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Epigenetics of the Synaptonemal Complex

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1. Introduction

Meiosis is a process composed of two divisions of the germ line cells without an intervenient S phase, thus there is no duplication of DNA between the first and the second meiotic divisions. The first meiotic division begins with the pre-leptotene that is the stage where the DNA replicates and chromosomes prepare to enter the meiotic prophase I in most of the organisms with sexual reproduction (Marston & Amon, 2004). The first meiotic division separates one homologue chromosome from the other member of the pair and in this way the two produced cells contain half number of chromosomes with two chromatids. During the metaphase of the first meiotic division the maternal and the paternal chromosomes of the bivalents are oriented at random, so the two new haploid cells receive a random number of chromosomes of each progenitor.

After a brief interphase the second division separates the sister chromatids of each chromosome and then the products of this division have the haploid number of chromosomes provided with one DNA double helix, frequently composed by segments of maternal and paternal DNA. In male mammals the final products of meiosis are four spermatids with half of the number of chromosomes of the species, with only one DNA double helix. However, in female organisms the final product of meiosis is one haploid oocyte and two small cells with a nucleus and a very small cytoplasm called polar bodies, which are not viable. During fecundation the union of two haploid gametes, the oocyte and the spermatozoa, recreates a diploid cell.

One of the biological significances of the meiosis is the production of genetic variability by the exchange of DNA between homologous chromosomes. Such exchange takes place during an extended meiotic prophase I and in most of the organisms proper meiotic genetic exchange depends on the accurate formation of a proteic structure between the homologous chromosomes, the synaptonemal complex (SC, for detailed revision see: Zickler & Kleckner 1998, 1999; Page & Hawley, 2004). There are several models used to study the SC and its importance for meiotic recombination, including yeast, Drosophila, C. elegans, plants and mice. Each model has its advantages and disadvantages. The mouse system has some advantages despite the low speed of genetics. Mouse genome and hence its chromosomes are larger than those of yeast and flies. This makes immunocytochemical analysis more powerful than in many other model organisms. Mouse genetics has been effectively used in combination with cytology to examine meiotic phenotypes produced as a result of targeted mutagenesis in embryonic stem cells.

2. Meiotic prophase I

Meiotic prophase I has been divided in five stages according to the chromosome morphology, meiotic recombination progression and the SC assembling. The interplay among these processes has been widely reviewed in different organisms (see Zickler & Kleckner 1998, 1999; Page & Hawley, 2004; Handel & Schimenti, 2010). Recently, with the identification of the histone code and its importance in gene regulation, chromatin structure and nuclear architecture (Turner, 2000; Jenuwein & Allis, 2001), old questions regarding chromosome structure and SC formation could be addressed. In this chapter we will focus our interest on the chromatin structure driven by epigenetic modifications and its relevance for SC formation and establishment, especially in mammals.

2.1 From chromosome homology recognition to synapsis

During the period G2 following meiotic phase S (some times called pre-leptotene) begins the recognition of similar sequences in the extended chromatin of homologous chromosomes. This process of recognition continues in leptotene and zygotene stages in microlampbrush chromosomes (Fig. 1).

