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SWI/SNF2 proteins in germinal and early embryonic development

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A b s t r a c t . Specific transcription factors participate in the decision making process that controls cell fate and differentiation. They function in the environment of chromatin and directly affect its structure and activity. This influence is especially apparent during the developmental regulation of gametes and in the course of the development of an early embryo. This review focuses on the role that Snf2h (Smarca 5) and Brg1 (Smarca 4), two factors belonging to the SWI/SNF2 family, play in the establishment of chromatin structure in germinal and early embryonic development.

Key words: ISWI, Snf2h, Smarca5, Brg1 (Smarca 4), chromatin, epigenetic, stem cell, primordial germ cell

Introduction

Both development and maintenance of gene expression patterns rely on epigenetic instructions provided by basic nuclear components: complexes of DNA and histone proteins referred to as chromatin (B e r n s t e i n et al. 2007). *De novo* establishment of the gene expression during development requires changes in the DNA methylation status, post-translational modifications of histones (K o u z a r i d e s 2007) and chromatin remodeling activity (d e l a S e r n a et al. 2006), all affecting chromatin accessibility to transcription factors throughout cell cycle progression. SWI/SNF2 (mating type switch/ sucrose non-fermenting) chromatin remodeling complexes utilize energy to perturb histone-DNA contacts in order to change the position of histone octamers on DNA resulting either in the nucleosome-depleted DNA regions or densely packed arrays of nucleosomes. The SWI/SNF2 family of ATP-dependent helicases (also known as translocases) is divided into four subfamilies, SWI/SNF2, ISWI, CHD and INO80 (Fig. 1), which are involved in mechanistically distinct types of chromatin remodeling (C a i r n s 2007). The regulation of chromatin mobility through SWI/SNF2 dependent remodeling is crucial for virtually all developmental and cell differentiation processes (some of which are reviewed in d e l a S e r n a et al. 2006), including changes in the germinal and postzygotic chromatin.

C h r o m a t i n i n p r i m o r d i a l g e r m i n a l s t e m c e l l s (P G C)

Mouse germinal cells originate from primordial germ cells (PGC) during early embryonic development around gastrulation (E5-E7) in the epiblast of the postimplantation egg cylinder. This process of the PGC origination is controlled by signals from the extraembryonic ectoderm and visceral endoderm represented by bone morphogenetic proteins (*Bmp2, Bmp4, Bmp8b*). PGC

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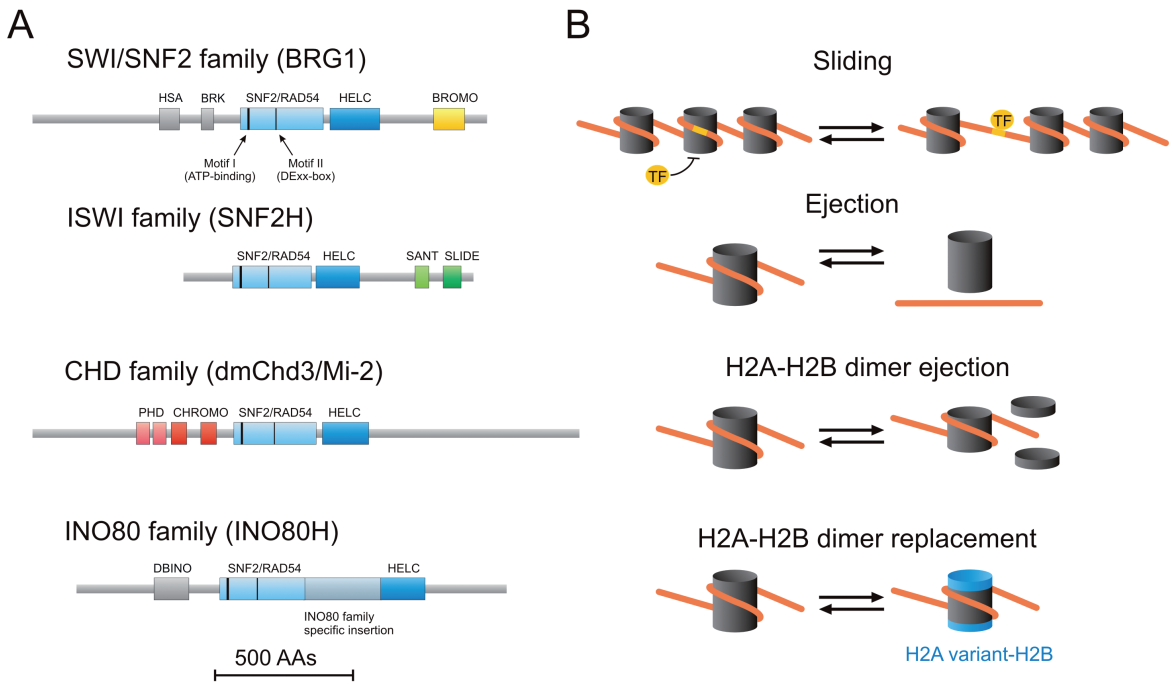

