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DNA Methylation and Histone Modifications Associated with Male Germ Cell Differentiation

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Abstract

Spermatogenesis is a highly regulated process in which undifferentiated spermatogonial stem cells differentiate to form highly specialized sperm cells capable of fusing with the ovum to form a zygote. This is achieved through tightly controlled regulation of gene expression which depends crucially on DNA accessibility. DNA accessibility is largely dependent on epigenetic modifications including DNA methylation and modifications of the histones. DNA methylation is catalysed by DNA methyltransferase (DNMT) enzymes. The spatial and temporal expression levels and functional features of the DNMTs are thought to landscape the gene expression in the male germ cells. On the other hand, the histone code is defined by an array of molecules that bring about post-translational modifications of various histones at various sites. All these intricate events orchestrate germ cell specification, stem cell maintenance, mitotic amplification, initiation of meiosis and post-meiotic differentiation events. This review summarizes the sequential changes in DNA methylation and the histone modification profiles in germ cells leading to the production of functional spermatozoa.

Keywords: Epigenetics, Histone, Meiosis, Spermatogenesis, Testis

1. Introduction

Epigenetic regulation of gene expression involves heritable mechanisms that can alter gene activity without changing the underlying DNA sequence[1]. It plays a major role in all the developmental processes of the cell and the organism[2]. DNA methylation, histone/chromatin modification and post-transcriptional gene regulation (PTG) are the three major epigenetic mechanisms through which the epigenome is tightly regulated during various cellular and biological processes[3-5]. In this review, we focus on DNA methylation and histone/chromatin modifications in relation to spermatogenesis and fertility. Table 1 summarizes the molecules involved in these processes.

In general, the epigenetic machinery uses three types of proteins, "writers", "readers" and "erasers"; "writers" establish epigenetic marks through DNA or histones, "readers" recognize/bind to epigenetic marks and influence gene regulation immediately, and "erasers" remove the epigenetic marks[6]. As the cells divide, the epigenetic marks are preserved as memory, referred to as epigenetic memory, while ensuring cell proliferation.

2. DNA Methylation

DNA methylation is the modification of DNA through the covalent attachment of methyl groups from S-adenosylmethionine as a methyl donor to DNA bases, primarily on the 5' position of cytosine bases predominantly located at cytosine-phosphate-guanine (CpG) dinucleotides; although occurrence of non-CpG methylation also have been reported[2,7,8]. Methylation marks of DNA are established by DNA methyltransferase enzymes (DNMTs) which convert cytosine to 5-methylcytosine (5mC) while the demethylation is mediated by ten-eleven translocation methylcytosine dioxygenase (TET) proteins and thymine DNA glycosylase (TDG) through the activation of components of the base excision repair (BER) pathway[9-12].

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Table 1. Selected Epigenetic Modifiers of Spermatogenesis

Serial No:	Epigenetic modifier	Molecular mechanism	Function	Reference(s)
1	BRCA1	Loading of γH2AX	Mediates DDR signal amplification and spreading on unsynapsed sex chromosomes; establishment of X -pericentric heterochromatin (X-PCH) that critical for XY body, effective MSCI	134
2	BRDT	A testis-specific member of BET subfamily of epigenetic reader proteins (Detects acetyllysine residues)	Regulates chromatin organization as well as the timing of appearance and disappearance of histone modifications essential for MSCI and subsequent transcriptional silencing as well as in histone eviction of postmeiotic spermatids	137,187
3	BRWD1	Dual bromodomain-containing protein	Essential for postmeiotic gene expression	159
4	CDYL	Negative regulator of histone KCr	Regulates postmeiotic gene expression and histone-protamine transition of elongating spermatids	188
5	DMRT 7		For the transition between MSCI and post-meiotic sex chromatin (PMSC) and its loss affects sex chromosome silencing	73
6	ESET	HMT of H3K9me3	Maintains SSC survival by inhibiting apoptosis	189
7	FANCB	-	PGC proliferation/or survival and maintenance of SSCs	138
8	FBXL10	H3K4me3	Proliferation of undifferentiated spermatogonial/ GSCs	190
10	G9A	HMT of H3K9me2	Maintenance and survival of spermatogonia inclusive of SSCs and repression of L1 elements	191
11	JMJD1A	Demethylates H3K9me1 and H3K9me2	Stage-specific germ cell hypomethylation of *JMJD1A* is associated with concurrent increase in histone acetylation; these modifications are crucial for expression of CREM and its coactivator ACT, which in turn affects the recruitment of CREM on promoters of target genes such as *Tnp1*, *Tnp2*, *Prm1*, *Prm2*, *Odf1*, and *Gsg3* genes and regulates their expression.	192
12	JMJD1C	H3K9 demethylase	Maintenance of SSC by promoting self-renewal through up-regulation of *Oct4* expression	193,194
13	KDM1A	H3K4me2 specific demethylase	Maintenance and survival of SSCs/progenitor cells; differentiation and meiotic progression of spermatogonia	195
14	KDM3A (JMJD1A/ TSGA/ JHDM2A)	H3K9 demethylase	Essential for cAMP-response element modulator-regulated gene expression and thereby critical for Tnp1 and Prm1 transcription	192,196,197
15	KDM4D (JMJD2D)	A lysine demethylase that removes tri- and di-methylated residues from H3K9	Particularly in spermatocytes and spermatids	198–201