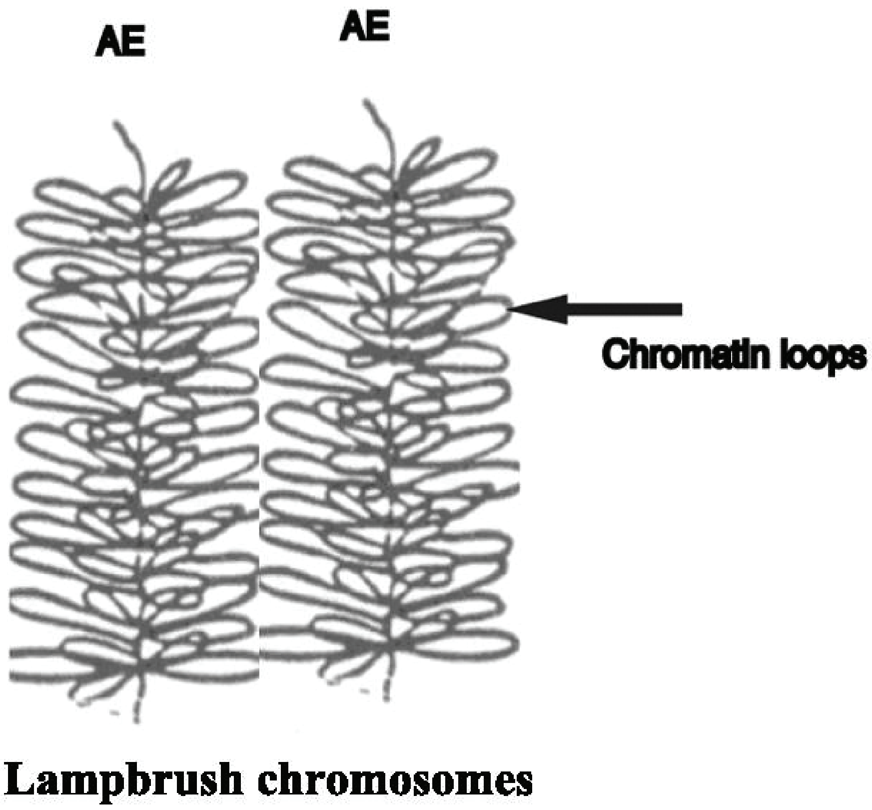

Fig. 1. Schematic drawing of the structure of homologous chromosomes in leptotene and zygotene stages of meiotic prophase during the process of alignment and recognition.

During pre-leptotene and leptotene the homologous chromosomes are not necessarily close to each other until the formation of the bouquet. The bouquet is a process that takes place during zygotene stage of the first meiotic prophase, the telomeres of the chromosomes slide associated to the nuclear membrane until they group in an area near the place of where the centrioles are located in the cytoplasm. In this way, the proximity of the chromosomes facilitates the recognition of homologies (Fig. 2)

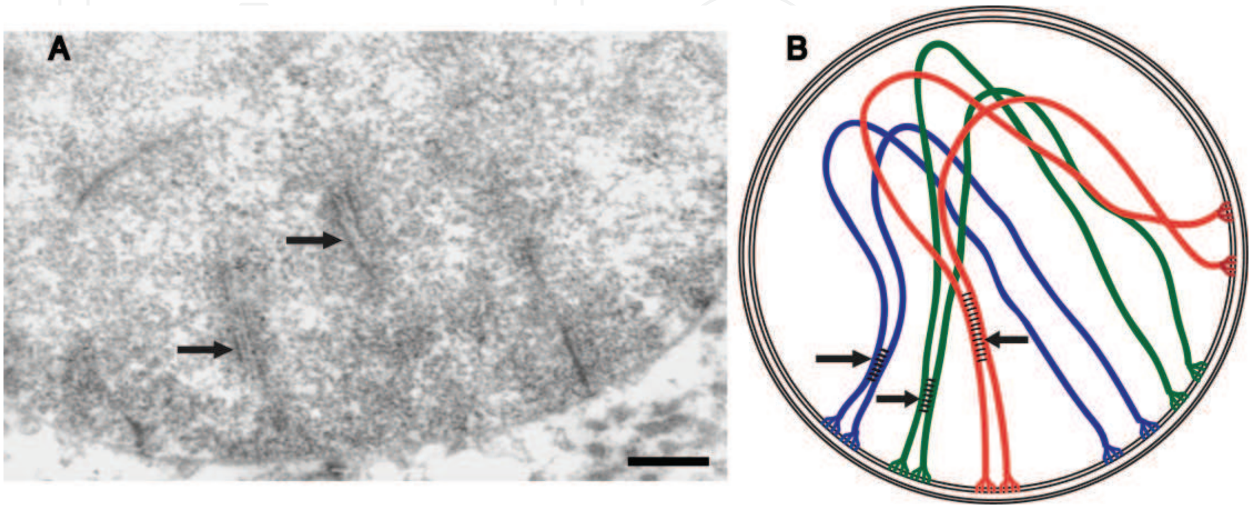

Fig. 2. A. - Electron microscopy image showing the pairing between homologous chromosomes (arrows) during the bouquet array and beginning of the formation of the synaptonemal complexes in zygotene stage. B. - Schematic representation of bouquet formation in zygotene stage. Homologous chromosomes migrate anchored to nuclear envelope until become close to each other, forming an array know as a bouquet. Synapsis takes place between homologous that are close enough to pair (arrows in A and B). Bar 500 nm.