Fig. 1. Structure of major SWI/SNF ATPases and their function. A) SWI/SNF2 superfamily of helicases consists of the SWI/SNF2, ISWI, CHD, and INO80 subfamilies. Primary protein structure of SWI/SNF2 proteins is shown relative to their sizes. Individual domains are shown in color boxes representing their homology within SWI/SNF2 superfamily. HSA = helicase/SANT-associated domain, BRK = BRM and KIS domain, SNF2/RAD54 = helicase N-terminal domain, HELC = helicase C-terminal domain, BROMO = bromodomain, SANT = Swi3, Ada2, NCoR, TFIIIB domain, SLIDE = SANT-like domain, PHD = (Plant homeodomain)-type zinc finger domain, CHROMO = chromodomain, DBINO = DNA binding domain of INO80. Helicase motifs I (Walker A) and II (Walker B) of the SNF2/RAD54 domain are indicated by arrows. B) Members of SWI/SNF2 superfamily regulate nucleosome structure and position by a mechanism of nucleosome sliding and disruption (ejection), histone dimer H2A-H2B removal and replacement. Differences exist between SWI/SNF2 and ISWI subfamilies in the sliding mechanism: most ISWI complexes equally space nucleosomes whereas SWI/SNF2 randomize position of a nucleosome on the template. In addition, SWI/SNF2 remodelers can eject nucleosomes. Both subfamilies are capable of histone dimer ejection whereas solely the INO80 remodeler can reverse this reaction, which is presumably involved in the DNA repair (adapted from C a i r n s 2007). SWI/SNF2 complexes alter the nucleosomal structure, and each probably recognizes particular epitopes on the nucleosome through specific domains including the bromodomain or chromodomain. H2A-H2B dimers are replaced with dimers bearing a histone H2A variant (Htz1 or H2A.Z) by the SWR1 complex. TF denotes a transcription factor with a DNA binding site masked by the nucleosome octamer.

specification involves both gene repression of somatic program (*Hoxb1, Fgf8* and *Snail*) and activation of PGC lineage-specific genes (*Sox2, Nanog*) (reviewed in H a y a s h i et al. 2007). Among the most important transcriptional regulators in PGCs, Blimp1 (*Prdm1*) appears to be involved in the establishment of the PGC founder program (O h i n a t a et al. 2005). Blimp1 recruits arginine-specific histone methyltransferase Prmt5 to mediate arginine dimethylation of histone H2AR3 and H4R3 tails. These histone modifications are found in PGCs together with two other histone methylations: H3K27Me3, H3K4Me2 and H3K4Me3, whereas H3K9Me3 is not detected in PGCs until E11.5 (reviewed in H a y a s h i e t al. 2007).

One of the most important factors in developing PGCs is the methylation status of certain developmental genes, retrotransposons and imprinted genes, all specifically modified by DNA methyltransferases (Dnmt), which either create a *de novo* methylation pattern (Dnmt3a and Dnmt3b) or maintain already existing methylation pattern (Dnmt1). Dnmt's are also developmentally regulated at the transcriptional level, leading to production of different germ cell-specific transcripts with multiple functional differences, including mRNA stability (e.g. oocyte-specific Dnmt1o). Interestingly, in the male germ line DNA methylation occurs premeiotically, whereas in oocytes it is executed postmeiotically at the diplotene stage (reviewed in S c h a e f e r et al. 2007). When the methylation apparatus in germinal cells fails, the biallelic expression of target genes appears. For example, maternal loss of Dnmt3l by gene inactivation results in biallelic expression of genes that are normally methylated and repressed, causing death of Dnmt3l heterozygote embryos (B o u r c ' h i s et al. 2001). In contrast, the loss of Dnmt3l in male germ cells results in the failure to silence retrotransposons, causing cell death at the pachytene stage (B o u r c ' h i s et al. 2001). Dnmt3l lacks DNA methyltransferase activity and probably cooperates with Dnmt3a and Dnmt3b specifically in germ cells by "interpreting" the preexisting mark(s) on DNA or on histones.