16	MDC1	Interacting patner of γH2AX	Loading and spreading of γH2AX and subsequent MSCI	135
17	Mll2	H3K4 methyltransferase	Transition of undifferentiated to differentiated spermatogonia	202
18	MOF	H4K16 acetyl transferase	Facilitates H2AX expansion that needed for MSCI through its recruitment of MDC1	136
19	MORC2B	A transcriptional target of PRDM9	May act as a key downstream effector of PRDM9 in meiosis	203
20	PRDM9 (MEISETZ)	KMT that mediates H3K4 trimethylation	Essential for proper meiotic progression	204,205
21	RNF8	Ubiquitination of histone; Histone acetylation and subsequent active epigenetic marks	Activation of escape genes in post-meiotic spermatids	145,148,206
22	SCML2	Recruitment of H3K27me3, ubiquitination on autosomes and deubiquitination on sex chromosomes	Making the bivalent domains for the poised state of genes; Deubiquitination through RNF8-SCML2 cooperative effect; heterochromatization in spermatids	75,77,78,125,147,148
23	SETDB1	HMT of H3K9me3	Maintain SSC survival by inhibiting apoptosis; Downstream H3K9me3 enrichment on the asynapsed X chromosome	139,207

The perturbations to DNA methylation in the male germline have been linked with lack of male germ cells and/or spermatogenic arrest and tumorigenesis[4,13,14]. Impairment of sperm DNA methylation has been associated with male factor infertility, with direct association with poor semen parameters, often manifested at imprinted and developmental genes[15–19].

The mammalian lifecycle accommodates two waves of genome-wide DNA methylation reprogramming: one at germline particularly in Primordial Germ Cells (PGCs) before sex determination and the other at early preimplantation embryos immediately after fertilization[8,20–23]. The epigenetic reprogramming, particularly through DNA methylation mechanism, is very crucial for germline development[7,8,28,29,20–27]. The purpose of germline DNA demethylation could be for erasing the epigenetic memory of somatic cells and to establish gamete specific epigenome capable of totipotency as well as sex-specific epigenetic landscape for the production of viable and healthy offspring through proper development[21,22,26]. The germline DNA methylation reprogramming can be subdivided into two: first phase initiating at 9.5 day post-coitum (dpc) by means of replication-dependent passive DNA demethylation and the second after PGC colonization during 10.5-13.5 dpc which is accomplished by TET mediated active DNA demethylation through conversion of 5mC to the intermediary base 5-hydroxymethylcytosine (5-hmC)[21,30].

Generally, DNA methylation marks at promoters (TSSs) are associated with the repressive state of the genome, and so the hypomethylation state implies the activation of gene expression. Besides the gene silencing, DNA methylation has effects on gene transcription, exon splicing, transcription factor binding dynamics and nucleosome positioning[31]. Interestingly, the DNA methylation (the 5mC pattern) residing in the gene bodies favors gene expression reflecting the fact that its association with the genomic location decides the gene activity. Remarkably, the connection between DNA methylation/demethylation pattern and gene regulation is not that simple. It is further complicated by the presence of histone modifications, which in turn influence the active or repressive state of gene expression. Though differentially methylated regions (DMRs) are associated with gene expression, allele specific DMRs on imprinting control regions (ICRs) results in parent-of-origin-specific expression of imprinted genes and has great implication

in proper embryonic development and offspring's phenotype[7,8,26]. The DMRs from imprinted genes are erased during global epigenetic reprogramming in PGCs which will later reestablish in ICRs in male-specific and female-specific manner. This germline derived DMRs of imprinted genes are further protected from the second wave of epigenetic erasure after fertilization.

Five different types of DNMTs have been identified in mammals which differ in structure and function: DNMT1, DNMT2, DNMT3A, DNMT3B and DNMT3L. The mammalian DNA methylation process occurs through two activities, viz., maintenance and *de novo*. DNMT1 is primarily involved in the maintenance of methylation via transferring methyl groups to the hemi-methylated DNA strands following DNA replication. DNMT2 carries out methylation of the cytosine 38 in the anticodon loop of aspartic acid transfer RNA. DNMT3A and DNMT3B are involved in *de-novo* methylation, methylating unmodified cytosine residues. DNMT3L does not participate directly, but acts as co-factor for de-novo methylation[14]. A recent study in rodents reported Dnmt3C as a *de novo* DNA methyltransferase gene, evolved *via* a duplication of Dnmt3B in rodents, and is responsible for methylating the promoters of evolutionarily young retrotransposons in the male germ line[32,33].

2.1. DNA Methylation During Primordial Germ Cell Development

The germ cell lineage arises as PGCs from the epiblast cells during early embryogenesis and later differentiates into either spermatozoa or oocytes while keeping PGCs as the origin of totipotency and also as the progenitor cells of both gametes. The remarkable epigenetic reprogramming associated with PGCs is the characteristic genome-wide DNA demethylation covering the parental imprints, a unique feature to PGCs that is not present in any other cell type[8,34]. The DNA methylation erasure program occurs in two phases which begins as early as 10.5 dpc and will get completed by 12.5 dpc[8,34,35]. This erasure occurs at different rates and times for different imprinted loci and finally the global hypomethylation status is achieved with some minor exceptions. The 5mC erasure and maintenance throughout PGC development are unidirectional, without any *de novo* methylation/maintenance, and is made possible through distinct mechanisms involving several factors directly or indirectly[36]. Additionally, PRDM14 ensures hypomethylation through transcriptional repression of the DNA methyltransferases *Dnmt3a/b/l* as well as by recruiting TET1 and TET2, thereby promoting active DNA demethylation[37,38]. *Prdm14* contributes to PGC specification through the repression of the DNA methylation machinery and fibroblast growth factor (FGF) signaling[39]. The re-establishment of DNA methylation occurs in a sex-specific, bi-allelic manner[40]. The genome wide methylation reprogramming also occurs in pre-implantation embryos during 0.5 to 3.5 dpc with the exception of imprinting loci and certain repeat elements[21,23].

