ends in menopause as a result of natural processes in the hypothalamic–pituitary–ovarian (HPO) axis. At menopause, the HPO axis is in a state of hypergonadotropic hypogonadism. This reflects a minimal ovarian estrogen production and an accompanying increase in pituitary gonadotropins. Most women become aware of reproductive aging by alterations in menstrual cyclicity or local/systemic symptoms of hypoestrogenism after their final menstrual period between age 49–51. At menopause, changes in the female reproductive organs occur rapidly and when it stops, and the ovaries stop producing estrogen [18, 19].

At menopause, changes in the female reproductive organs occur rapidly and when it stops, and the ovaries stop producing estrogen. Moreover, atrophy sets in after menopause such that the tissues of the labia minora, clitoris, vagina, and urethra

become thin. A resultant effect of such thinning is chronic irritation and dryness of the vagina [20]. In addition, there is a more likely chance of women at this stage to develop urinary tract infections and vaginal discharge apart from the fact that the ovaries, uterus, and fallopian tubes. There is also decrease in the amount of muscle and connective tissue (including that in muscles, ligaments, and other tissues that support the bladder, uterus, vagina, and rectum) with aging.

More importantly, changes in reproductive organs associated with age do not interfere with sexual pleasure even though the dryness of the vaginal after menopause causes pain during sexual activity while there might also be a drop in the desire to have sex in some women [21, 22].

3. Epigenetic changes associated with reproductive aging

Epigenome is an all-important and targets capable of being modified. They include the methylation of DNA, nuclear protein constituents (and detailed modifications to protein tails of histone) and may also include various RNA species. These epigenetic targets have the ability to regulate the expression of gene and being able to be passed onto the embryo proceeding fertilization. The epigenetic profile of cells in the body is unique specific attributed function owing to the role of epigenomes in the regulation of genes. In humans, sperm and egg cells also have these features and this is the basis of the uniqueness of cell type with a highly specialized epigenome well suited for morphologically and functionally distinct attributes [23].

Epigenetics can be described as heritable covalent modifications of the DNA bases and chromatin proteins whereby the DNA sequence is not altered but regulate its transcriptional process by influencing the chromatin structure and transcription factor binding [24]. Epigenetics are vital to the usual development and functioning, and as well as participate as an essential constituent or characteristic in both normal cellular function and disease. Generally, epigenetics changes with age as part of the normal human development or aging, and as a reaction to human behaviors and environment. The three major epigenetic modifications include DNA methylation, histone modification, and chromatin remodeling [25].

As far as human development is concerned, epigenetic changes begin before birth since all cells have the same genes but phenotypically different. Epigenetics determines the functional role of each cell as either a heart cell, nerve cell, or skin cell with growth and development. For example, the nerve cells and muscle cells may have the same DNA, they exhibit different functional roles. While a nerve cell transfers information to other cells, a muscle cell has a structurally helps the body movement. In this regard, epigenetics modulates the muscle cell to turn "on" genes to make proteins important for its job and turn "off" genes important for a nerve cell's function [25].

Also with age, epigenetics changes throughout the reproductive life in human. The epigenetics at birth is different from at childhood or adulthood. For instance, in a study that compared the epigenetics of an infant, 26-year-old and 103-year-old using DNA methylation at millions of sites, it was reported that the level of DNA methylation decreased with age. The infant had the most eminent DNA methylation while the 103-year-old had the most depleted DNA methylation. The DNA methylation level of the 26-year-old was an intermediate of the newborn and 103-year-old [26]. In addition, epigenetics is reversible. There are epigenetic changes that may be gotten rid of or added as a result of behavior or environment changes, an indication that epigenetic changes can be temporal. In a comparative among a smokers, non-smokers,

and former smokers, it was found that smoking can result in epigenetic changes. DNA methylation at specific parts of the *AHRR* gene tend to be lower in smokers compared to non-smokers, while there was a wide difference for heavy smokers and long-term smokers. After quitting smoking, former smokers had increased DNA methylation at this gene and eventually reached similar levels as those of non-smokers [27].

Epigenetic alterations symbolize one of the distinctive characteristics of aging. It is a significant and crucial mechanism associated with the degenerated cellular activities and functions during aging. Epigenetics therefore explains why aging pattern vary between two identical twins. Genomic instability transcriptional drift occur as a result of unevenness in the pattern of epigenetic information within individual cells in the population during aging (**Figure 1**) [28].

Furthermore, the information encoded within different epigenome includes DNA methylation, chromatin remodeling, posttranslational modifications of the histone proteins, structural and functional variants of histones, and transcription of non-coding RNAs (ncRNAs). The combination of all these different types of epigenetic information comprises the function and fate of all cells and tissues [29].

DNA methylation (one of the best-characterized and most widely studied epigenetic modifications during aging) involves adding a methyl group, primarily from S-adenosylmethionine to the fifth carbon position of cytosine bases in the CpG dinucleotide regions [30]. The DNA methyltransferase group of enzymes catalyzes DNA methylation. DNA methylation represses the transcription of a gene by condensing the chromatin structure, preventing transcription factors from binding and decreasing the process of histone acetylation, whereas DNA methylation of the 3' CpG islands activates the transcription of genes. Epigenetic

