Вавиловский журнал генетики и селекции. 2019;23(2):160-167
DOI 10.18699/VJ19.476

The role of ATP-dependent chromatin remodeling factors in chromatin assembly *in vivo*

Iu.A. Il'ina, A.Y. Konev ✉

Petersburg Nuclear Physics Institute named by B.P. Konstantinov of National Research Centre "Kurchatov Institute", Gatchina, Russia
✉ e-mail: konev_ay@pnpi.nrcki.ru

Chromatin assembly is a fundamental process essential for chromosome duplication subsequent to DNA replication. In addition, histone removal and incorporation take place constantly throughout the cell cycle in the course of DNA-utilizing processes, such as transcription, damage repair or recombination. *In vitro* studies have revealed that nucleosome assembly relies on the combined action of core histone chaperones and ATP-utilizing molecular motor proteins such as ACF or CHD1. Despite extensive biochemical characterization of ATP-dependent chromatin assembly and remodeling factors, it has remained unclear to what extent nucleosome assembly is an ATP-dependent process *in vivo*. Our original and published data about the functions of ATP-dependent chromatin assembly and remodeling factors clearly demonstrated that these proteins are important for nucleosome assembly and histone exchange *in vivo*. During male pronucleus reorganization after fertilization CHD1 has a critical role in the genome-scale, replication-independent nucleosome assembly involving the histone variant H3.3. Thus, the molecular motor proteins, such as CHD1, function not only in the remodeling of existing nucleosomes but also in *de novo* nucleosome assembly from DNA and histones *in vivo*. ATP-dependent chromatin assembly and remodeling factors have been implicated in the process of histone exchange during transcription and DNA repair, in the maintenance of centromeric chromatin and in the loading and remodeling of nucleosomes behind a replication fork. Thus, chromatin remodeling factors are involved in the processes of both replication-dependent and replication-independent chromatin assembly. The role of these proteins is especially prominent in the processes of large-scale chromatin reorganization; for example, during male pronucleus formation or in DNA repair. Together, ATP-dependent chromatin assembly factors, histone chaperones and chromatin modifying enzymes form a "chromatin integrity network" to ensure proper maintenance and propagation of chromatin landscape.
Key words: chromatin; chromatin assembly; ATP-dependent remodeling factors.

For citation: Il'ina Iu.A., Konev A.Y. The role of ATP-dependent chromatin remodeling factors in chromatin assembly *in vivo*. Vavilovskii Zhurnal Genetiki i Selektsii = Vavilov Journal of Genetics and Breeding. 2019;23(2):160-167. DOI 10.18699/VJ19.476

Роль АТФ-зависимых хроматин-ремоделирующих факторов в процессе сборки хроматина *in vivo*

Ю.А. Ильина, А.Ю. Конев ✉

Петербургский институт ядерной физики им. Б.П. Константинова Национального исследовательского центра «Курчатовский институт», Гатчина, Россия
✉ e-mail: konev_ay@pnpi.nrcki.ru

Сборка хроматина – фундаментальный процесс, необходимый для дупликации хромосом в процессе репликации ДНК. Кроме того, удаление гистонов и их инкорпорирование постоянно происходят в течение клеточного цикла в ходе процессов метаболизма ДНК, таких как транскрипция, восстановление повреждений или рекомбинация. Исследования *in vitro* показали, что сборка хроматина требует совместного действия гистоновых шаперонов и использующих энергию АТФ хроматин-ремоделирующих факторов – ACF или CHD1. Несмотря то, что АТФ-зависимые факторы сборки и ремоделирования хроматина хорошо охарактеризованы биохимически, оставалось неясным, до какой степени сборка нуклеосом является АТФ-зависимым процессом *in vivo*. Наши собственные и опубликованные в литературе данные о функциях АТФ-зависимых хроматин-ремоделирующих факторов показывают, что эти белки существенны для сборки нуклеосом и обмена гистонов и *in vivo*. CHD1 – критически важный фактор при реорганизации мужского пронуклеуса после оплодотворения, в процессе которой происходит независимая от репликации сборка хроматина, содержащего вариантный гистон H3.3. Следовательно, молекулярные моторные белки, такие как CHD1, функционируют *in vivo* не только в ремоделировании существующих нуклеосом, но также и в сборке нуклеосом *de novo* из ДНК и гистонов. АТФ-зависимые факторы сборки и ремоделирования хроматина участвуют в процессе обмена гистонов во время транскрипции и репарации ДНК, в поддержании центромерного хроматина и образовании и ремоделировании нуклеосом позади прохождения репликационной вилки. Таким образом, хроматин-ремоделирующие факторы участвуют в процессах как зависимой, так и не зависимой от репликации сборки хроматина. Их роль особенно заметна в процессах крупномасштабной реорганизации хроматина,

например при реорганизации хроматина мужского пронуклеуса или при восстановлении повреждений ДНК. Гистоновые шапероны, модифицирующие хроматин ферменты и АТФ-зависимые факторы сборки хроматина совместно образуют сеть факторов, обеспечивающих поддержание целостности хроматина.
Ключевые слова: хроматин; сборка хроматина; АТФ-зависимые хроматин-ремоделирующие факторы.