The nature of the molecular mechanisms for this recognition of homologue sequences is not known, however, there are at least two processes proposed, one dependent on the distribution of transcription sites or factories (Cook, 1997) and the other dependent of non-spliced nascent RNA (Vázquez-Nin et al., 2003). According to the first view each chromosome has a unique array of transcription units along its length. Therefore, the chromatin fibrils with polymerases and transcription factors are folded into an array of loops, only the homologous chromosomes share similar distribution of loops with transcription factories and become zipped together (Cook, 1997). The second proposition also involves transcription as a possible mechanism of homology recognition. The study of the meiotic S phase (pre-leptotene), as well as leptotene and zygotene stages of meiotic prophase -that is the period of homology recognition and pairing- demonstrated an intense transcription but a very reduced pre-mRNA splicing. In this condition the newly synthesized mRNA could not be exported to the cytoplasm, as was demonstrated by quantitative autoradiography. So the function of newly synthesized mRNA must be inside the nucleus and in this period the main functions that were taking place inside the nuclei were homology recognition and pairing. Furthermore, electron microscope studies demonstrated a micro lampbrush structure of the chromosomes, which are in intense transcriptional activity. In pre-leptotene some loops of the micro lampbrush chromosomes contact loops of other chromosomes and the first parallel alignments of chromosomes take place (Fig. 1). Therefore, it was proposed that homologous chromosomes are in physical contact already at pre-leptotene stage (Vázquez-Nin et al., 2003). However it has not been shown a direct relationship of this chromosomal array with homology recognition.

During zygotene, as homologous chromosomes become aligned in pairs, the proteins of the lateral elements of the synaptonemal complex are incorporated to the chromosomal axis and the loops located between the axes leave the inter-axial space creating a region without DNA, which is the precursor of the central space of the synaptonemal complex.

3. The synaptonemal complex

The SC is a tripartite structure, which was described by Moses (1956) in spermatocytes of the crayfish. Since then it was found in all eukaryotic kingdoms (see reviews by Moses, 1956, 1968, 1969; Sotelo, 1969; Westergaard & von Wettstein 1972; Gillies, 1975; Loidl, 1990, 1991). SC morphology has been studied by means of electron microscopy. It is composed by two lateral elements (LEs) and a central region (CR). Each replicated homologous chromosome is anchored to one LE (Fig. 3), while completion of meiotic recombination (referred as crossover) takes place at late recombination nodules (RN) that are located in the CR (Fig. 3).