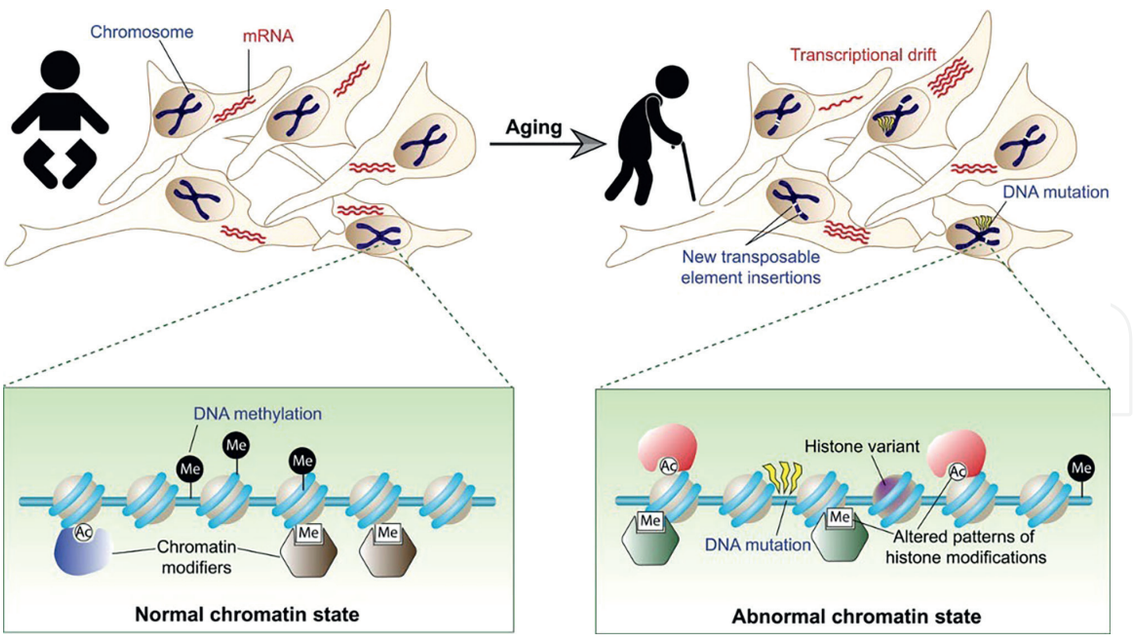

Figure 1.
Summary of epigenetic changes associated with reproductive aging. The cells within each cell type in young persons have an almost the same pattern of gene expression, mostly determined by each cell with related epigenetic information. However, these epigenetic information changes in a sporadic manner as one age because of endogenous and exogenous factors. The resultant effect is abnormal chromatin state with the uniqueness of altered patterns of DNA methylation, incorporated histone variants of different origins, and altered patterns of histone modification, which leads to different chromatin modifiers. Insertion of new transposable elements into the genome and genomic instability (including DNA mutation) is also a resultant effect of abnormal chromatin state in old cells.

drift results to irregular divergences in the methylome among aging individuals. Aging in humans as in all other mammals is associated with hypomethylation of CpG (although with a few exceptions) especially at repetitive DNA sequences. As a whole, age-related DNA methylation changes are more prominent in CpG islands (**Figure 2**) [31].

In addition, epigenetic modifications involves the complexity of epigenetic processes, associated with DNA modifications—5-methylcytosine (5mC) DNA methylation, 5-hydroxymethylcytosine (5hmC) DNA methylation; Histone modifications—Acetylation, Methylation, Phosphorylation, Poly-ADP ribosylation, Ubiquitination; Non-coding RNA interactions—piwi RNA (piRNA), small interfering RNA (siRNA), long non-coding RNA (lncRNA), micro RNA (miRNA); RNA modifications—6-methyladenosine (6 mA) RNA methylation, 5-methylcytosine (5mC) RNA methylation, 7-methylguanosine (7mG) RNA methylation, mRNA CAP, 5-hydroxymethylcytosine (5hmC) RNA methylation (**Figure 3**).

Histone modification occurs in varying forms: acetylation, methylation, phosphorylation, ubiquination, and sumoylation. These forms either repress or activate transcription based on the location of histone modification [32, 33]. Chromatin remodeling is the rearrangement of chromatin from the condensed heterochromatin state to the relaxed euchromatin state, allowing transcription factors or other DNA-binding proteins to access DNA and regulate gene expression. Chromatin remodeling is highly implicated in epigenetics and generally results in transcription activation [34]. Non-histone protein methylation forms another crucial cellular function regulator as post-translational modifications that takes place on proteins and have the ability alter their function. The modifications allow for the addition of methyl groups to lysine or arginine residues of specific proteins. Even though the functional role of