After migration into gonads around E11.5, PGCs undergo a marked DNA demethylation accompanied with extensive erasure of several histone modifications (H a j k o v a et al. 2008). Mechanisms, which are involved in such change of chromatin architecture, involve histone exchange that is responsible for generation of totipotency by cooperating with yet unknown chromatin remodeling machinery. Initiation of chromatin changes at E11.5 represents "loosening of chromatin" by depletion of histone H1, followed by disappearance or redistribution of HP1s (α, β, and γ), Atrx, Cbx2, and also repressive histone marks: H3K9Me3, H3K27Me3, and H4/H2AR3Me2 (H a j k o v a et al. 2008). However, the permissive chromatin structure established by the aforementioned processes persists only transiently and already at E12.5 the chromatin of PGCs resembles the chromatin state of surrounding somatic cells. Histone exchange between modified histones and "back up" histone variants H2A.Z and H3.3 as well as histone H1 depletion during the transient chromatin change likely require histone chaperones such as chromatin assembly factor 1 (CAF-1) and nucleosome assembly protein 1 (NAP-1). In *Drosophila,* NAP-1 has been shown to genetically interact with dACF (ATP-utilizing chromatin assembly and remodeling factor), a complex that catalyzes the ATP-dependent assembly of periodic nucleosome arrays in vitro, and consists of the Acf1 protein and Iswi ATPase (F y o d o r o v et al. 2004). In addition, H1 has been shown to be deposited into chromatin by ISWI and experiments using a dominant negative form of ISWI resulted in dramatic alteration of higher-order chromatin structure (decondensation) and significant reduction of H1 associated with chromatin *in vivo* (C o r o n a et al. 2007). Thus SWI/SNF2 factors are candidate molecules for involvement in chromatin regulation in PGCs around day E11.5.

Further specification of PGCs is instructed by Blimp1/Prmt5 complex until they reach the genital ridges (Ohinata et al. 2005), where they differentiate into gonocytes and stay in G0 until birth. Development of male germinal stem cells, so called *spermatogonial stem cells (SSCs)*, residing near the basal membrane of the seminiferous tubule in the testis involves development of a specific microenvironment (or niche) containing Sertoli cells. SSCs in this niche retain their stem cell potential, which allows them to be successfully transplanted into acceptor animals and form stem cell colonies and differentiating spermatogonia (reviewed in Brinster 2002). Oct4 (*Pou5f1*) and SRY-box containing gene 2 (*Sox2*), known determinants of embryonic stem (ES) cell pluripotency, are among the most important transcriptional regulators controlling SSC development. *In vitro* cultivation of SSCs require Glial cell line-derived neurotrophic factor (*Gdnf*) and also similarly as ES cells grow on feeder layer in cell islands (reviewed in Brinster 2007). Gdnf signalling thus appears to be important for the regulation of those nuclear components in SSCs (including N-myc (*Mycn*) and other transcription factors such as *Creb1, Atf1, Crem* and *Fos* that regulate cell proliferation and self-renewal (reviewed in Hofmann 2008). In addition, other factors such as Fibroblast growth factor 2 (*Fgf2*) and Notch signaling are also important for SSC proliferation and self-renewal (reviewed in Hofmann 2008). The germinal stem cells maturate into primary spermatocytes, that enter meiosis consisting of two rounds of cell division, during which the cellular DNA content is reduced twice by mechanisms involving replication of DNA, homologous recombination between sister chromatids, and subsequent separation of diploid material into the haploid round spermatid. The following steps (particularly evident during spermiogenesis) include *histone-to-protamine* transition, that represents replacement of histone proteins in chromatin with transition nuclear protein (Tnp1, Tnp2) and subsequently with the protamines (Prm1, Prm2) (reviewed in Kimmins et al. 2004, Zamudio et al. 2008). In females, PGCs finish their stem cell potential in response to extracellular signals and meiotic division in order to finally become oocytes. The maturated oocytes, which become fertilized, proceed from metaphase of meiosis II, and transform to zygote and pronuclei. At the zygote formation stage no transcription occurs and instead mRNAs encoding homeostatic genes are mobilized from cytoplasmic complexes, that block translation initiation (reviewed in Stitzel & Seydoux 2007).

The growing evidence suggests that ATP-dependent proteins of SWI/SNF2 family are responsible for some structural properties of chromatin in the developing germinal cells. Major ATPases from the SWI/SNF2 superfamily, *Brahma-related gene 1* (*Brg1, Smarca4*) and *Sucrose non-fermenting 2 homologue* (*Snf2h, Smarca5*), are highly expressed in germinal cells indicating high turnover of chromatin remodeling, however their exact roles in germinal cell differentiation and gamete development remain largely unknown. Recently it has been reported that decreased levels of ISWI ATPase Snf2h in males heterozygous for the *Smarca5* null-allele (Stopka & Skoultchi 2003) in the paternal line affected gene expression in wild-type offspring as compared to offspring derived from wild-type males (Chong et al. 2007), thus indicating that chromatin structure can be at least in part inherited. Other chromatin modifiers present in germinal cells such as DNA and histone modification enzymes (Chong et al. 2007, Ashe et al. 2008) also influence the overall chromatin structure. It is not clear how the effect of Snf2h on chromatin structure in germinal cells is preserved through the process of meiosis, *histone-to-protamine* transition, zygote formation and *de novo* chromatin formation at the morula stage. One possibility is that certain histone modification changes may be preserved (and inherited) in the