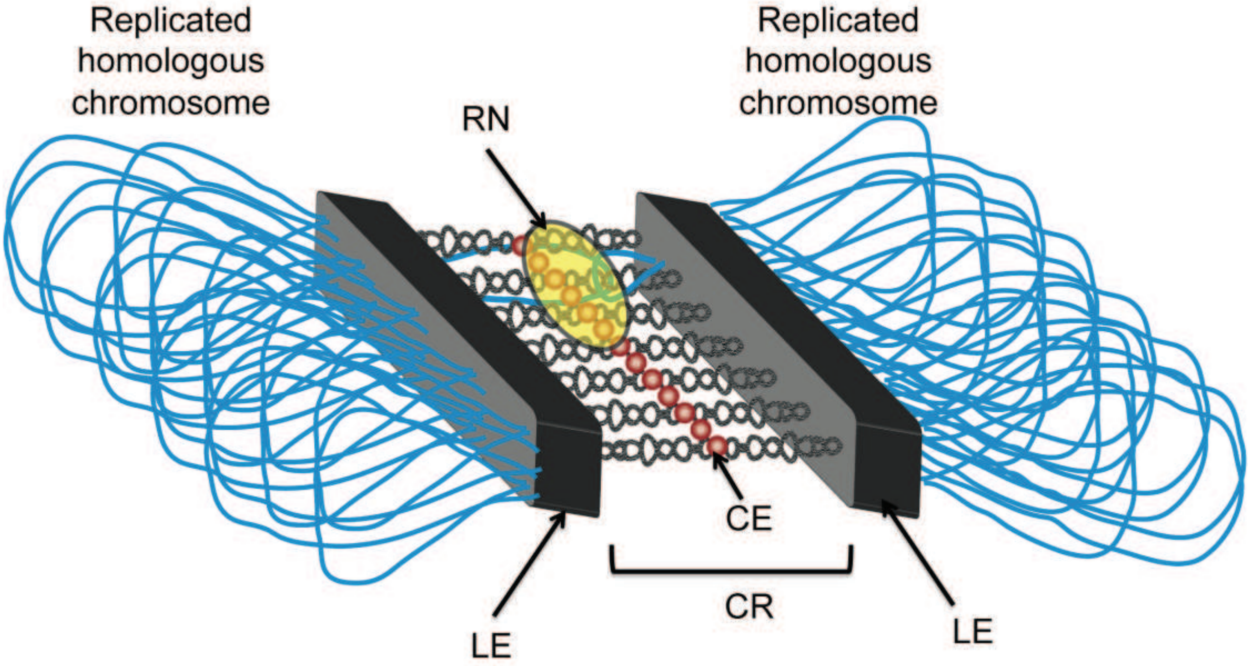

Fig. 3. Schematic representation of synaptonemal complex. The replicated homologous chromosomes are anchored to the lateral elements (LEs) of the synaptonemal complex (SC) while the genetic exchange between these homologous (referred as crossing over) takes place at the late recombination nodule (RN), that is tethered to the central region (CR).

The major protein components of the LEs are the meiosis specific proteins SYCP2 and SYCP3 (Dobson et al., 1994; Lammers et al., 1994; Offenberg et al., 1998; Winkel et al., 2009) as well as cohesion complexes (described below), whereas the CR is composed by SYCP1, SYCE1, SYCE2, SYCE3 and Tex12 (Figure 3) (Meuwissen et al., 1992; Costa et al., 2005; Hamer et al., 2008; Schramm et al., 2011). SYCP3 is a major structural component of vertebrate synaptonemal complexes. The evolutionary conserved domains of SYCP3, the alpha helix together with two flanking motif CM1 and CM2, are necessary and sufficient for SYCP3 polymerization and assembly of high order structures (Baier et al., 2007). Nevertheless, some differences in the SYCP3 expression have been found among mammals. In contrast to other vertebrates, rat and mouse SYCP3 exists in two isoforms. The short isoform is conserved among vertebrates. However, the longer isoform, which represents an N-terminal extension of the shorter one, most likely appeared about 15 millions years ago in a common ancestor of rat and mouse and after the separation of the hamster branch (Alsheimer et al., 2010). SYCP2 and SYCP3 incorporate to the axial elements of chromosomes during lepto-zygotene, forming fibrous cores in the homologous chromosomes (Hamer et al., 2008 and references therein).

The C-terminus of SYCP1 directly interacts with SYCP2 (Winkel et al., 2009). These authors proposed that SYCP2 acts as a linker between SYCP1 and SYCP3 and therefore it could be the connecting link between lateral elements and transverse filaments of the CR (Winkel et al., 2009). On the other hand, the N-terminus of SYCP1 is associated in the middle of the CR with another N-terminus of SYCP1 forming the central element (CE) of the CR. At the CE are also found the proteins SYCE1, SYCE2, SYCE3 and Tex12, which are important for the proper CR assembling and for the crossover resolution (Bolcun-Filas et al., 2007, 2009; Hamer et al., 2008, Schramm et al., 2011). Defects in the organization of the synaptonemal complex result in alterations of the meiotic recombination and infertility.

Cohesins are chromosomal proteins that form complexes involved in the maintenance of sister chromatid cohesion during division of somatic and germ cells. Three meiotic cohesins subunits have been reported in mammals, REC8, STAG3 and SMC1 beta, their expression has been found in mouse spermatocytes (Prieto et al., 2004) and human oocytes (García-Cruz et al., 2010). SMC1 beta, SMC3 and STAG3 are localized along axial fibers of leptotene-zygotene chromosomes and then to the LE of the SC. Cohesins are essential for completion of recombination, pairing, meiotic chromosome axis formation, and assembly of the SC. Rec8 is involved in several functions as cohesion, pairing, recombination, chromosome axis and SC assembly (Brar et al., 2009). At difference from meiosis in male mice, the cohesin axis is progressively lost in oocytes, with parallel destruction of the axial elements at dictyated arrest (Prieto et al., 2004).

The SC is important for the normal formation of crossovers. In many, but not all, organisms, the homology search, that occurs mediated by DNA-DNA interactions, is also intimately associated with the movement of homologous chromosomes to bring them into close juxtaposition (Székvölgyi & Nicolas, 2010).

Chiasmata formed by crossovers are central for the process of chromosome segregation as they hold together the homologous chromosomes at metaphase of the first meiotic division; at least one crossover per pair of homologs allows that each member of the pair migrates to an opposite pole of the spindle (Székvölgyi & Nicolas, 2010).

Most eukaryotes possess two recombinases, Rad51 and Dmc1. Homologues of these proteins are widely conserved in nature, from virus to humans. In eukaryotes Rad51 is required for most homologous recombination pathways in both mitotic and meiotic cells (Kagawa & Kurumizaka, 2009 and references therein).