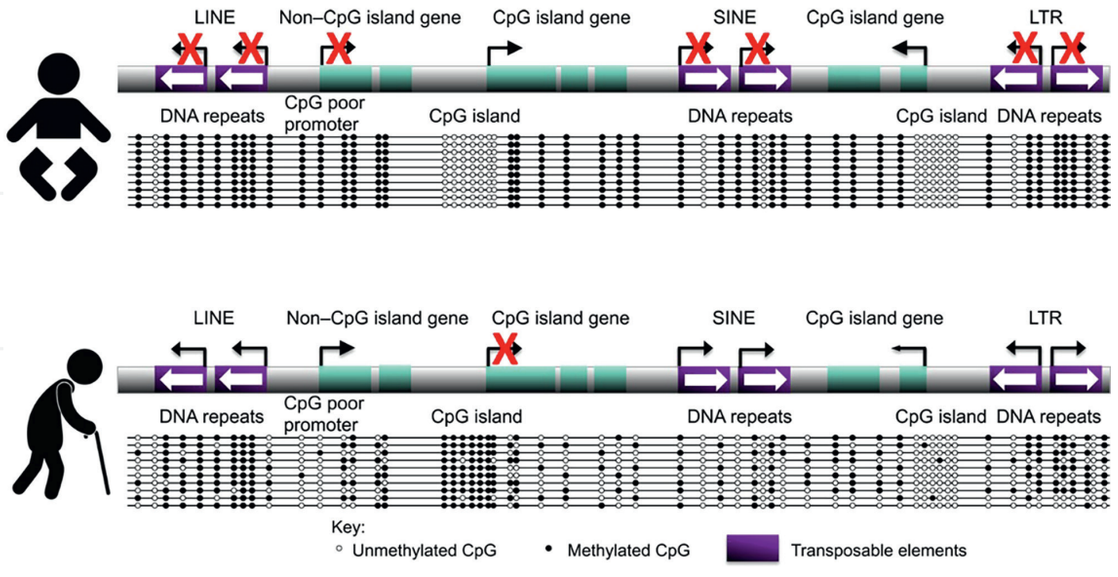

Figure 2.
Summary of changes in DNA methylation during reproductive aging. Young mammalian cells are distinguishable by hypermethylation of DNA over the genome, except for CpG islands within the promoters of expressed genes. DNA repeats (like as LINE, SINE, and long terminal repeat transposable elements) are DNA-methylated to a great extent which aids their upkeep in a state of constitutive heterochromatin. Hypomethylation of DNA (within the cell population in a stochastic manner) generally occur over the genome during aging but the loss of DNA methylation results to the activation of the transposable elements as an example of other normally silenced DNA sequences. Also in a stochastic manner, methylation of DNA increases over the CpG islands of certain genes in relation with their silencing and heterochromatinization.

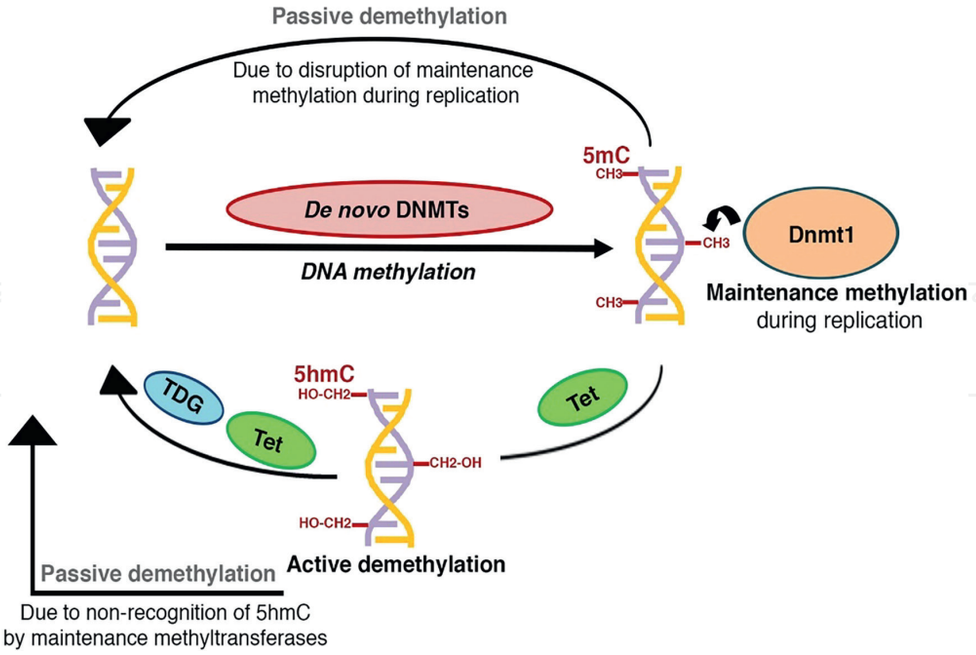

Figure 3.
Schematic illustration of DNA methylation patterning. During development, de novo DNA methyltransferases regulates the formation of new DNA methylation patterns. During regular succession of cell division, DNA methylation patterning is made to continue by activity of maintenance DNA methyltransferases. However, active demethylation [successive enzymatic oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC),5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) by TET (ten-eleven translocation) dioxygenases, followed by thymine DNA glycosylase (TDG) dependent removal of 5fC and 5caC, coupled with base-excision repair to a cytosine (C)] or passive demethylation could reverse DNA methylation marks. A passive demethylation ensues when there an unrecognized hemi-methylated 5hmC by the maintenance DNA methyltransferases because of being diluted and lost during replication. Disruption of maintenance methyltransferase activity can similarly result in replication dependent dilution of DNA methylation.

these modifications is poorly understood, they are more likely to affect the structure and function of DNA, synthesis and metabolism of protein and RNA, as well as apoptosis and cell cycle [35].

3.1 Epigenetic changes associated with female reproductive aging

Epigenetic changes and epigenetic related enzymes in the oocytes of aged females are found to have altered DNA methylation and DNA methyltransferase levels. They also have altered patterns of methylation and acetylation of histone [6].

DNA methylation is catalyzed by the DNA methyltransferase group of enzymes. In mammals, there are five known forms of the enzyme viz.: DNMT 1, DNMT 2, DNMT 3a, DNMT 3b, and DNMT 3 L [6]. DNA methylation occurs either as maintenance or *de novo*. In methylation maintenance, a hemimethylated DNA becomes fully methylated. This process occurs after semi-conservative DNA replication and is carried out by DNMT1 [36]. In *de novo* methylation, a nascent and completely unmethylated double-stranded DNA is methylated. This process is the sole responsibility of DNMT 3a and DNMT 3b. DNMT 3 L does not methylate DNA but facilitates the activity of DNMT 3a and DNMT 3b, while DNMT 2 is separately involved in the methylation of transfer RNA [37].

The levels of DNMT 3a, 3b, and 3 L in developing oocytes have been shown to correlate with their levels of growth and DNA methylation, associating them with a unique role in oocyte development [6]. The pattern of DNMT regulation is altered

with aging, and a decrease in DNA methylation due to decreased level of DNMT transcription is observed in aging oocytes [38].

