Available online at www.sciencedirect.com

ScienceDirect

Journal of Genetics and Genomics 41 (2014) 97−106

JGG

REVIEW

The Role of Chromatin Modifications in Progression through Mouse Meiotic Prophase

James H. Crichton, Christopher J. Playfoot, Ian R. Adams*

MRC Human Genetics Unit, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK

Received 15 October 2013; revised 10 December 2013; accepted 6 January 2014
Available online 22 January 2014

ABSTRACT

Meiosis is a key event in gametogenesis that generates new combinations of genetic information and is required to reduce the chromosome content of the gametes. Meiotic chromosomes undergo a number of specialised events during prophase to allow meiotic recombination, homologous chromosome synapsis and reductional chromosome segregation to occur. In mammalian cells, DNA physically associates with histones to form chromatin, which can be modified by methylation, phosphorylation, ubiquitination and acetylation to help regulate higher order chromatin structure, gene expression, and chromosome organisation. Recent studies have identified some of the enzymes responsible for generating chromatin modifications in meiotic mammalian cells, and shown that these chromatin modifying enzymes are required for key meiosis-specific events that occur during meiotic prophase. This review will discuss the role of chromatin modifications in meiotic recombination, homologous chromosome synapsis and regulation of meiotic gene expression in mammals.

KEYWORDS: Mouse; Meiosis; Chromatin; Chromosome; Histone modification; DNA methylation

INTRODUCTION

Meiosis is a specialised cell division involving a single round of DNA replication followed by two rounds of chromosome segregation to produce haploid gametes. During meiosis, chromosomes form a meiosis-specific organisational structure known as the synaptonemal complex (SC), and undergo homologous recombination to enable the pairing and subsequent segregation of homologous chromosomes (Cohen et al., 2006; Handel and Schimenti, 2010; Ollinger et al., 2010). The progressive formation of the SC is used to cytologically define the substages of meiotic prophase during which recombination takes place (Fig. 1). SC formation begins in leptotene with short filaments of proteinacious axial element assembling along each homologous chromosome, providing anchorage points for chromatin loops. Recombination also begins in leptotene with the generation of hundreds of targeted DNA double strand breaks (DSBs) across the genome. DSBs recruit recombination proteins such as RAD51 and DMC1 which promote a search for the chromosome's homologous partner to repair the damage. The axial element extends across the length of each chromosome axis and the homology search brings homologous chromosomes into close proximity stimulating synapsis in zygotene stage nuclei. Synapsis spreads along the axis of all paired chromosomes with the exception of the X and Y sex chromosomes in male spermatocytes which only pair in their region of homology, the pseudoautosomal region. Complete synapsis is a characteristic of pachytene nuclei. DSBs progressively mature by

Abbreviations: 5mC, 5-methylcytosine; DSB, double strand breaks; γH2AX, phosphorylated histone H2AX; H3K27me3, histone H3 lysine 27 tri-methylation; H3K4me3, histone H3 lysine 4 tri-methylation; H3K9me1/2/3, histone H3 lysine 9 mono-/di-/tri-methylation; MSCI, meiotic sex chromosome inactivation; MSUC, meiotic silencing of unsynapsed chromatin; PCH, pericentromeric heterochromatin; PRC, polycomb repressive complex; SC, synaptonemal complex; UbH2A, ubiquitinated histone H2A.

* Corresponding author. Tel: +44 131 332 2471, fax: +44 131 467 8456.
E-mail address: Ian.Adams@igmm.ed.ac.uk (I.R. Adams).