4. Chromosome organization on the synaptonemal complex

As mentioned above, the SC is essential for meiotic recombination completion; this is because crossover formation depends in the accurate formation of the CR of the SC. The crossovers are observed as dense structures associated to the CR, as showed by electron microscopy. Crossovers are referred as late recombination nodules (RN, Fig. 3) and they are observed tether to the CR of the SC (Carpenter, 1975, 1979, 1981). Therefore, the SC is considered as the scaffold to which the chromosomes are anchored while they exchange genetic material.

After DNA replication at pre-leptotene stage, replicated sister chromatids are held together at specific points by the cohesion component SMC3 and the meiosis-specific cohesin Rec8 is incorporated to this scaffold. As the cells progress to leptotene stage, the chromosomes undergo condensation and SMC1 beta/STAG3, other meiosis-specific cohesins, are incorporated to the cohesion scaffold. At this stage fine filaments formed by the cohesin scaffold can be identified by immunocytochemical approaches. These filaments, called axial elements (AEs) are the precursors of the LEs and are surrounded by chromatin loops protruding out of them (Fig. 1). In this stage, SYCP2 and SYCP3 are incorporated to the AEs and in zygotene stage SYCP1 and accessory proteins begin to synapse the aligned AEs. During pachytene the SC is fully formed throughout the whole length of LEs. The homologous chromosomes are anchored to the AEs in early stages and to the LEs in pachytene stage. However the mechanism of association of the chromosomes to the AEs/LEs has been controversial and poorly understood.

The presence of DNA in the LEs was documented by enzymatic digestion followed by staining methods almost at the same time as the SC was observed (Coleman & Moses, 1964) and corroborated by immunocytochemical approaches in later studies (Vázquez-Nin et al., 1993). There have been few studies trying to identify DNA sequences associated to the LEs of the SC. In C. elegans, the chromosomes pair at specific areas known as pairing centers, recently it has been shown that repeat sequences motifs are at these pairing centers (Phillips et al., 2009). It has been suggested that in mammals repeat sequences interspersed through the genome, are responsible to anchor the chromosomes to the LEs (Pearlman et al., 1992; Hernández-Hernández et al., 2008). However not all the bulk of repeat sequences are incorporated into the LEs, suggesting a mechanism of selection of specific sequences to be anchored to the LE. Further experiments have shown that the chromatin structure at these lateral element-associated repeated sequences (LEARS) is in part responsible for their association to the SC (Hernández-Hernández et al., 2010).

4.1 Chromosomes anchor to the lateral elements by means of specific DNA sequences

The presence of DNA in the inner part of the LEs suggested that chromosomes are anchored by means of specific sequences. Two different studies have shown that LEs contain specific DNA sequences. One of the studies suggested that LEs associate DNA consist in repeat sequences like long and short interspersed elements (LINE/SINE) (Pearlman et al., 1992). In the second study the authors used chromatin immunoprecipitation (ChIP) using anti-sycp3 antibody to pull down DNA sequences associated to the LE (Hernández-Hernández et al., 2008). All the immunoprecipitated sequences consisted of repeat DNA, like LINE, SINE, long terminal repeats (LTR), satellite, and simple repeats. The presence of these sequences in the LEs has been corroborated by means of DNA in situ hybridization at the optical and electron microscope level (Hernández-Hernández et al., 2008; Spangenberg et al., 2010). Therefore, these specific sequences have been called lateral element-associated repeat sequences or LEARS. However the presence of some other sequences can not be ruled out with these studies, more analysis are needed to determinate whether these are the only sequences helping the chromosomes to anchor to the LEs.

5. Chromatin structure in the LEs of the SC

Chromatin immunoprecipitation experiment using the LEs specific protein SYCP3, demonstrated enrichment of repeat DNA sequences, which localize to the LEs, as well as in the bulk of the chromatin, as shown by in situ hybridization (Hernández-Hernández et al., 2008). However, features in the primary structure of LEARS did not reveal any obvious consensus sequence, suggesting that secondary structure might be responsible for recruitment of LEARS to the LEs. In somatic cells, most of these transcriptionally inactive repeat sequences are subject to epigenetic modifications favoring their organization in heterochromatin (Martens et al., 2005). Furthermore, chromatin structure dictated by epigenetic modifications during meiosis is critical for accurate SC assembly and meiosis progression (Hernández-Hernández et al., 2009). Therefore, it is possible that specific epigenetic modifications of LEARS influence their interaction with LEs. To address this hypothesis our group has performed immunofluorescent detection (IF) of histone post translation modifications (PTM) that are associated to repeat sequences in somatic cells (Martens et al., 2005). We found specific association of PTM with the SC during pachytene stage. Tri-methylation of histone H3 on lysine 9 and tri-methylation of histone H4 on lysine 20 (H3K9me3 and H4K20me3 respectively) co-localize with one extreme of the SCs (Fig. 4), whereas tri-methylation of histone H3 on lysine 27 (H3K27me3) co-localizes to the SC in almost all its length (Fig. 4). We then followed the dynamics of co localization of these specific marks throughout the meiotic prophase I.