The demethylation and remethylation patterns of the DNA observed during oocyte development are altered with maternal aging. These alterations have been associated with decreased expression of many important genes. With increasing maternal age, expression was decreased in over 800 genes including many genes that are critical for cell cycle control and meiotic chromosomal segregation and are potential causes of aneuploidy [39].

3.1.1 Alterations of DNA methyltransferase during reproductive aging in females

The class of enzymes involved to add methyl groups to DNA is regarded as DNA methyltransferase (DNMT). DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L are the five types of DNA methyltransferase known with mammals while *de novo* and maintenance methylation are the two types of DNA methylation [40]. There is uncertainty in the levels of the various types of DNMT when an oocyte develops during normal developmental stages from primordial to primary, to secondary follicle, and then from the germinal vesicle (GV) through MII and beyond. The expression of DNMT1 is first noticed in the secondary follicle stage and then at the zygotic stage and beyond [6]. In the case of DNMT3a, the expression is right from the primordial stage while the expression of DNMT3b is from the primary follicle stage. Furthermore, while DNMT3L is found in pre-implantation embryos, DNMT2a is not observed at any stage. Changes are associated with cellular location of the enzymes as either cytoplasmic or nucleic at the different stages of development. DNA methylation and the levels of growth of the developing oocytes have correlations with the levels DNMT 3a, 3b, and 3 L in the oocytes, which is associated with the maturation of the oocytes [38, 41]. Similarly, embryonic death as a result of imprinting failure (epigenetic silencing of either maternal or paternal DNA linked to the expression of just one chromosome for specific trait) associated with lack of methylation are the resultant effects of targeted gene deletions of DNMT3a or DNMT3L. This suggests the crucial function of DNMT3a or DNMT3L as demonstrated in the development of oocytes such that oocytes without DNMT3b do not exhibit grave abnormality [42].

As a female age, the regulation pattern of DNMT is altered. In experimental study on young mice of about 6 weeks old and aged mice of about 45 weeks old using MII oocytes, it was found that there was altered levels of genes transcription (including DNMT1, DNMT3L, and higher levels of DNMT3b transcription) associated with setting up and preserving DNA methylation [6]. In a similar manner, in a study that used 66 weeks old older mice, it was found that there was diminished level of transcription of DNMT3a. Furthermore, the human oocytes from aged females in another study revealed a decreased transcription of the genes associated with the cell cycle checkpoint as well as transcription and the DNA damage repair [6, 43].

Furthermore, it was found that there was a noticeable and obvious decrease in the aged mice of 40 weeks relative to the young ones of about 8 weeks old in the attempt to compare pre-implantation embryos (2 cell, 4 cell, 8 cell, and morula) and levels of DNMT1, DNMT3a, DNMT3b, and DNMT3L in MII oocytes. Such decrease can be linked to a wider reduction in DNA methylation of aging oocytes [38].

3.1.2 Alterations in methylation of DNA during reproductive aging in females

Dynamism is associated with DNA methylation in both early embryos and in germ cells. Methylation of DNA is crucial in aging. The stability and highly methylated

DNA associated with somatic cells afford them the regulations of expression their genes for easy functions specific to tissues. Also, oocytes and sperm exhibit high methylation levels as they go through constant changes all through their development state [44]. At the initial primordial stage, mouse germ cells undergo genome wide demethylation. Oocytes then enter meiotic arrest, and undergo remethylation only after birth, during oocyte growth from primary to secondary follicles. Male germ cells replicate throughout the life of the male and enter meiosis in the adult male. Remethylation in male germ cells occurs antepartum at the pro-spermatagonia stage [45]. Both the maternal and paternal chromosomes are physically separate at post fertilization whereby they undergo varying methylation changes. As for the paternal genome, it is actively-demethylated prior to DNA replication, while a passive demethylation occurs with the maternal genome. As at the blastocyst stage close to the time of implantation, both genomes are again remethylated. This cycle of demethylation and remethylation is crucial for the removal of parental epigenetic modifications to the germ cell genome, and for setting up totipotency in the new embryo [6, 44].

As a female age, these patterns of alterations change. As previously described, it has been demonstrated that level of DNA methylation in older mice of about 40 weeks old were lower than those younger mice of about 8 weeks in a study that compared pre-implantation embryos (2 cell, 4 cell, 8 cell, and morula) and 5-MeC fluorescence intensity in MII oocytes [6, 38]. However, DNA methylation did not produce any noticeable change in the blastocysts and the whole observation was linked to *de novo* methylation that takes place through DNMT3a and DNMT3b before the implantation happens. Furthermore, there were indications that with aging, the usual attainment and preservation of DNA methylation patterning is associated with the capability of embryo to develop to mid-gestation [46, 47]. DNA demethylation is what is achieved as the opposite of DNA methylation is DNA demethylation. DNA demethylation has been found to increase with age, a direct opposite of low levels of DNA methylation associated with old age. This demethylation cascade demonstrated using mouse oocytes can be linked with decreased methylation and increased demethylation [48]. In addition to this, chemically induced accelerated aging as been shown to demonstrate a varying category of demethylation-pathway-intermediates relative to the normal process aging. This may find usefulness in differentiating natural aging from accelerated aging, and importantly help to evaluate the rate of reproductive aging in women to achieve an estimated reproductive longevity [6, 49].

The consequential effect of alteration of DNA methylation in aged females is associated with decreased expression of several crucial genes. For instance, decrease in more than 800 genes (including several important genes for the meiotic chromosomal segregation and control of cell cycle) were found in the aged, analyzed for genetic expression of human blastocysts using single embryo RNA-seq. The crucial role epigenetics plays in normal reproduction was described in all these [39].