2.2. DNA Methylation During Prospermatogonia Development

The formation of spermatogonia (the starting cells of spermatogenesis) is not directly from PGCs, rather PGCs first transform into prospermatogonia, also termed gonocytes, during 12-15 dpc following sex determination. This prospermatogonial phase of male germline development, accommodating three stages- M, T1 and T2, extends from fetal to neonatal stages until the initial development of spermatogonia[41–43]. The initial propspermatogonia derived from PGCs constitute M-prospermatogonia and are far away from the basal lamina and mainly located at the centre of the testicular cords. In the prenatal testis, these cells enter G0/G1 mitotic arrest stage, constituting T1 prospermatogonia during 16.5 dpc, and maintain this quiescent state up to birth[44]. After birth, T1 prospermatogonia re-enter cell cycle and transform into T2 prospermatogonia during 1-2 days post partum (dpp),[45] which proliferate in the middle of seminiferous cords and give rise to Type A,[41] thereby ending the prespermatogenesis phase and then beginning the spermatogenesis phase. During 3-6 dpp, the spermatogonial population migrates towards basement membrane of seminiferous cords and this heterogeneous population can be characterized as undifferentiated (A_{undiff}) and differentiating (A_{diff}) cell population, the former group as undifferentiated progenitors that are poised to differentiate, constitute foundational pool of the spermatogonial stem cells (SSCs),[46,47] and the latter enter directly into the first round of spermatogenesis[44]. The SSCs are derived from prospermatogonia and are capable of undergoing self-renewal and differentiation so that they can provide constant supply of progenitors for spermatogenesis and thereby sustain steady-state spermatogenesis throughout the reproductive lifespan of the male[48].

Though gonocytes are the prime source of a functional reservoir of SSCs, only a small fraction of gonocytes transform into SSCs; the rest enter first wave of spermatogenesis directly[49]. The transition of gonocyte sub-population into SSCs is very critical; any aberration during this event leads to male infertility and germ cell tumors, and the molecular mechanisms regulating mammalian gonocyte and spermatogonial differentiation has been previously reviewed[49]. The epigenetic reprogramming in fetal prospermatogonia and its fine tuning in postnatal SSCs, with focus on the DNA methylation and its mediators and associated major histone modifications have also been reviewed[43]. In fact, the epigenetic landscape established in prospermatogonia is almost maintained in the SSCs without great differences. The re-establishment of epigenome, the global genome remethylation along with histone modifications, is initiated in T1 prospermatogonia and is almost completed before transition into T2 prospermatogonia[41,43]. However, some gene-specific reprogramming, including paternal imprinting genes and spermatogenic stage specific genes, continues in neonatal prospermatogonia and even in early spermatogonia[41]. It was noted that prospermatogonia at 16.5 dpc attained significant level of DNA methylation except around the lamin-associated domains (LADs), while at birth it showed a nearly fully methylated pattern and this pattern is similar to Kit^{-ve}/Kit^{+ve} spermatogonia at 7 dpp and mature mature spermatozoa[50]. Unlike somatic cells and PGCs, methylation in non-CpG sequences is a characteristic feature of prospermatogonia[43].

The quantitative RT-PCR and *in situ* hybridization revealed the dynamic expression of distinct histone genes in different spermatogenic cells, and it is suggestive of the systematic regulatory role of various histone variants for the progression of different stages of spermatogenesis[51]. The prospermatogonia enriched testes from mice at 2 dpp showed predominant expression of thirteen histone variant genes and the presence of similar histone variants in embryonic stem cells (ESCs), which imply that those histones are more closely associated with pluripotency control[51]. A recent study noted that the epigenetic reprogramming during PGC to prospermatogonia transition entails a composite erasure of the epigenetic marks ensuring the timely and efficient activation of germline reprogramming responsive (GRR) genes, which can promote the progression towards spermatogenesis[52]. These epigenetic modifications include the high level promoter occupancy of both 5mC and 5hmC as well as a combined loss of DNA methylation and PRC1 repression for GRR gene activation. In addition to the DNA demethylation role after 11.5 dpc, TET1 binding at GRR gene promoters is also essential for GRR gene activation[52].

2.3. DNA Methylation During Spermatogonial Stem Cell (SSC) Differentiation

The DNA methylation profiling of human SSCs (hSSCs) showed a great resemblance to that of spermatozoa at promoters, putative enhancers and imprinted loci[53]. The epigenetic switch particularly through upregulated Dnmt3a2/3b expression, increase in global DNA methylation, changes in DNA methylation of regulatory genes, accumulation of H3K9me2 modification, localization/distribution changes of H3K9me3 with nuclear DAPI foci is crucial for transition of c-Kit^{-ve} undifferentiated spermatogonia to c-Kit^{+ve} differentiated state[54]. The reported 5mC levels of SSCs/undifferentiated spermatogonia and differentiated spermatogonia are varying with each other;[54-56] the study by Kubo et al[56] identified as comparable DNA methylation levels between these cell types with exceptions at DMRs. It is also noted that the genomic regions with stage specific DNA methylation changes are closely associated with subsequent gene activities including stem cell function, cell proliferation and spermatogenesis[56]. The hypomethylation and open chromatin in a favor for expression of germline genes *DDX4* and *DAZL* marking germ cell epigenetic/transcriptional status of hSSCs as distinct from that of ESCs[53]. The meiosis related genes that were repressed in PGCs exhibited gradual upregulation in hSSCs through DNA hypomethylation[53]. The expression of major pluripotent genes are differently regulated in hSSCs and this could be for unipotent germline activation. *OCT4* and *NANOG* were repressed by DNA methylation. *SOX2,* though hypomethylated, remained repressed by some other mechanisms, while other pluripotent genes were active or poised possibly for regain the totipotency after fertilization[53,57]. In hSSCs, the major repeat elements LINE, SINE and LTR are hypermethylated as like in somatic cells whereas satellite elements especially ACRO1 satellites and LTR subfamilies are hypomethylated[53]. The recent single cell analysis of hSSCs revealed that spermatogonial developmental trajectory includes five sequential transcriptional/developmental states, with the novel one as "State 0", with very limited changes in open chromatin and DNA methylation enabling transcriptional plasticity to

encourage the state transitions for maintaining a constant SSC pool for life time male fertility and its replenishment in case of damage[58].