Leptotene stage: at this stage, sycp3 antibody stains fine filaments that correspond to the axial elements. H3K9me3 and H4K20me3 are already co-localizing with one of the extremities of the AE. Centromeres are located close to the end of acrocentric chromosomes and in rat they are mainly composed of minor and mayor satellite DNA repeats. These sequences are enriched with the PTMs H3K9me3 and H4K20me3 (Martens et al., 2005). In cells undergoing meiosis and SC assembling, the centromeres are located near one of the extremes of the AE nearby the nuclear envelope. The staining pattern of H3K9me3 and H4K20me3 in the AE therefore may correspond to the satellite repeats present in the centromeric and pericentromeric region. H3K27me3 was absent from the whole nucleus at this stage.

Zigotene: the AEs of homologous chromosomes start to synapse. H3K9me3 and H4K20me3 are located in the extreme of the SC in formation.

Pachytene: The SC between homologous chromosomes is completely formed. H3K9me3 and H4K20me3 continue associated to one of the extremes of the SC (Fig. 4). In this stage

H3K27me3 staining pattern is visible and this PTM is co-localizing with SYCP3 throughout patches of the SC (Fig. 4). The results of these IFs suggest that these three histone marks may be involved in the chromatin structure at the LEARS in the LEs.

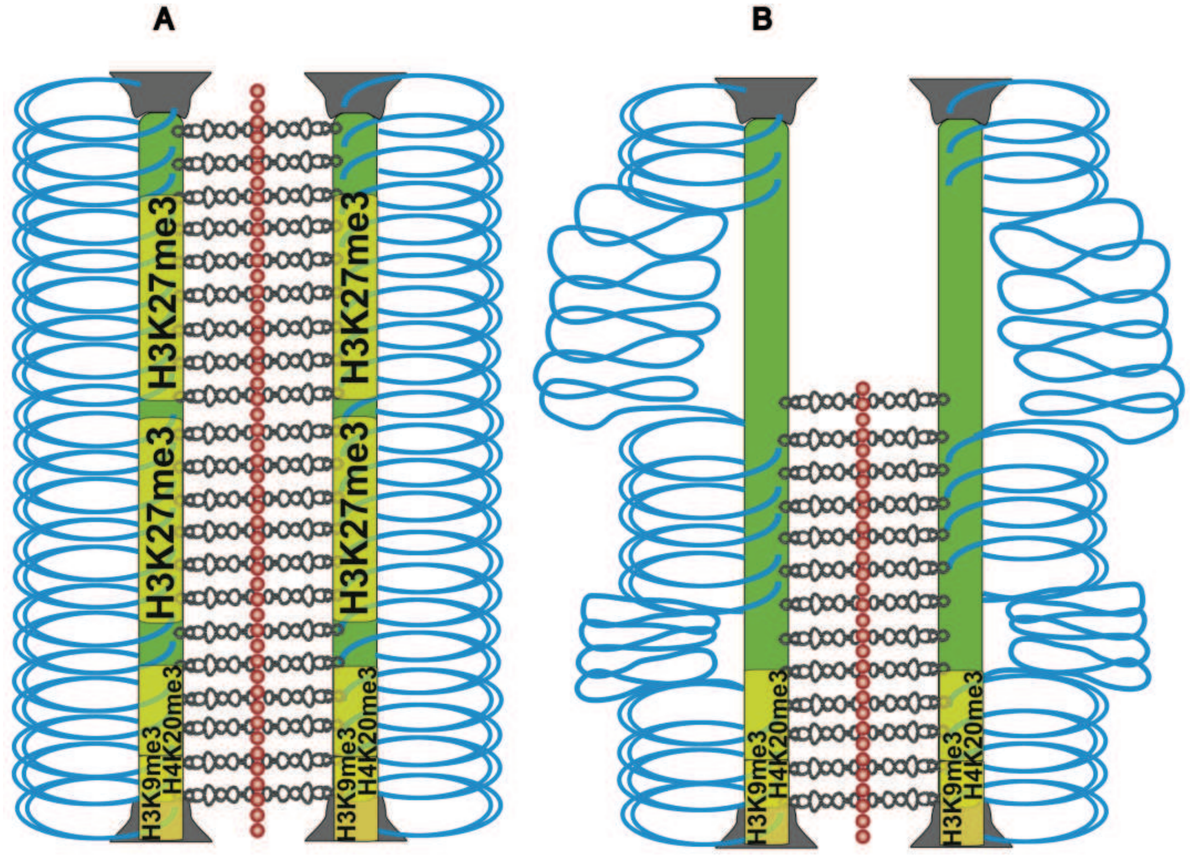

Fig. 4. Model of chromatin structure in the LEs of the SC. A. – Homologous chromosomes are attached to the LEs of the SC by means of specific DNA sequences (LEARS). These anchorage DNA sequences are enriched with histone PTMs that determinate their chromatin structure. B. – Blocking of chromatin structure leads to a defective chromosome anchorage to the LEs. H3K27me3 is not longer associated with SINE and LTR sequences producing their detachment from the LEs.

5.1 Epigenetic profile of LEARS

In order to understand whether the specific PTM are associated with the LEARS, we performed two rounds of ChIP assays (re-ChIP). The first round of ChIP analyses was done using the SYCP3 antibody to pull down the LEARS and the chromatin proteins associated to them. As a template for the second round of ChIP, we used the pulled down complexes from the first round of ChIP (SYCP3 and chromatin of LEARS) and pulled down DNA sequences associated with the distinct PTM of interest (H3K9me3, H3K27me3 and H4K20me3). Enrichment of the different LEARS with PTM marks was assessed by semi quantitative polymerase chain reaction (sqPCR) (Hernandez-Hernandez et al., 2010). Table 1 summarizes the enrichment of PTM in the different LEARS. Satellite repeats are enriched with H3K9me3 and H4K20me3, whereas LINE sequences are enriched with H4K20me3. SINE and LTR sequences are enriched with H3K27me3.