heterochromatin; a notion supported by the germinal cell requirement of H3K9 histone methyl transferases (HMTs), Suv39h or G9a (Peters et al. 2001, Tachibana et al. 2007). Another possible mode of transmitting the specificity of chromatin structure is that some histone modifications are reflected in the DNA methylation pattern in germinal cells. This idea is supported by germinal cell requirement for *de novo* (*Dnmt3a, Dnmt3b, Dnmt3l*) and maintenance (*Dnmt1*) DNA methyltranferases (reviewed in Goll & Bestor 2005), which regulate DNA methylation pattern of both germinal cells and the progeny derived from these cells. Once established, gene expression pattern in germinal cells is presumably marked by histone modification and sequence specific chromatin compaction, so later at zygotic stage the transcription factors may rapidly target specific early genes and activate their transcription. Members of SWI/SNF2 family are major candidates to be involved in these processes (reviewed in Zamudio et al. 2008). Lessons on how SWI/SNF2 proteins coordinate their activities with histone modification enzymes at specific genes may be learned from somatic cells, where the mechanistic link exists between histone modification and chromatin remodeling proteins (summarized in the Table 1). For example, Snf2h and Brg1 are enriched at actively transcribed regions at promoters marked by methylated H3K4 and H3K79 (Kouskouti & Talianidis 2005). As transcription is blocked by exogenously added α-amanitin, most factors are expelled from chromatin while the histone modifications remain suggesting that the interplay between SWI/SNF2 factors and nucleosomal histones may induce relatively stable epigenetic memory (Jenuwein & Allis 2001, Kouskouti & Talianidis 2005). Snf2h also cooperates with another chromatin remodeling factor, Acf1, to establish global nucleosome assembly (Fyodorov et al. 2004). The bromodomain-contaning Acf1 subunit allows both histone modification recognition and DNA binding, while Snf2h allows DNA binding through its helicase domain.

Snf2h cooperates with specific transcription factors, histone proteins and also with DNA methylation machinery, either directly or indirectly: Snf2h is known to be recruited by Tip5 during nucleolar silencing of rRNA genes leading to inhibition of RNA polymerase I and distinct heterochromatin formation with a specific DNA methylation outcome (reviewed in Fyodorov et al. 2004, Grummt & Ladurner 2008 and references therein). There are examples of interactions of Snf2h with tissue specific transcription factors and specific DNA regions in somatic cell systems including Gata-1 during erythropoiesis (Rodriguez et al. 2005) and c-Maf during lens development at αA-crystalline promoter (Yang et al. 2006). Snf2h can also be targeted by the Rad21 subunit of the cohesin complex (together with Chd3/4, Hdac2 and RbAp48) onto DNA near Alu sequences and this targeting is further facilitated by an inhibitor of DNA methylation (Hakimi et al. 2002). Snf2h is a major candidate for global chromatin guidance as it cooperates with another protein called 'Special AT-rich binding 1', Satb1, (in a complex together with Acf1, Chd3/4, Mta2, and Hdac1, Hdac2 and Sin3A) and is responsible for creating approximately 7-kb nucleosomal positioning at Il2rα locus that is needed for its silencing during T-cell development (Yasui et al. 2002). Cooperation of chromatin remodeling and histone modification enzymes is also supported by the fact that ISWI binds and co-localizes at specific chromosome domains with the histone deacetylase (HDAC) complex containing the adaptor Sin3A, that regulates histone H4 deacetylation (Burgio et al. 2008).

Chromatin in early zygote development

During the 'maternal-to-zygotic' transition the embryonic transcription starts while "unwanted" mRNA is degraded. This process of the zygotic transcriptional activation is still not well

Table 1. Histone modifications associated with SWI/SNF2 superfamily. Each SWI/SNF2 ATPase forms distinct complexes that are involved in the transcriptional regulation: both activation and repression. Histone modifications that associate with these SWI/SNF2 complexes are also shown.