A recent study in hSSCs illustrated the existence of four distinct cellular states as a developmental trajectory accounting the transition from quiescence to proliferation and differentiation, and that revealed the unique epigenetic landscape of SSCs with specific DNA methylation and open chromatin patterns ensuring proper development, niche responsiveness and poised pluripotency[53]. Existence of heterogeneous SSC population in mouse testes displaying extensive DNA methylation/imprinting/chromatin dynamics has been demonstrated in juvenile mice too[59–61]. The SSCs' quiescent state is very essential for preventing premature activation as well as stem cell exhaustion, and the DNMT3L promotes quiescence by regulating the delicate balance between the cycling and quiescence of SSCs and progenitors[62]. DNMT3L modulate cell fate transitions during postnatal period through regulation of CDK2 expression, PLZF stability and SALL4B repression, thereby ensuring lifelong maintenance of germline pool. PLZF is a well known transcription factor (TF) and surface marker of undifferentiated spermatogonia including SSCs and plays critical role in SSCs for their exit from quiescence, self-renewal and maintenance of the stem cell pool, and balance between self-renewal and differentiation[63,64]. The epigenetic mode of gene expression regulation as well as L1 repression by PLZF had been demonstrated[65,66].

2.4. DNA Methylation During Mitosis-Meiosis Transition

Various molecules and/or mechanisms have been identified which promote or prevent mitosis-to-meiosis transition[40,67]. With the current knowledge, retinoic acid (RA)-STRA8 signaling act as the main gateway for the precise mitosis-to-meiosis transition in male germ cells,[68–71] and the factors demonstrated to have key role in this transition, for example, DMRT1/6, NANOS2, etc. regulate the meiotic entry through their regulation on *Stra 8* expression,[72,73] making STRA8 as the gate keeper for meiotic entry. The ubiquitin ligase β-TrCP functions as a critical regulator for mitosis-to-meiosis transition in male germ cells by targeting DMRT1 for its degradation[74].

Remarkably, this transition towards meiosis is accompanied with massive transcriptome changes with activation of late spermatogenesis genes along with silencing of somatic/progenitor genes[75,76]. SCML2 mediated bivalent domain mechanism is used at somatic/progenitor genes for their future activation after fertilization through repressive H3K27me3 and active H3K4me2/3 domains; this poised chromatin and bivalent domains facilitate the mitosis-to-meiosis transition[76,77]. This recruitment of H3K27me3 at genes by SCML2 is made possible through its binding to hypomethylated CpG promoters enriched with H3K4me2/3 and it interacts with PRC2 for H3K27me3 regulation on bivalent domains[77]. The recent study demonstrated that during mitosis-to-meiosis transition, the dynamic chromatin reorganization is accomplished in intergenic and intronic regions in such a way that open mitotic-type chromatin is closed while *de novo* formation of meiotic-type open chromatin is achieved[78]. Additionally, several genetic and epigenetic factors are essential for the sustained progression of meiotic divisions and their perturbation to meiotic arrest which may result in male infertility/sub-fertility. The epigenetic regulations during meiotic progression is also previously reviewed by several authors[79–81].

Since genome wide DNA methylation patterns are regained before meiosis and persist through out spermatogenesis,[82] the chromatin/histone modifications of haploid cells were attained more concern and investigated deeply. But a recent study in adult mice noted the transient reduction of DNA methylation (TRDM) in the meiotic S phase of spermatocytes and presence of specific hemimethylated DNA in prophase I as in favor of meiotic events[83]. In relation with this, DNA methylation mediated epigenetic regulations in meiotic cells was noticed. For example, several epigenetic mechanisms mainly DNA methylation regulate the transient expression of *GPAT2* in pachytene spermatocytes[84]. Dynamic methylation pattern with spermatocyte-specifc inverted methylation patterns between CpG and non-CpG sites in the *Dnmt1o* 5'-upstream region was observed during spermatogenesis[85]. The DNMLT3 association during meiotic progression suggests the essentiality of the *de novo* DNA methylation during meiotic phase[80,81]. The expression of testis specific TF SOX 30, which regulates the expression of several meiotic/postmeiotic genes and IncRNAs which are critical for spermiogenesis and subsequent male fertility[86–88] well regulated in male germline through DNA hypomethylation at CpG islands of its promoters[89]. USF, another TF, regulate MIWI expression from midpachy-

tene to round spermatid stage through its inverse correlation with CpG methylation of MIWI promoter[90].