3.1.3 Modifications of histone during reproductive aging in females

Acetylation of the N-terminal of histones takes place on lysine (K) residues and promotes transcription. Methylation of histone occurs on lysine or arginine residues. Depending on location, histone modification function to either help in transcription suppression or promotion. While the transcription suppression is linked with the methylation of histone H3 K9, transcription promotion is associated with methylation of H3 K4, or methylation of arginine on H3 or H4. Modifications of histone are crucial to normal gametogenesis and just like the methylation of DNA, they are in constant

change during the development of germ cells. Similarity was found in the acetylation of histone patterns in porcine, bovine, and sheep although slightly different pattern were noticed. However, there were relatively stable during oocyte maturation in histone methylation [31].

As a female age just with alteration in DNA methylation changes, the patterns of modification also shift. It was found that the reduced levels of acetylation at H4K12 and H4K16 in aged mice of about 10 months old relative to younger mice of about 2 months old using the germinal vesicle oocytes. In the younger mice, 100% was recorded for both H4K12 and H4K16 as against 67/81 for H4K12 and 55/92 in the H4K16 of the aged mice [6, 43]. Furthermore, 40% of oocytes from older mice were acetylated at H4K12 as against the 100% complete deacetylation at H4K12 of all oocytes from young mice. Moreover, while using an inhibitor of histone deacetylase, Trichostatin A (TSA), corrections were made to errors in acetylation of aging related MII stage related to acetylation of germinal vesicle oocytes [50]. In a similar manner, another evidence was provided in a comparison study of MII oocytes from the same mouse to get rid of genetic interactions. In the 10 months old mice, found higher H4K12 acetylation levels was recorded relative to the 3 weeks old young mice. This further shows the clinical usefulness of H4K12 acetylation levels as a biomarker for oocyte quality [51, 52]. These changes in histone modification results in oocyte dysfunction and infertility. An increased levels of histone acetylation in MII mouse oocytes described the associated between inhibiting histone deacetylase during meiosis, and a high frequency of oocyte aneuploidy and embryo death [53].

The age of oocyte has also been found to correlate with unusual high histone acetylation levels on H4K12 in the MI and MII of human oocytes. This suggests a greater tendency of misalignment among chromosome which may lead to more segregation errors in older oocytes and by implication, becomes a useful clinical tool. In a similar vein, histone modification patterns, particularly histone acetylation and methylation, are markedly altered with maternal aging and can lead to oocyte dysfunction and infertility [54]. The alterations that occur during histone phosphorylation, ubiquination, and sumoylation in the oocytes of older females are still poorly understood but dysregulation in histone ubiquination in aged oocytes has been observed suggesting oocyte dysfunction in aged females [55].

3.2 Epigenetic changes associated with reproductive aging in males

Epigenetic alterations have been associated with the sperm of aged males and are demonstrated to impact male fertility, embryogenesis, and even offspring health [56]. Oakes *et al*. observed that age-associated alterations in DNA methylation occur at specific genomic loci of the sperm of male rats. Other research efforts have also brought to light the profound alterations in DNA methylation that occur in aged spermatozoa [57–59]. However, a consensus on the mechanism of alterations in DNA methylation has not been reached due to the varying experimental approaches utilized by the researchers.

Very limited studies are available on the alterations in histone modification patterns with respect to age. Indeed, only two studies are available where histone modifications in spermatozoa are analyzed in relation to age and certain alterations were observed in the histone modification patterns between young and aged mice [60, 61].

3.2.1 Involvement of epigenetics in spermatogenesis

Mitotic proliferation of spermatogonia, meiotic divisions, and morphological differentiation of sperm precursors (spermiogenesis) are the processes involved to form a matured sperm. These processes are also associated with specialization of cells distinguished by the presence of a head, an intermediate portion, and a flagellum [62, 63]. Such a specific system of arrangement of the male germ cells allows the movement of sperms through a potentially uncongenial female reproductive tract, penetrate the cumulus oophorus and the zona pellucida, penetrate the oocyte, and eventually make a complete multiple post-penetration [64, 65]. Spermatogenesis is initiated in the seminiferous tubules during fetal development from a spermatogonia (undifferentiated diploid cells) which go through some stages of mitotic divisions to make germ cells precursors more available [66]. At maturity in males, there are about three stages of transformation of spermatogonia. During the first meiotic division, some are transformed in type I spermatocytes that produces haploid type II spermatocytes while haploid spermatids are formed during the second meiotic division. The last and third stage portrayed by structural and morphological transformation complex action of the round spermatid is symbolized by spermiogenesis. This last stage of spermatogenesis which ends subsequent cell division forms the mature sperm with definite characteristics of differentiated flagellum and acrosome that forms a vital requirement for motility of the produced sperm as well as the fertilization capacity [67].

3.2.2 Main epigenetic change in sperms: histone: protamine substitution

A well-arranged and coordinated chromatin structure is essential to characterize sperms asides their distinctive morphology and motility. During spermiogenesis sperm chromatin are further condensed due to the substitution of about 95% of the histones with protamines (sperm-specific basic proteins) which leads to disulfide bonds (SS) formation [68]. These bonds give core of the sperm nucleus a high degree of stability responsible for desirable sperm motility, shielding from ROS and toxicants within female reproductive tract, blockage of the transcriptional activity of the sperm DNA, and other notable effects to the sperm [69]. This cascade of reaction of multi-step process of conversion of histone to protamine is highly regulated. At first step regarded as histone hyperacetylation, there is the replacement of the histones in round spermatids by transition proteins (TP, heterogeneous group of nuclear proteins). The second stage has to do with the substitution of TP1 and TP2 with protamines and takes place in elongating spermatids. Protamines in this regard function to ensure the genetic wholeness of the sperm and epigenetic imprinting via making the nucleus more compact. Two types of protamines (the P1 protamine and the P2 family of protamines, made up of P2 as the most abundant, P3, and P4 members) are notably known with nuclei of a matured spermatid [70]. The ratio of P1P2 to play a crucial role in male fertility. For instance, P1/P2 ratio, which in fertile males is close to 1 (range 0.8–1.2), is altered in infertile patients. Therefore, patients having a P1/P2 ratio less than 0.8 demonstrate insufficient DNA condensation and the characteristics of sperm (such as motility, viability, vitality, and counts, and morphology) are resultantly altered. A lower P1/P2 ratios may also be linked with an increased DNA fragmentation, which in contrary manner have correlations with the levels of global sperm P1 and P2 [71, 72]. This confers a protective