LEARS	Histone mark (PTM)		
	H3K9me3	H4K20me3	H3K27me3
LINE	-	Enriched	
SINE	-		Enriched
LTR	-		Enriched
Satellite	Enriched	Enriched	

Table 1. LEARS and their enrichment with histone marks

By analyzing the patterns of IF for PTMs/SC proteins during the meiotic prophase and the enrichment of PTM in the LEARS, we can predict whether or not histone PTMs have a role in the recruitment of LEARS to the LE of the SC.

H3K9me3 and H4K20me3 are already enriched in the satellite repeats of the centromeric region when the AE is formed during leptotene stage. Probably these marks are constitutive for satellite repeats, since in somatic cells this enrichment has been reported before (Marten et al., 2005). Therefore the likelihood that these PTMs are important for LEARS recruitment is scarce. LINE sequences are enriched with H4K20me3, the same PTM present in satellite sequences. However the staining pattern only resembles that for satellite sequences. LINE sequences are not confined to centromeric regions, rather they are present all along the chromosomes, therefore it would be expected that the staining pattern would be co localizing with SYCP3 not only at one of the extremes, but to the entire length of the SC. A possible explanation for the absence of IF signal for H3K20me3 in the whole length of the SC is that LINE sequences are not highly clustered as the satellite sequences in specific regions of the chromosome. The clustered satellite regions in one of the extremities of the SC produce a strong IF signal, making difficult to detect the signal of LINE sequences in regions were there is not clustering, for example along the LEs. Thus, LINE sequences are enriched with H4K20me3, but they are masked by the signal from satellite DNA regions.

5.2 A specific histone mark appears at the time the SC is mature

H3K27me3 colocalizes with SYCP3 along patches through the whole length of the SC. Strikingly; this pattern is only seen in pachytene stage when the SC is mature (Hernández-Hernández et al., 2010). Furthermore, this histone mark was enriched in SINE- and LTR-LEARS. These evidences suggest that SINE and LTR sequences are enriched with H3K27me3, conferring a specific chromatin structure that in turn is contributing to the LE structure, probably anchoring and/or maintaining the attachments of these sequences to the LEs.