2.5. DNA Methylation During Post-Meiotic Phase

Though DNA methylation dynamics of male germ cell-specific single-exon genes are associated with CpG content, some intronless genes with lower CpG number showed expression in round spermatids even having hypermethylated CpGs[91]. It has been noted that in round spermatids a distinct set of gene expression occurs from TSS bearing DNA methylation and these atypical promoters as enriched with DNA methylation, H3K4me3, 5hmC, RNAPol2 and high acetylation levels (H3K27ac and H3K9ac)[55]. The dynamic expression of DNMTs including the isoforms such as DNMT3a2 and DNMT3b2 are noticed throughout spermatogenesis with expression in round spermatids, but some disappear in elongating spermatids[92]. The round spermatids of mice and human exhibited the expression of various DNMTs: DNMT3a2 and DNMT3b could be for *de novo* methylation, but the role of DNMT1 in post-meiotic cells needs to be elucidated[14,29]. Towards the end of elongation phase, the gene expression is ceased while the chromatin condensation and compaction occurs with the replacement of nucleosomes/histones with protamines. The two paralogous chromatin modifying proteins CTCF and BORIS regulated gene expression in spermatids and chromatin organization in sperm in cooperation with several other testis-specific transcriptional regulators (TSTRs). They associated with regions which were strongly linked to protamine-refractory, histone-retaining regions in mature sperm[93].

3. Histone/Chromatin Modifications

Eukaryotic chromatin is a highly dynamic macromolecular assembly that undergoes local structural alterations, referred to as chromatin remodeling, for regulating gene expression during various cellular processes[94,95]. The chromatin remodelers, in an ATP-dependent mechanism, alter the structure and stability of the nucleosomes and thereby, provide an access to the underlying DNA for regulatory proteins/factors ensuring DNA-templated processes like replication, transcription, repair, and other cellular processes[96,97]. Nucleosomes, the basic units of chromatin, are specialized chromatin structures primarily made up of histones along with DNA. Histones are basic proteins that can be divided into core histones (usually H2A, H2B, H3 and H4) and linker histone (H1) depending on their association with nucleosome assembly[98]. The core histones constitute an octameric configuration in the nucleosome, [H2A–H2B][$\{H3\text{-}H4\}_2$] [H2A–H2B] wrapped by DNA sequence of about 147 bp, and play crucial role in chromatin assembly and its compaction[99]. The linker histone H1 binds to the DNA sequences, linking the nucelosomes and determine the distances between nucleosomes and chromatin folding to higher order structures (51). The chromatin remodeling through histone modifications includes incorporation of histone variants and/or the post translations modifications of existing histones. These histone modifications affect chromatin structure by influencing histone-DNA and histone-histone contacts and that can lead to the active or repressive state of that region for gene expression[95,97,100].

The covalent bonding of various functional groups to the N-terminal or C-terminal tails or globular core domains[101,102] of histone are collectively called as histone post translational modifications (PTMs) and are linked to essentially all cellular processes requiring DNA access including transcription, DNA repair, replication, recombination and apoptosis[96,97,100]. PTMs are one among the components of epigenome and play a key role in defining and maintaining functionally distinct regions of the chromatins. The establishment of histone PTMs through specific chromatin modifying enzymes becomes the histone language of that chromatin, and that can be sensed by particular chromatin remodelers, thereby influence their action and specificity[94,96]. Various chromatin regulators[97] sense the PTMs on the chromatin and render the compact architecture of chromatin differently either positively or negatively on gene expression. Studies on histone modifications have identified a diverse array of histone PTMs and the well characterized ones are acetylation, methylation, phosphorylation, ubiquitination and crotonylation. The use of mass spectrometry and associated high-throughput technologies revealed the existence of more types of PTMs associated with histones, termed as novel/non-classical PTMs, and the different PTMs' combinatory patterns, but much of their biological functions are still intriguing. The distinct histone languages on one or more tails act sequentially or in combination to constitute "a histone code"[100]. The hierarchy of multiple

PTMs as well as their establishment and maintenance around the localized chromatin regions are still unexplored mechanisms giving open questions to researchers.

The different histone PTMs, their marking and erasing by two distinct oppositely functioning enzymes (writers and erasers), and their influence on gene expression are well explained in a previous review[103]. Briefly, acetylation, phosphorylation, crotonylation and ubiquitination lead to gene activation while methylation and butyrylation lead to gene silencing. But at times, binary signatures (promoter bivalency) are present through the incorporation of active and repressive marks that lead to poised chromatin especially in developmental genes.

3.1. Histone Modifications During PGC and SSC Development

Various histone or chromatin modifications including genome wide downregulation of H3K9me2 as well as upregulation of H3K27me[336,104,105] occur during PGC specification. Since PGC state spans from 6.5 to 13.5 dpc, the overall epigenome reprogramming in PGCs can be categorized into PGC reprogramming I encompassing 8.0 to 9.25 dpc and PGC reprogramming II between 10.5 to 13.5 dpc[10,34,35,106,107]. The PGC reprogramming I encompasses the initiation of global DNA demethylation with genome wide loss of H3K9me2. During the period in between the major epigenetic rearrangements (9.25-10.5 dpc), the PGCs undergo a major shift in the intrinsic developmental program with the exit from the G2 pause, phosphorylation of the C-terminal domain (CTD) of RNA polymerase II, expression of gonadal-stage germline genes and the initiation of reprograming II[108]. The second epigenetic reprogramming phase coincides with the methylation erasure from ICRs and single copy genes to establish germline epigenetic ground state[34,35] along with chromatin alteration including histone replacement[10,106,107].

Male germline undergoes a sex-specific remethylation during 15.5-18.5 dpc and completes it by termination of meiotic pachytene by 10-19 dpp. In the male germline, the imprinted loci undergo paternal imprinting following sex determination from 14.5 dpc to after birth whereas maternal imprinting occurs only after birth[36,40]. The transposon loci escape from this global DNA demethylation program, possibly for the protection of genomic integrity during the germ cell development[34,35]. The male germline of mice remains in hypomethylated state for a few days while that of humans is comparatively longer for several weeks[109].