ATPase	Complexes	Role in transcriptional regulation	Recognized histone modifications	Reference
BRG1/BRM*	BAF Complexes*	Transcriptional activation	rec. H3K14Ac rec. Ac	Shen et al. 2007
	PBAF Complexes*	Transcriptional activation	rec. H3K14Ac rec. Ac	Shen et al. 2007
	WINAC complex	Transcriptional activation	rec. H3K14Ac	Shen et al. 2007
	NUMAC complex	Transcriptional activation	rec. H3K14Ac iMe H3R2, H3R17, H3H26	Shen et al. 2007 Chen et al.. 1999
	NCoR complex	Transcriptional repression, gene silencing	rec. H3K14Ac dAc	Shen et al. 2007
	mSin3A/HDAC complex	Transcriptional repression, gene silencing	rec. H3K14Ac iMe H4R3, iMe H3R8 and dAc	Shen et al. 2007 Pal et al. 2004
SNF2H/SNF2L**	ACF	Chromatin assembly	?	
	CHRAC	Chromatin assembly	?	
	WICH**	Nucleosome assembly and transcriptional repression rRNA genes	?	
	NORC	Transcriptional repression of rRNA genes	rec. H4K16Ac	Zhou et al. 2005
	RSF	Nucleosome spacing	rec. Me ?	
	SNF2H-Cohesin complex	Chromosome segregation	rec. $H3K4Me_3$? rec. MeCpG, dAc	
	NURF**	Transcriptional activation	rec. $H3K4Me_3$	Li et al. 2006
	CERF**	Transcriptional activation	rec. $H3K4Me_3$?	
CHD1	NuRD complex	Transcriptional repression by histone deacetylation and nucleosome remodeling	rec. $H3K4Me_3$	Sims et al. 2005
CHD1L			rec. Me ?	
CHD2			rec. Me ?	
CHD3 and CHD4			rec. $H3K4Me_3$? rec. MeCpG, dAc	
CHD5			rec. Me ?	
CHD6			rec. Me ?	
CHD7			rec. Me ?	
CHD8	CTCF-CHD8	Insulation and epigenetic regulation at active insulator sites	rec. Me ?	
CHD9		Transcriptional coactivator for NRs	rec. Me ?	
INO80H	INO80 complex	DNA repair and histone dimer exchange	?	

rec – recognition histone mark, d – decreased, i – increased, Ac – acetylation, Me – methylation, ? – expected/unknown

understood, but it appears to be regulated at multiple chromatin levels including; (a) specific chromatin proteins such as histone and DNA modifiers; (b) transcription factor and cofactor availability (such as TATA-binding protein, TBP); and (c) cell cycle regulators (reviewed in Schier 2007). SWI/SNF2 superfamily members are involved in the zygote formation and subsequent developmental steps. Both Brg1 and Snf2h cooperate with the Transcription Intermediary Factor 1 alpha (*TIF1α*, *Trim24*), which modulate gene expression during the first wave of transcription activation at 1-cell stage (Bultman et al. 2006, Torres-Padilla & Zernicka-Goetz 2006). TIF1α is a candidate for the targeting of RNA polymerase II and some other chromatin associated proteins (*Hmgb1, Brg1, Brm, Snf2h*) to actively transcribed loci in the pronuclei during the late zygote stage and up to the inner cell mass (ICM) stage. Bromodomain, a structural motif of TIF1α, is likely to be responsible for the chromatin context recognition and allows to dock proteins from SWI/SNF2 family at predetermined sites. Although, TIF1α recognizes actively transcribed regions and facilitates the loading of chromatin remodeling proteins at these sites, apparently it is not involved in the initiation, but rather in the maintenance of transcription. Snf2h is directly involved in this process since its downregulation causes inappropriate expression of TIF1α target genes at the zygote stage (Torres-Padilla & Zernicka-Goetz 2006). Role of Snf2h at the postzygotic gene regulation is supported by the data from the studies of *Xenopus*, which demonstrate the requirement of ISWI for TATA binding protein-mediated gene expression reprogramming of the somatic nuclei transplanted into unfertilized eggs (Kikyo et al. 2000). Key roles of Snf2h and Brg1 in the early zygote suggest that chromatin structure remodeling is required for the establishment of the embryonic transcription profile. At the early zygote development several histone H3 modifications of chromatin can be recognized by antibodies for H3K4Me and H3K9Me, that stain the maternal and markedly less the paternal pronucleus (Sarmento et al. 2004). Latter, at morula and blastocyst stages, these modifications are still similarly detectable in the nuclear staining (Sarmento et al. 2004). However, there are histone modifications, including H4 acetylation (K5, K8, K12, and K16) and methylation of R3 and R17 residues of H4, that dynamically change during early blastocyst stage and appear early during sperm chromatin decondensation (Sarmento et al. 2004). As the embryo develops at ICM stage, additional regulators including key transcription factor Oct4, become crucial for the control of the pluripotency of the stem cells (Niwa 2001, Tielens et al. 2006). This notion is supported by recent work demonstrating requirement of Oct4 together with other transcription factors Klf4 or c-Myc for reprogramming of human adult somatic cells into pluripotent stem cells (Kim et al. 2008, Meissner et al. 2008). Pluripotency of stem cells also requires precise regulation of the chromatin structure (Gao et al. 2008). Mice deficient for major SWI/SNF2 factors, *Smarca4* (Brg1) and *Smarca5* (Snf2h), display lethal phenotype at the pluripotent developmental stage around implantation (Bultman et al. 2000, Stopka & Skoultchi 2003). In addition, further studies identify specific roles for SWI/SNF2 factors in regulating adult transcription programs during blood cell commitment at the multipotential progenitor stage (Gebuhr et al. 2003, Stopka & Skoultchi 2003, Kim & Bresnick 2007).