http://dx.doi.org/10.1016/j.jgg.2014.01.003

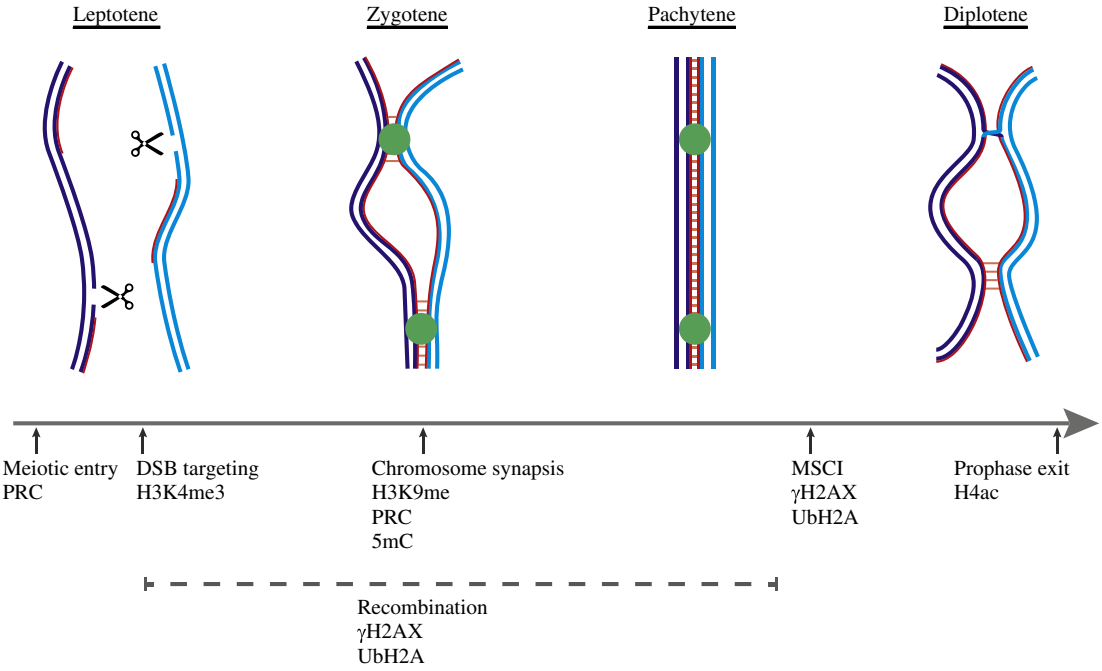

Fig. 1. Meiotic prophase and events requiring chromatin modifications.
Replicated homologous chromosomes (light and dark blue) are held together during meiotic prophase. DNA double strand breaks (DSBs) are generated by the endonuclease SPO11 in leptotene (indicated by scissors) while the axial element of the synaptonemal complex (red) assembles on chromosomes. DSBs recruit recombination proteins (green foci) and homologous chromosomes begin to pair and synapse (red connections) in zygotene. Synapsis is completed in pachytene and DSBs repair, with some producing crossovers connecting homologous chromosomes in diplotene as the synaptonemal complex disassembles. Abbreviations for chromatin modifications are as described in the text; H4ac, histone H4 acetylation.

association with recombination machinery and are repaired through prophase. Repair of a sub-population of DSBs generates crossovers in late pachytene which physically link homologous chromosomes together after the SC disassembles during diplotene. Crossover interference helps distribute the crossovers between chromosomes so that every chromosome pair has at least one (Cohen et al., 2006; Handel and Schimenti, 2010; Ollinger et al., 2010).

The chromosomes in meiotic cells, like those in mitotic cells, comprise a complex of DNA and protein known as chromatin. The basic structural unit of chromatin is the nucleosome: approximately 200 base pairs of DNA wound round a central octamer of the core histones H2A, H2B, H3 and H4 (Fig. 2). Histone H1, a linker histone, can associate with the core nucleosomes to mediate their organisation into higher order structures with different levels of compaction (Bannister and Kouzarides, 2011; Musselman et al., 2012; Zentner and Henikoff, 2013). Chromatin can be modified by methylation of the DNA, and methylation, acetylation, ubiquitylation and phosphorylation of the core histones. Chromatin modifications are generated and removed by specific 'writer' and 'eraser' enzymes, and these modifications can influence chromatin function by directly altering its structure and by recruiting 'reader' proteins that recognise these modifications. Chromatin modifications play important roles in the regulation of gene expression, chromosome compaction and organisation, and DNA repair in mitotic cells (Bannister and Kouzarides, 2011; Deaton and Bird, 2011; Cedar and Bergman, 2012; Musselman et al., 2012; Zentner and Henikoff, 2013), and there is also growing evidence to suggest these modifications play similar roles in meiosis. Here we will review the role of chromatin modifications, and the proteins that read, write and erase those modifications, during meiotic prophase in mice.

POLYCOMB REPRESSIVE COMPLEXES AND MEIOTIC ENTRY

Polycomb repressive complexes (PRCs) are one of the major regulators of gene expression in mammalian cells, binding target gene loci to induce specific histone modifications, chromatin compaction and transcriptional repression (Simon and Kingston, 2013). PRC1 and PRC2 catalyse the mono-ubiquitination of histone H2A at lysine 119 (UbH2A) and the tri-methylation of histone H3 at lysine 27 (H3K27me3), respectively (Cao et al., 2002, 2005; Simon and Kingston, 2013). Canonical repression through PRC1 and PRC2 is thought to involve initial recruitment of PRC2 to target loci, which then induces H3K27me3 at these sites. PRC1 is recruited by H3K27me3, which in turn induces UbH2A (Simon and Kingston, 2013). Hence, PRC1 is both a reader and writer of chromatin modifications. At least for some target genes PRC1-dependent chromatin compaction and repression of gene expression does not depend on its ability to ubiquitinate histones (Eskeland et al., 2010; Endoh et al., 2012), suggesting that PRC1 may be capable of repressing gene expression directly. In addition to canonical PRC repression, PRC1 and PRC2 can act independently to repress