PRMT5 mediates SMDA on H2A and H4 histones and exhibits dynamic intracellular localization pattern in germline, particularly during PGC specification as well as development[110,111]. The cytoplasmic translocation of PRMT5 along with master germline/PGC determinant BLIMP1 at 11.5 dpc, [112] and a similar observation in human fetal germ cells,[113] is suggested to act as a key mechanism for PGC specification in relation with activation of stemness pathway as a consequence of downregulation of H2A/H4R3me2. Further studies with germline conditional knockout models reframed the concept that PRMT5 is not essential for PGC specification; it is rather indispensable for PGC proliferation, survival and expression of the gonadal germline program during 9.5-10.5 dpc[110,114]. The loss of PRMT5 in PGCs leads to the activation of genes associated with DNA damage response (DDR) and apoptosis pathways[114]. Remarkably, PRMT5 preserves genomic integrity and is involved in genome defense during PGC specification and later development by silencing transposable elements in two different ways. In the earlier PGCs, PRMT5 translocates to nucleus from cytoplasm at 8.5 dpc and marks H2A/H4R3me2s repressive modifications on IAP and LINE1 elements causing their repression[114]. Later its relocation back to cytoplasm coincide with the onset of the expression of PIWI proteins, thereby enabling them to participate in TE silencing indirectly through a pi-RNA pathway[114,115].

PLZF has been shown to colocalize with SPOC1[116]. SPOC1 (PHF13) is an H3K4me2/3 chromatin reader and transcriptional co-regulator and its interactions with PRC2 RNA Pol II regulate gene expression during various cellular events including cell differentiation,[117] and it is demonstrated that SPOC1 as indispensible for SSC differentiation in the testis and for sustained spermatogenesis[116]. The TF Yin yang 1 (YY1) is essential for the stemness of SSCs and had shown its association with heterochromatin nuclei of gonocytes of 14.5 dpc testis as well as stage-dependent testicular expression during postnatal life and throughout the spermatogenic cycle[118]. Remarkably, CP2c, another TF, showed reciprocal localization in relation with YY1 suggesting as critical for the commitment of spermatogonia and during the progression of spermatogonia to spermatids[118]. The DMRT genes act sequentially in male germline for establishment and maintenance of spermatogenesis with DMRT1 as involved in SSC maintenance and replenishment whereas DMRT6 acts as a mitotic/meiotic switch regulating timely entry to meiotic/spermatocyte program[73]. DMRT1 in differentiated spermatogonia permits differentiation and mitotic proliferation, and prevent

premature meiotic initiation[73]. DMRT1 act as a bifunctional transcription regulator in juvenile testes, binds at promoters of specific genes differently in germ cells and Sertoli cells, and their gene regulation is correlated through H3K4me3 modifications[119].

The establishment of SSCs from gonocytes is characterized by stage specific enrichment of eight histone variant genes, two of H1, two of H2a, three of H2b and one H3 variant genes, along with high expression of some gonocyte enriched histone genes. As mentioned in gonocytes, the histone variants present in SSCs were also present in ESCs, thereby suggested to associate with maintaining pluripotency of these cells[51]. SSC enriched histone genes may associate with cell fate determination to specific adult stem cell line since during the differentiated cells express different set of histones[51]. The histone PTM profiling of hESCs revealed that the balance between self renewal and differentiation into different lineages is regulated by histone PTM landscape of hESCs particularly through specific lysine acetylation (Kac) and lysine methylation (Kme)[120]. The enrichment of acetylation at H3K4, 9, 14, 18, 56 and 122 as well as H4K5, 8, 12 and 16 marks the pluripotent state while its loss/decrease leads to differentiation. Thus self-renewal is characterized by specific histone acetylation patterns with chromatin openness. Also methylation especially of H3 at K9, K20, K27 and K36 are associated with differentiation initiation[120]. The promoter bivalency through H3K4me3/H3K27me3 is enriched in SSCs specifically in developmental genes making them poised state and this bivalent mark is maintained in undifferentiated and differentiated spermatogonia as well as in further stages of male germline; the promoter bivalency as a germline epigenetic mark preserved form PGCs to final spermatozoa ensuring a stable epigenetic memory to next generation[55,77,121]. The bivalent domains are established on not only developmental genes, but also somatic/progenitor genes through SCML2 which recruits the repressive H3K27me3 mark on H3K4me2/3 rich hypomethylated promoters[77]. Recently, it was demonstrated in hSSCs that only minor changes are associated with the open chromatin landscape that occurs during the commitment of undifferentiated SSEA4^{+} SSCs into c-Kit^{+ve} differentiating spermatogonia, in spite of transcriptional variation of hundreds of genes[58].

3.2. Histone Modifications During Mitosis-Meiosis Transition

Though the molecular mechanisms behind meiotic sex chromosome inactivation (MSCI) are not fully elucidated, some epigenetic signatures specific to MSCI were identified and detailed in previous reviews[79–81,122]. The MSCI/XY body epigenetic landscape is very complicated with the inclusion of different histone variants (γH2AX, macroH2A, H2AZ and H3.3), dynamic and diverse histone PTMs (Kme, Kac, lysine crotonylation (KCr). phosphorylation, ubiquitylation, and sumoylation) and histone modifiers (PRDM9, RNF8, SCML2, FANCD2, FANCB, SUV39H, and various DDR signals). Despite the significance of heterochromatin during various stages of spermatogenesis,[123,124] sex chromosome wide heterochromatin formation is a characteristic of MSCI[75,78,125,126] and the HP1α (CBX5), HP1β (CBX1) and HP1γ (CBX3) were present in XY body: HP1β and γ occupy on entire XY body in late pachytene whereas HP1α concentrates in more condensed heterochromatic areas, particularly in Y chromosome[127,128]. MSCI is associated with silencing of not only protein coding genes, but also X-linked miRNA (X-miRNA) genes[129]. The defects in the MSCI or XY body or X-miRNAs silencing leads to spermatogenic failure particularly through pachytene arrest resulting in male infertility[129,130].