Conclusions

Epigenetic regulation of gene expression patterns is initiated during germinal and early postzygotic development. There are indications that some of the structural properties of chromatin are initiated at the germinal stage and that proteins of SWI/SNF2 family including

Snf2h are closely involved in their formation and preservation. The SWI/SNF2 family of chromatin remodelers has been extensively studied in the contexts of normal differentiation (reviewed in de la Serna et al. 2006) and human pathology (reviewed in Kokavec et al. 2008). Here we summarized the evidence for mechanisms involving SWI/SNF2 family proteins, specifically Snf2h, in the regulation of chromatin structure changes in germinal cells, during formation of the zygote, and in the development up to the pluripotent stem cell stage.

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LITERATURE

Ashe A., Morgan D.K., Whitelaw N.C., Bruxner T.J., Vickaryous N.K., Cox L.L., Butterfield N.C., Wicking C., Blewitt M.E., Wilkins S.J., Anderson G.J., Cox T.C. & Whitelaw E. 2008: A genome-wide screen for modifiers of transgene variegation identifies genes with critical roles in development. *Genome Biol. 9: R182*.

Bernstein B.E., Meissner A. & Lander E.S. 2007: The mammalian epigenome. *Cell 128: 669–681*.

Bourc'his D., Xu G.L., Lin C.S., Bollman B. & Bestor T.H. 2001: Dnmt3L and the establishment of maternal genomic imprints. *Science 294: 2536–2539*.

Brinster R.L. 2002: Germline stem cell transplantation and transgenesis. *Science 296: 2174–2176*.

Brinster R.L. 2007: Male germline stem cells: from mice to men. *Science 316: 404–405*.

Bultman S., Gebuhr T., Yee D., La Mantia C., Nicholson J., Gilliam A., Randazzo F., Metzger D., Chambon P., Crabtree G. & Magnuson T. 2000: A Brg1 null mutation in the mouse reveals functional differences among mammalian SWI/SNF complexes. *Mol. Cell 6: 1287–1295*.

Bultman S.J., Gebuhr T.C., Pan H., Svoboda P., Schultz R.M. & Magnuson T. 2006: Maternal BRG1 regulates zygotic genome activation in the mouse. *Genes. Dev. 20: 1744–1754*.

Burgio G., La Rocca G., Sala A., Arancio W., Di Gesu D., Collesano M., Sperling A.S., Armstrong J.A., Van Heeringen S.J., Logie C., Tamkun J.W. & Corona D.F. 2008: Genetic identification of a network of factors that functionally interact with the nucleosome remodeling ATPase ISWI. *PLoS Genet. 4: e1000089*.

Cairns B.R. 2007: Chromatin remodeling: insights and intrigue from single-molecule studies. *Nat. Struct. Mol. Biol. 14: 989–996*.

Chong S., Vickaryous N., Ashe A., Zamudio N., Youngson N., Hemley S., Stopka T., Skoultchi A., Matthews J., Scott H.S., De Kretser D., O'bryan M., Blewitt M. & Whitelaw E. 2007: Modifiers of epigenetic reprogramming show paternal effects in the mouse. *Nat. Genet. 39: 614–622*.

Corona D.F., Siriaco G., Armstrong J.A., Snarskaya N., Mcclymont S.A., Scott M.P. & Tamkun J.W. 2007: ISWI regulates higher-order chromatin structure and histone H1 assembly in vivo. *PLoS Biol. 5: e232*.

De La Serna I.L., Ohkawa Y. & Imbalzano A.N. 2006: Chromatin remodelling in mammalian differentiation: lessons from ATP-dependent remodellers. *Nature Reviews Genetics 7: 461–473*.

Fyodorov D.V., Blower M.D., Karpen G.H. & Kadonaga J.T. 2004: Acf1 confers unique activities to ACF/CHRAC and promotes the formation rather than disruption of chromatin in vivo. *Genes. Dev. 18: 170–183*.

Gao X., Tate P., Hu P., Tjian R., Skarnes W.C. & Wang Z. 2008: ES cell pluripotency and germ-layer formation require the SWI/SNF chromatin remodeling component BAF250a. *Proc. Natl. Acad. Sci. USA 105: 6656–6661*.