S/N	Model(s)	Markers	Epigenetic change noted with reproductive aging
1	*Caenorhabditis elegans*	Reduction in HP1 and H3K9me3, changed lamin A	Reduced global heterochromatin
	Drosophila		
	Human fibroblasts		
	Progeria patient cells		
2	Mice	Increase in HP1 and H3K9me3, as well as increase in macroH2A and HMGA	Senescence-associated heterochromatin foci (SAHF)
	Baboons		
	Human fibroblasts		
3	Yeast	Loss of core histone proteins	Remodeling and loss of nucleosome
	Worms		
	Human fibroblasts		
4	Mouse brain	H3.3, H3.3cs1	Increased histone variants
	Human fibroblasts		
5	Yeast	Increase in H3K4me3 and H4K16ac (globally active marks) and decrease in H3K9me3 and H3K27me3 (repressive marks)	Changed histone marks
	Drosophila		
	C. elegans		
	Killifish		
	Rats		
	Mouse brain		
	Mouse stem cells		
	Mouse fibroblasts		
	Progeria mouse models		
	Progeria patient cells		
	Human fibroblasts		
	Human brain tissue		
6	Salmon	Hypomethylation of lobal DNA, hypermethylation of CpG island	Changes in DNA methylation
	Mice		
	Rats		
	Dogs		
	Rhesus monkeys		
	Human fibroblasts		
	Human stem cells		
	Humans		
7	Yeast	SIRT-1, PARP-1, REST, HDAC-1	Re-localization of chromatin-modifying factors (RCM)
	Mice		

S/N	Model(s)	Markers	Epigenetic change noted with reproductive aging
8	Yeast	H19, Dicer, lin-4, lin-14, mir-34	Changes in ncRNA
	C. elegans		
	Mice		
	AD mouse models		
	Humans		

Table 1.
Epigenetics changed genes in reproductive aging.

role on protamines against sperm DNA damage. Furthermore, a surplus protamine P2 precursors (pre-P2) may be linked with subfertility which alters the process of formation of mature protamine P2 [73].

3.2.3 Methylation of DNA and modifications of histone during spermatogenesis

For thoroughly maturation of gametes in male, there are need for several and specific epigenetic marks during gametogenesis. For instance, demethylation of DNA can be said to be the initial epigenetic occurrences prior to meiosis but during meiosis, the de novo DNA methylation levels are regulated by the activity of DNMT3A, DNMT3B, and cofactor DNMT3L, to complete this process after birth at the pachytene spermatocyte stage [44, 74]. Thereafter, DNMT1 activity maintains methylation profile during which the modification of histone (methylation and acetylation) takes place. This modification eventually alters the DNA accessibility to transcription factors. Most importantly, histone demethylase (HDM) and histone methyltransferase (HMT), specific for this action regulate methylation sequence of histone H3 (H3-K4) and lysine 9 of histone H3 (H3-K9) [31]. In a typical setting, methylation of histone H3-K9 which is eminent known in meiosis is absent at the termination of the process for the promotion of genes. On the other hand, methylation of histone H3-K4 is greatly reduced during meiosis for DNA silencing. Furthermore, HAT and HDAC and other enzymes are involved on the regulation of H3 and H4 lysine residues acetylation and deacetylation during spermatogenesis. In this process of spermiogenesis hyperacetylation of H4 is crucial to make the right conversion of histone to protamine and as well the disassembling of nucleosome seamless in elongating spermatids [31]. **Table 1** gives summary of epigenetics changed genes in reproductive aging [75].

4. Interconnection among oxidative stress, reproductive aging, and epigenetics

4.1 Link between reproductive aging and oxidative stress

Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) in cells and tissues and their rate of elimination or detoxification. Typically, oxidative phosphorylation in the mitochondria produces ROS as a byproduct. For the body to operate normally, there must be a moderate quantity of

ROS. ROS have a critical role as a second messenger in intercellular signal transduction, the control of gene expression, and immunological function in addition to their roles in the manufacture of active chemicals, cellular detoxification, and immune function [1]. But when ROS are overproduced or antioxidant use rises, redox processes become unbalanced and the body enters an oxidative stress state [76].

The process of aging in the ovaries exacerbates the production of reactive oxygen species. In particular, age-related ovarian aging causes the accumulation of ROS in the oocytes [77]. Age-related oocyte aging has been associated with a lowered expression of key genes in the ETC of oocytes [78]. For example, the succinate dehydrogenase complex flavoprotein subunit A (Sdha) and coenzyme Q10 (CoQ10) proteins that are responsible for shuttling electrons through the electron transport chain, have an age-related down regulation in mouse oocytes [79]. The dysfunctional shuttling of the electrons through the electron transport chain results in electron leakage from the mitochondria. The leaked electrons initiate a chain reaction where electrons are extracted from lipids, predominately polyunsaturated fatty acids including arachidonic acid and linoleic acid, and ultimately results in lipid peroxidation. Lipid peroxidation produces numerous lipid aldehyde byproducts that have the potential of damaging mitochondrial DNA/RNA and proteins. In addition, age-related oocyte aging has been linked to the accumulation of advanced glycation end-products (AGEs). AGEs increase ROS generation by the induction of hypoxia through collagen crosslinking and the impairment of perifollicular vascularization [80]. Moreover, the decreased antioxidant capacity in age-related ovarian aging is another cause of ROS generation in oocytes [78, 81].