Though distinct epigenetic modifications are present on both autosomes and sex chromosomes, we are focusing on epigenetic programming of sex chromosomes during MSCI. The DDR signals mediates MSCI initiation in early pachytene, leads to chromosome wide signal amplification and DDR pathway functions in sex chromosomes for triggering the epigenetic programming of MSCI and post meiotic sex chromatin (PMSC) (details of PMSC mentioned in next section)[131]. The recruitment of Ser-139 phosphorylated H2AX (gH2AX) on sex chromosomes at pachytene stage is considered as the signal for MSCI initiation and this phosphorylation is mediated by ATR along with TOPBP1 partner,[132,133] both of them will be loaded on sex chromosomes through BRCA1 in BRCA1-TOPBP1:ATR pathway[134]. The BRCA1 mediates DDR signal amplification and spreading on unsynapsed sex chromosomes whereas suppresses ATR signals on synapsed autosomes. MDC1, the interacting partner of γH2AX, also facilitates the chromosome wide accumulation of γH2AX on sex chromosomes in MDC1-dependent pathway and leads to chromosome wide silencing of XY axes as well as XY body formation[135]. The H4K16 acetyl transferase MOF, which is responsible for three waves of γH2AX expansion of Prophase I, enables the third wave of H2AX expansion needed for MSCI through its recruitment of MDC1[136]. BRCA1, additionally, promotes establishment of X -pericentric heterochromatin

(X-PCH), which is critical for XY body morphogenesis and subsequent meiotic progression, and is followed by accumulation of macroH2A1 on X-pericentric region and pseudo-autosomal region (PAR) after the mid pachytene stage and on the Y-pericentric region after the late pachytene stage and this BRCA1-dependent X-PCH facilitates formation of γH2AX domains on XY body[134]. H3K9me3 present on both sex chromosomes in early pachynema, then restricted to Y chromosome during early to mid pachytene transition and disappears from late pachynema with the reappearance in the unsynapsed sex chromatin of diplonema[137,138]. The downstream H3K9me3 enrichment on the asynapsed X chromosome that occurs at onset of silencing is established by H3K9 methyltransferase SETDB1 and its recruitment in DDR network is mediated by TRIM28 through γH2AX[139].

Various histone ubiquitin enzymes had been shown as critical for meiosis[140,141] and ubiquitinated H2A and H2B forms were located in XY body[135,140]. The monoubiquitination by RNF8 and polyubiquitination by RAD6 were shown as essential for male fertility[142]. Though exact role of histone ubiquitination in MSCI is not clear, ubH2A is associated with gene silencing[143] while ubH2B is associated with gene transcription as well as elongation[144]. RNF8 promotes establishment of active epigenetic marks on sex chromosomes including H3K4me2 (after the diplotene stage) as downstream of RNF8-dependent ubiquitination of H2A and concomitant H4K20me1 (during early pachytene to the mid-diplotene stage), and these RNF8 mediated active epigenetic memory persists into post-meiotic spermatids[145]. The Fanconi Anemia (FA) core proteins including FANCA, FANCB, FANCC and FANCD2 mediates H3K9 methylation, positively for H3K9me2 and negatively for H3K9me3[138,146]. RNF8 dependent H3K4me2 establishment is enabled through FANCD2 independently of FA pathway, acting as downstream to RNF8[146]. Thus the DDR and FA pathways functions in meiotic sex chromosomes with RNF8 as in central position. Though the sex chromosomes are transcriptionally silenced during MSCI, *de novo* formation of accessible chromatin at the sex chromosomes occurs with the closure of open chromatin at autosomes[78]. This distinct chromatin dynamics is regulated by SCML2 which also facilitate monoubiquitination of H2AK119 (H2AK119ub) positively on autosomes and negatively on sex chromosomes through the interaction of USP7[75,78,147]. Interestingly, the repressive H327me3 is excluded from sex chromosomes particularly from X chromosomes while accumulating H3K9me2 during MSCI[76]. RNF8 mediated monoH2AK119ub at early pachytene sex chromosomes undergoes gradual decrease through deubiquitination by SCML2 and this RNF8-SCML2 cooperative regulation of ubiquitination during meiosis is essential for establishment of active enhancer mark H3K27ac and subsequent promoter mark H3K4me2 for poised state of genes could be for their activation in post meiotic cells[148]. The H2A.Z starts to accumulate during pachytene stage and becomes predominant in later stages with the concomitant decrease of macroH2A and its presence is correlated with the dynamic nuclear relocalization of heterochromatic marks (HP1β and H3K9me2/3), which become concentrated in the inactive XY body, and that could be for keeping transcriptional repressed state of sex chromosomes[149]. In an *in-vitro* study, it was shown that the HP1α recruitment is regulated by the interplay of linker histone H1.4, H2A.Z and H3K9me3 implying their essential association within the heterochromaticregions[150]. The localization of transcriptional regulator TRIM27 as well as several translation regulating factors were noticed in XY body[151,152] and the presence of translation regulating factors suggesting the role of XY body as for controlling mRNA metabolism and/or "poising" protein translation complexes[152]. EXOSC10, a catalytic subunit of the multimeric exosome, is present in the mitotic, meiotic and early post-meiotic germ cells and transiently localizes to XY body with colocalization with γ-H2AX in late pachynema, suggesting its role in epigenetic silencing, and its disruption leads to impaired germ cell differentiation and male subfertility[153].