To address this hypothesis, we decided to treat rat testicles with tricostatin-A (TSA), a histone desacetylase (HDACs) inhibitor, during nine days. After this period of treatment, pachytene cells have received the treatment since leptotene stage, according to the duration of meiotic prophase I (Adler, 1996). TSA has been shown to effectively inhibit HDACs, blocking downstream reactions and finally methylation of histone lysine residues (Ekwall et al., 1997). Then we perform IF, ChIP and re-ChIP experiments to assess the effect of HDACs inhibition on the SC structure (Hernández-Hernández et al., 2010).

H3K9me3 and H4K20me3 IF signal was reduced at pachytene stage, but the pattern is the same as that of non-treated animals. Suggesting that most of these marks were deposited on centromers before leptotene stage. In agreement with this, leptotene and zygotene cells, which have been treated since they were at pre-leptotene stages, showed reduced signal and more scattered IF pattern that in non-treated animals. TSA treatment therefore, partially affected deposition of these PTMs and chromatin structure as well. Enrichment of H3K9me3 and H4K20me3 in satellite sequences and H4K20me3 in LINE sequences was significantly reduced. However these two classes of LEARS are still attached to the LEs of the SC as shown by ChIP assays in treated and control animals (Hernández-Hernández et al., 2010). In summary, TSA affected enrichment of H3K9me3 and H4K20me3 in satellite and LINE sequences, but this loss of enrichment does not produce loss of these two LEARS from the LE of the SC. Implying that satellite and LINE sequences may have another unidentified PTM that is involved in their association to the LE or that these sequences do not associate to the LE via histone modifications. Moreover, staining pattern in treated animal at one of the extremes of the EA/LE, suggest that most of this mark was not altered during such a short period of treatment (Hernández-Hernández et al., 2010).

The most striking result was the observed for H3K27me3. The staining pattern for H3K27me3 is specific for pachytene cells, co localizing with SYCP3 along stretches of the SC. This PTM is also enriched in the SINE and LTR sequences attached to the LEs. After TSA treatment, the IF signal for H3K27me3 almost disappears from the nucleus of pachytene cells. Furthermore, the enrichment of this PTM in SINE and LTR was significantly reduced and these sequences were not longer associated to the LEs of the SC. These results suggest that H3K27me3 appears in pachytene stage and is important for attachment and/or maintenance of SINE and LTR sequences in the LEs o the SC (Hernández-Hernández et al., 2010).

5.3 Failures in pairing between homologous chromosomes and loss of DNA-associated to the LE

To evaluate the direct effect of loss of LEARS from the LEs of the SC, we analyzed the ultrastructure of the SC by means of optical and electron microscopy. IF staining of LEs and CR of the SC in sections allowed us to identify that homologous chromosomes are paired but synapsis is not complete. By means of electron microscopy we found a high incidence of LEs that were not synapsed. These defects in SC formation in turn activate the programmed cell death of spermatocytes in late pachytene stage observed in sections of seminiferous tubules. Furthermore, when homologous were partially synapsed, we identified failures in the CR structure. The CR was formed between the homologous but not throughout the entire length of the SC. By means of a specific ultrastructural DNA staining, we observed that the DNA pattern was less dense in the LEs of treated animals than in the LEs from non-treated rats (Hernández-Hernández et al., 2010). This suggested that DNA association to the LEs was altered and that the CR in not completely formed between the homologous chromosomes.

6. A model of the chromatin structure in the LEs of the SC

Taking in account all the evidences, we proposed that chromatin structure of a sub set of LEARS (SINE and LTR) is important for LEARS recruitment and/or maintenance in the LEs of the SC. Blocking of this specific chromatin structure leads to failures in SC structure, detachment of DNA sequences form the LEs (SINE, LTR DNA sequences) and finally to cell death. Therefore we suggest that H3K27me3 is an indispensable histone PTM important for chromosome attachment to the LEs and hence SC structure.

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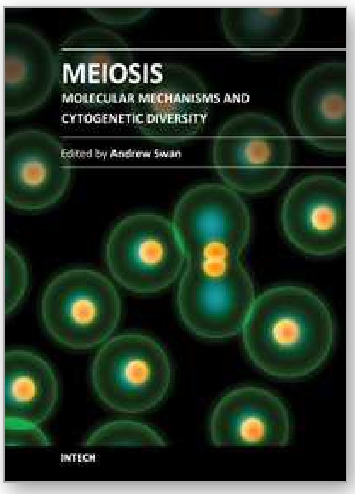

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