Similarly, oxidative stress has been associated with age-related DNA sperm damage. In fact, the majority of DNA sperm damage is a result of oxidative stress, as evidenced by high correlations observed between the production of the major oxidative adduct 8-hydroxy-2′ deoxyguanosine (8-OHdG) and DNA fragmentation in sperm cells [82]. DNA sperm damage reduces male fertility and leads to inappropriate oocyte fertilization (**Figure 4**). This type of fertilization is associated with maternal miscarriages, preterm births, genetic diseases, neurological disorders, and juvenile cancer [83]. Furthermore, age-induced oxidative stress can result in the loss of membrane fluidity in sperm cells, consequently reducing sperm motility [3].

Several theories have been raised as a result of the consequential effect of oxidative stress in the biological system especially in aging. One of such theories regarded as the "free radical theory of aging" posit that aging is a resultant deleterious effects of free radicals accumulated overtime. Meanwhile in agreement with this postulation, mitochondria production of ROS (proposed as the key causative factor of aging) has been found to increase in aged tissues [84]. There are more scientific evidence to support this theory whereby increased oxidative damages in cells are associated with aging. The resultant effects of this were reported to be cellular dysfunction from accumulated damages in nucleic acids, lipids, carbohydrates, and proteins that exposes the body to harmful attacks of external agents easily. Furthermore, 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) are found in mtDNA in a more eminent concentration compared to the nuclear DNA [85]. This indicates that mtDNA is highly vulnerable to oxidative damage; moreover, the mitochondria of mammalian cells are major producer of ROS. This further improve on the previous theory on free radical regarded as the mitochondrial theory of aging. This latter theory posits that oxidative phosphorylation of mitochondrial macromolecules (including lipids, proteins, and mtDNA) generates oxidative damages that result to aging [86]. In addition, since the regulation of apoptosis is majorly modulated in the mitochondria, it is suggested that

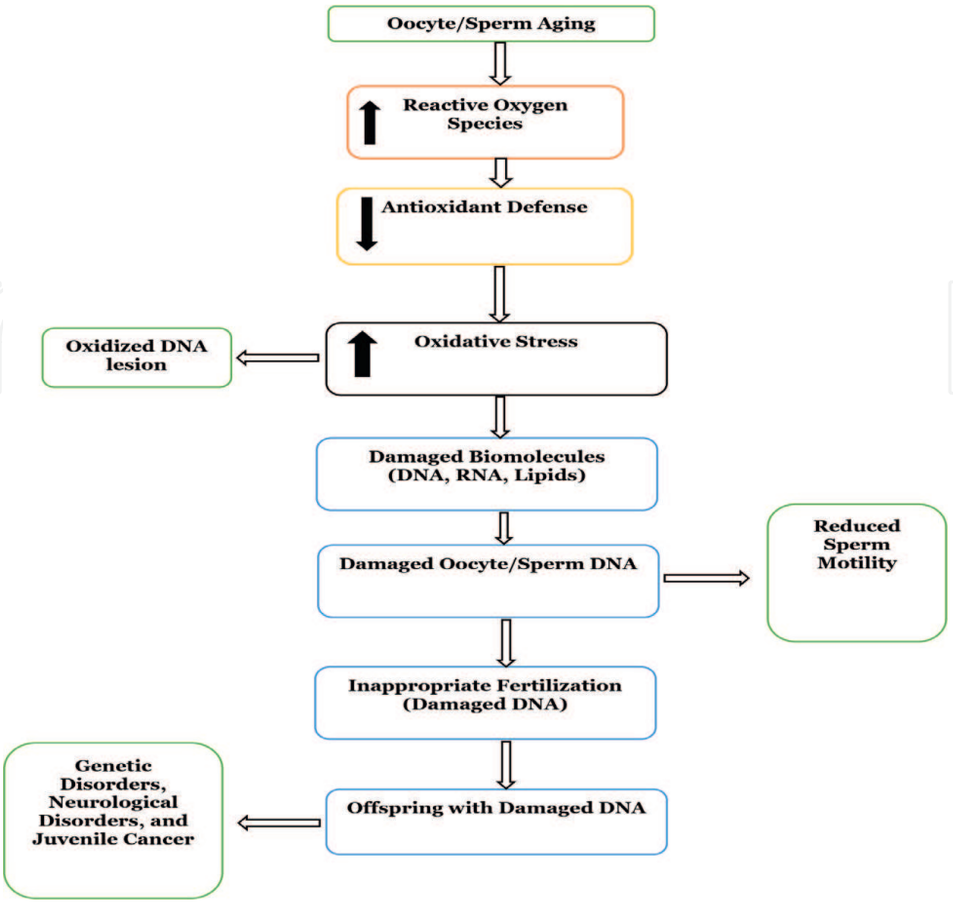

Figure 4.
Consequences of oocyte/sperm aging. Oocyte and sperm aging results in the production of reactive oxygen species through electron leakage from the mitochondria. Also, it causes a reduction in the cellular antioxidant system. The combination of these factors causes oxidative stress, which can directly result in oxidized DNA lesions or indirectly cause damaged biomolecules (DNA, RNA, lipids). In particular, the oocyte/sperm DNA is damaged, resulting in reduced sperm motility in aged males and inappropriate fertilization during copulation. Upon birth, offspring with damaged DNA exacerbates the possibility of genetic disorders, neurological disorders, and juvenile cancer.

aging due to apoptosis are associated with age-related mitochondrial oxidative stress. Asides, the beneficial outcome of antioxidants targeted at the mitochondria has been reported by several studies, which are indications that targeted antioxidants protect against oxidative damage better than the untargeted cellular antioxidants in the mitochondria [85, 87]. One suitable reason for this is ability of the targeted antioxidants to get rid of ROS at specific points for being able to cross the mitochondrial phospholipid bilayer [88].