3.3 Histone Modifications During Post-Meiotic Phase

The major epigenetic marks of PMSC include H3K9me2 and H3K9me3, HP1β and HP1γ, H3K27me1 and H3K27me3, and H3-K9 acetylation. Though PMSC is generally considered as silencing event, sex chromosomes are believed to be in a distinctive epigenetic constraint, enriched with active marks KCr and H4K9me3[154].

The gene expression in spermatids is regulated by master genes. The deletion of MSYq demonstrated the deregulation of multi-copy and single-copy genes with epigenetic abnormalities with complete loss of H4K8Ac and reduction in H3K9me3 and HP1β[155]. The *Sly* deficiency alone leads to upregulation of spermatid genes as well as sperm deformities with defective repressive marks on the

sex chromatin including reduced levels of the HP1β band H3K9 methylation[156–158]. The spermatid specific SLY had shown promoter occupancy of active genes having overlaps with active chromatin marks H3K4me3 and KCr, and interacts with SMRT/N-CoR repressor complex, particularly with TBL1XR1, and regulates gene expression of spermatids particularly sex chromosome-encoded H2A variants (such as H2A.B3) and of the H3K79 methyltransferase DOT1L[156]. This study showed that SLY deficiency affects the spermatid gene expression with up-regulation of XY genes while distinct regulation on autosomes. *Sly* has critical role in post-meiotic sex chromosome repression (PMSR), either directly through spermatid sex chromatin or via interaction with sex chromatin protein partners[158]. In addition, *Sly* deficiency results in the deregulation of DOT1L and subsequent decrease of H3K79me2 and H4 acetylation, both of which are necessary prior to histone eviction[156]. Corroborating with the previous report of *Sly's* role in chromatin condensation,[157] the *Sly* KO mice exhibited abnormal chromatin remodeling with higher proportion of residual histones, significant reduction of protamine 2 and increased DNA oxidation[156].

The Y escape genes contribute major role as in PMSR while RNF8 mediated H2AK119ub mediates active epigenetic marks including KCr, H2A.Z etc could be contributing to the activation of gene expression[145]. RNF8 –SCML2 cooperative effect, mentioned in meiotic phase, leads to the incorporation of active marks H3K27ac and subsequent H3K4me2 on escape genes[148]. Additionally, RNF8 mediated H2AK119ub imparts H4 acetylation which is implied for the subsequent histone-to-protamine transition. SCML2 is associated with induction of facultative heterochromatization in haploid spermatids and associated marks. Bromodomain has role in gene expression. The dual bromodomain-containing protein BRWD1 is essential for postmeiotic gene expression without affecting the pericentric heterochromatin and histone landscape of round spermatids and its deficiency alter ~ 300 spermatid specific gene transcription, including protamines and transition proteins[159].

The epigenetic landscape of spermatozoa is also discussed in previous reviews[28,160–162]. Two studies with high throughput mass spectroscopy revealed the details of the histone landscape including histones/histone variants and histone PTMs associated with mature spermatozoa of mice and human[101,163]. In addition, the sperm promoters exhibited three patterns- class I with depletion of H3K4me3, class II with enrichment of H3K4me3 and Class III with bivalent promoters (both H3K4me3 and H3K27me3), and the open chromatin in TSS of round spermatid state is maintained in H3K4me3 enriched promoters of spermatozoa[78]. Though histones are replaced with protamines during spermiogenesis, around 1-10 % histones are retained in the mature spermatozoa. The recent method by using histone replacement-completed sperm (HRCS) also had shown that histones are retained at specific promoter regions in HRCS[164] and the retained histones are localized in intergenic regions as their association with gene desert areas[165]. The H3K4me3-containing nucleosomes preferentially occurs at CpG-rich promoters of development-associated genes while H3K9me3-containing nucleosomes occupy satellite repeats including centromere and pericentromere[165]. The proper retention of core histones and histone variants are critical for sperm nuclear architecture and that can be altered by impaired poly(ADP-ribose) (PAR) metabolism[166–168]. Also the retained sperm histones act as potential mediators of epigenetic information to the zygote that regulates the gene expression in the early embryos, thereby PAR metabolism can modulate the transcription in early embryos[168].

4. Epigenetics and Fertility

The environment as well as life style factors including diet and smoking can alter the sperm associated epigenetic landscape and that altered epigenetic signatures including induced differential histone retention sites (DHRs) can be transmitted to the next generations[12,169–172]. Such altered sperm epigenome is associated with male infertility[16,173–175] and that epimutations can become involved in transgenerational inheritance[176,177]. Moreover, the aberrant paternal epigenetic signatures can affect the reprogramming of embryos, its development as well as offspring phenotypes[178,179]. A recent integrative proteome and transcriptome analyses identified that sperm proteins including epigenetic regulators contribute to correct embryogenesis and, possibly, for modulation of the offspring phenotype[180]. So the pre-checking of sperm quality through epigenetic biomarkers can effectively treat male infertility via ART and can avoid dysfunctions of embryogenesis and altered offspring phenotypes, as well as improve ART outcomes[160,181]. DNA methylation is altered in combination chemotherapy of testicular cancer in rodents[182] and the altered promoter DNA methylation in testicular tumor can be used as a diagnostic tool[183].

A recent study in mice demonstrated that altered histone-to-protamine transition with the administration of leptin can be restored by concurrent administration of melatonin[184]. These observations suggest the significance of better understanding of epigenetic regulation of spermatogenesis and its application as for diagnosis and improvisation of current treatment methods of testicular cancer and infertility. The single cell transcriptome analysis facilitated the identification of subcellular populations with continuous developmental trajectory as existing in male germ cells with dynamic processes and critical regulators[185,186] and this in future might improve the current realization of epigenetic reprogramming during spermatogenesis.

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