Gebuhr T.C., Kovalev G.I., Bultman S., Godfrey V., Su L. & Magnuson T. 2003: The role of Brg1, a catalytic subunit of mammalian chromatin-remodeling complexes, in T cell development. *J. Exp. Med. 198: 1937–1949*.

Goll M.G. & Bestor T.H. 2005: Eukaryotic cytosine methyltransferases. *Annu. Rev. Biochem. 74: 481–514*.

Grummt I. & Ladurner A.G. 2008: A metabolic throttle regulates the epigenetic state of rDNA. *Cell 133: 577–580.*

Hajkova P., Ancelin K., Waldmann T., Lacoste N., Lange U.C., Cesari F., Lee C., Almouzni G., Schneider R. & Surani M.A. 2008: Chromatin dynamics during epigenetic reprogramming in the mouse germ line. *Nature 452: 877–881*.

Hakimi M.A., Bochar D.A., Schmiesing J.A., Dong Y., Barak O.G., Speicher D.W., Yokomori K. & Shiekhattar R. 2002: A chromatin remodelling complex that loads cohesin onto human chromosomes. *Nature 418: 994–998*.

Hayashi K., De Sousa Lopes S.M. & Surani M.A. 2007: Germ cell specification in mice. *Science 316: 394–396*.

Hofmann M.C. 2008: Gdnf signaling pathways within the mammalian spermatogonial stem cell niche. *Mol. Cell. Endocrinol. 288: 95–103*.

Jenuwein T. & Allis C.D. 2001: Translating the histone code. *Science 293: 1074–1080*.

Kikyo N., Wade P.A., Guschin D., Ge H. & Wolffe A.P. 2000: Active remodeling of somatic nuclei in egg cytoplasm by the nucleosomal ATPase ISWI. *Science 289: 2360–2362*.

Kim J.B., Zaehres H., Wu G., Gentile L., Ko K., Sebastiano V., Arauzo-Bravo M.J., Ruau D., Han D.W., Zenke M. & Scholer H.R. 2008: Pluripotent stem cells induced from adult neural stem cells by reprogramming with two factors. *Nature 454: 646–650*.

Kim S.I. & Bresnick E.H. 2007: Transcriptional control of erythropoiesis: emerging mechanisms and principles. *Oncogene 26: 6777–6794*.

Kimmins S., Kotaja N., Fienga G., Kolthur U.S., Brancorsini S., Hogeveen K., Monaco L. & Sassone-Corsi P. 2004: A specific programme of gene transcription in male germ cells. *Reproductive Biomedicine Online 8: 496–500*.

Kokavec J., Podskocova J., Zavadil J. & Stopka T. 2008: Chromatin remodeling and SWI/SNF2 factors in human disease. *Front. Biosci. 13: 6126–6134*.

Kouskouti A. & Talianidis I. 2005: Histone modifications defining active genes persist after transcriptional and mitotic inactivation. *EMBO J. 24: 347–357*.

Kouzarides T. 2007: Chromatin modifications and their function. *Cell 128: 693–705*.

Li J., Langst G. & Grummt I. 2006: NoRC-dependent nucleosome positioning silences rRNA genes. *EMBO J. 25: 5735–5741*.

Meissner A., Mikkelsen T.S., Gu H., Wernig M., Hanna J., Sivachenko A., Zhang X., Bernstein B.E., Nusbaum C., Jaffe D.B., Gnirke A., Jaenisch R. & Lander E.S. 2008: Genome-scale DNA methylation maps of pluripotent and differentiated cells. *Nature 454: 766–770*.

Niwa H. 2001: Molecular mechanism to maintain stem cell renewal of ES cells. *Cell. Struct. Funct. 26: 137–148*.

Ohinata Y., Payer B., O'carroll D., Ancelin K., Ono Y., Sano M., Barton S.C., Obukhanych T., Nussenzweig M., Tarakhovsky A., Saitou M. & Surani M.A. 2005: Blimp1 is a critical determinant of the germ cell lineage in mice. *Nature 436: 207–213*.

Pal S., Vishwanath S.N., Erdjument-Bromage H., Tempst P. & Sif S. 2004: Human SWI/SNF-associated PRMT5 methylates histone H3 arginine 8 and negatively regulates expression of ST7 and NM23 tumor suppressor genes. *Mol. Cell. Biol. 24: 9630–9645*.

Peters A.H., O'carroll D., Scherthan H., Mechtler K., Sauer S., Schofer C., Weipoltshammer K., Pagani M., Lachner M., Kohlmaier A., Opravil S., Doyle M., Sibilia M. & Jenuwein T. 2001: Loss of the Suv39h histone methyltransferases impairs mammalian heterochromatin and genome stability. *Cell 107: 323–337*.