4.2 Interplay between oxidative stress and epigenetics

Oxidative stress is a resultant effect of accumulated ROS which increases with age. It is also associated with a declination of the cells' repair machinery that consequentially generate a broad scope of DNA lesions [89]. This cascade of events results to mutated genes and a disrupted epigenetic state of the cell. Several studies have suggested the interplay that exists between epigenetics and oxidative stress viewpoint. For instance, demethylation of DNA by the oxidation of DNA and hydroxymethylation (mediated by TET) can be influenced by ROS. Also, ROS affects the methylome via oxidized DNA lesions formation [a resultant effect of

hydroxylation of 5-methylcytosine (5mC) and pyrimidines]. This hydroxylation reaction however may be a hinderance owing to the similarity in structure with epigenetic signals associated with 5-hmC [90, 91]. Furthermore, essential metabolites such as S-adenosylmethionine, acetyl-CoA, ketoglutarate, NAD^+, and Fe modulates histone-modifying enzymes that participates in epigenetic machinery [92]. However, activity of the epigenetic machinery can be influenced by ROS which suggests that epigenetic changes are associated with energy capacity of the cell and entire cellular metabolism. Oxidative stress, therefore, have a great impact on the epigenetic expanse of the cells at various control point ranging from DNA and histones to histone modifiers [93].

4.3 Oxidative stress and epigenetic deregulation

Oxidative stress from several factors causes epigenetic modifications. Moreover, molecular mechanisms associated with aging are involved in processes like the methylation of DNA, noncoding RNA, and histone change, generally regarded as epigenetic modifications [90]. In males, the loss DNA methyltransferases results to an incomplete formation and maturation of gamete. Specifically, impairment of sperm DNA methylation occur with oxidative stress on the cytosine-guanine (CpG) islands. Moreover, 8-oxodeoxyguanosine is formed from oxidation of guanine while 5-OH C, 5,6-diOH C, C glycol are formed from alteration of cytosine whereby 5-hydroxymethylcytosine formed as physiological product of the oxidation is the needed for the demethylation of DNA [5]. Also, the deamination of 8-oxoG, 5-MeC, or 5-MeC to 5HmC leads to the formation of thymine which hinders the methyl CpG-binding domain proteins to be bonded to matching CpG. This results to a poor methylation because of a weak binding of the DNA for DNMT3A [5, 94]. By consequence, oxidative damage to DNA generates changes in heritable epigenetics via alterations to the chromatin arrangement. An uncontrolled concentration of 5HmC (the oxidative product of cytosine) also results in the stimulation the process of active aberrant demethylation of DNA. Loss of KMT2D (Lysine methyltranseferase 2D also known as H3K3 monomethyltransferase) expression is also presumed to be associated with DNA damages mediated by ROS. Loss of KMT2D expression results to a reduction in the number of enhancers like H3K4me1 and H3K27ac regarded as enhancer activity markers. This reduction in their abundance hinders the binding of transcription factor like the FOXO3 and resultantly confer protection against oxidative stress through the upregulation of enzymes like superoxide dismutase and catalase and other antioxidant enzymes [95]. Furthermore, suppressed action of KMT2D is associated with DNA damage via the accumulation of ROS in prostate cancer condition. For instance, it was shown that there is a connection in lower sperm count and DNA methylation in men that has altered spermatogenesis in H19 and PEG1/MEST regions [96]. Similarly, hypomethylation induced by ROS is also associated with del Castillo syndrome or germ cell aplasia, cancer of the testes, and hypospermatogenesis. An aberrant protamine substitution is also resultant effect of high histone methylation concentration that adversely affects quality of sperm. Protamines found in spermatozoa might undergo alkylation as a result of oxidative imbalance with results effect by impairment in spermatogenesis via chromatin condensation. Therefore, a lower concentration of nuclear protamine in the spermatozoa indicates that such is vulnerable to oxidative damage owing to easy accessibility DNA [97, 98]. Acetylation of histone is also a vital epigenetic regulation mechanism that could be impaired by oxidative stress in oocyte formation or spermatogenesis.

Several studies have reported the interconnection of altered chromatin remodeling and sperm DNA damage initiation [99].

5. Conclusion

Oxidative stress as a result of accumulated free radicals adversely affects the reproductive process in human by posing a negative impact on both the male and female gametes and rate of development of the embryo. Age also adversely effects oxidative stress and DNA methylation with a resultant effect in epigenetic disorders transmission by the elderly to their offspring. This chapter discussed the interplay among epigenetics, reproductive aging and oxidative stress and provided a broader overview of the molecular basis of reproductive aging associated with ROS production and the consequential effects on the epigenetic machinery in both male and female. This in essence give an overall understanding on the molecular processes associated with reproductive aging and diseases that may arise due to aging for a better approach in ameliorating or managing the physiological process.

From the foregoing, it is crystal clear that aging is attended by several physiological and cellular alterations. The role of oxidative stress in the furtherance of these alterations is profound. Oxidative stress increases with age due to a weakened antioxidant defense system and results in profound consequences. The epigenetic alterations that come with reproductive aging were discussed. However, a literature search shows that more work needs to be done on the influence of reproductive aging on histone modifications in sperm and oocytes.

Conflict of interest

The authors do not have any conflict of interest to declare.

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