Rodriguez P., Bonte E., Krijgsveld J., Kolodziej K.E., Guyot B., Heck A.J., Vyas P., De Boer E., Grosveld F. & Strouboulis J. 2005: GATA-1 forms distinct activating and repressive complexes in erythroid cells. *EMBO J. 24: 2354–2366*.

Sarmento O.F., Digilio L.C., Wang Y., Perlin J., Herr J.C., Allis C.D. & Coonrod S.A. 2004: Dynamic alterations of specific histone modifications during early murine development. *J. Cell. Sci. 117: 4449–4459*.

Shen W., Xu C., Huang W., Zhang J., Carlson J.E., Tu X., Wu J. & Shi Y. 2007: Solution structure of human Brg1 bromodomain and its specific binding to acetylated histone tails. *Biochemistry 46: 2100–2110*.

Schaefer C.B., Ooi S.K., Bestor T.H. & Bourc'his D. 2007: Epigenetic decisions in mammalian germ cells. *Science 316: 398–399*.

Schier A.F. 2007: The maternal-zygotic transition: death and birth of RNAs. *Science 316: 406–407*.

Sims R.J., Chen C.F., Santos-Rosa H., Kouzarides T., Patel S.S. & Reinberg D. 2005: Human but not yeast CHD1 binds directly and selectively to histone H3 methylated at lysine 4 via its tandem chromodomains. *J. Biol. Chem. 280: 41789–41792*.

Stitzel M.L. & Seydoux G. 2007: Regulation of the oocyte-to-zygote transition. *Science 316: 407–408*.

Stopka T. & Skoultchi A.I. 2003: The ISWI ATPase Snf2h is required for early mouse development. *Proc. Natl. Acad. Sci. USA 100: 14097–14102*.

Tachibana M., Nozaki M., Takeda N. & Shinkai Y. 2007: Functional dynamics of H3K9 methylation during meiotic prophase progression. *EMBO J. 26: 3346–3359.*

Tielens S., Verhasselt B., Liu J., Dhont M., Van Der Elst J. & Cornelissen M. 2006: Generation of embryonic stem cell lines from mouse blastocysts developed in vivo and in vitro: relation to Oct-4 expression. *Reproduction 132: 59–66.*

Torres-Padilla M.E. & Zernicka-Goetz M. 2006: Role of TIF1alpha as a modulator of embryonic transcription in the mouse zygote. *J. Cell. Biol. 174: 329–338.*

Yang Y., Stopka T., Golestaneh N., Wang Y., Wu K., Li A., Chauhan B.K., Gao C.Y., Cveklova K., Duncan M.K., Pestell R.G., Chepelinsky A.B., Skoultchi A.I. & Cvekl A. 2006: Regulation of alphaA-crystallin via Pax6, c-Maf, CREB and a broad domain of lens-specific chromatin. *EMBO J. 25: 2107–2118.*

Yasui D., Miyano M., Cai S., Varga-Weisz P. & Kohwi-Shigematsu T. 2002: SATB1 targets chromatin remodelling to regulate genes over long distances. *Nature 419: 641–645.*

Zamudio N.M., Chong S. & O'bryan M.K. 2008: Epigenetic regulation in male germ cells. *Reproduction 136: 131–146.*

Zhou Y. & Grummt I. 2005: The PHD finger/bromodomain of NoRC interacts with acetylated histone H4K16 and is sufficient for rDNA silencing. *Curr. Biol. 15: 1434–1438.*

Appendix. Abbreviations used.

ACF	ATP-utilizing chromatin assembly and remodelling factor
ARID	AT-rich interaction domain
BAF	BRG1/hBrm-associated factors
BAZ	Bromodomain adjacent to zinc finger domain protein
BRG1	Brahma-related gene-1
BRM	Human brahma homolog
CERF	CECR2-containing remodelling factor
CHRAC	Chromatin accessibility complex
CTCF	CCCTC-binding factor
HDAC	Histone deacetylase
INO80	Inositol-requiring protein 80
MBD	Methyl CpG-binding protein
NCoR	Nuclear receptor corepressor
NoRC	Nucleolar remodelling complex
NR	Nuclear receptor
NUMAC	Nucleosomal methylation activator complex
NuRD	Nucleosome remodelling and histone deacetylation complex
NURF	Nucleosome-remodelling factor
PBAF	Polybromo-associated BAF
RSF	Remodelling and spacing factor
SMARCA5	SWI/SNF related, matrix associated, dependent regulator of chromatin, member 5
SWI/SNF	Mating-type switching and sucrose non-fermenting
WICH	WSTF-ISWI chromatin remodelling complex
WINAC	WSTF including nucleosome assembly complex
WSTF	Williams syndrome transcription factor