Itroduction

Chromatin assembly is a fundamentally important process, which is essential for chromosome duplication subsequent to DNA replication (Krude, Keller, 2001; Vincent et al., 2008), but also take place constantly throughout the cell cycle in the course of DNA-utilizing processes, such as transcription, damage repair or recombination (Venkatesh, Workman, 2015; Hauer, Gasser, 2017; Serra-Cardona, Zhang, 2018). Replication-independent chromatin assembly generally involves histone variants (e.g. H3.3, H2A.Z), while the so-called canonical histones (H2A, H2B, H3.1, H3.2, H4) are incorporated in the course of replication (Henikoff, Ahmad, 2005).

In vitro studies suggest that nucleosome assembly relies on the combined action of core histone chaperones and ATP-utilizing molecular motor proteins (Tyler, 2002; Haushalter, Kadonaga, 2003). The histone chaperones mediate the stepwise processes of disassembly and reassembly of nucleosomes and shield histones from promiscuous interactions and aggregation to ensure their proper storage, transport, post-translational modification, nucleosome assembly and turnover (Hammond et al., 2017). Various chaperones have been identified that specifically interact with certain histone variants driving nucleosome assembly and disassembly during replication-independent and replication-dependent processes. For example, H3.1 is found in a complex containing histone chaperones Asf1 and CAF-1, whereas H3.3 forms a complex with HIRA and Asf1 or with the DAXX chaperone (Tagami et al., 2004; Elsasser et al., 2012).

Biochemical evidence, however, has revealed that nucleosome assembly is an ATP-dependent process and requires the action of ATP-hydrolyzing molecular motor proteins such as ACF or CHD1 (Ito et al., 1997; Haushalter, Kadonaga, 2003; Lusser et al., 2005). These evolutionarily conserved factors promote the efficiency of core histone deposition as well as mediate the spacing of nucleosome arrays. ATP-utilizing molecular machines modify chromatin structure by modulating histone-DNA contacts, resulting in the repositioning or disruption of the nucleosome, changing the conformation of nucleosomal DNA or changing the composition of the histone octamer (Morettini et al., 2008; Narlikar et al., 2013; Clapier et al., 2017). Chromatin remodeling factors are compositionally and functionally diverse multi-protein complexes, yet they share the presence of a motor subunit that belongs to the SNF2-family of ATPases. The DNA-translocating core of SNF2-type proteins consists of two paired RecA-like domains or lobes, capable of rearranging during the ATP hydrolysis cycle to create a ratchet-like motion along DNA in single base increments (Clapier et al., 2017). Recent studies provided mechanistic insights into nucleosome assembly by the combined action of histone chaperones and ATP-dependent molecular motors.

These studies revealed the rapid formation of a stable non-nucleosomal histone-DNA intermediate, a prenucleosome, due to histone deposition by chaperones; this intermediate is then converted into nucleosomes by a motor protein such as ACF (Torigoe et al., 2011). The prenucleosome is a stable conformational isomer of the nucleosome, which consists of a histone octamer associated with 80 base pairs of DNA located at a position that corresponds to the central 80 bp of a nucleosome core particle (Fei et al., 2015). Monomeric prenucleosomes with free flanking DNA do not spontaneously fold into nucleosomes, but can be converted into canonical nucleosomes by ATP-dependent chromatin remodelers such as ACF or Chd1 (Torigoe et al., 2013). Analyses of the remodeling-defective Chd1 motor protein revealed a functional distinction between ATP-dependent nucleosome assembly and chromatin remodeling, and proposed a model for chromatin assembly in which randomly distributed nucleosomes are formed by the nucleosome assembly function of Chd1, and then regularly spaced nucleosome arrays are generated by the chromatin remodeling activity (Torigoe et al., 2013).

To date, the ATP-dependent assembly of extended, periodic arrays of nucleosomes has been observed *in vitro* with the *Drosophila* ACF, CHRAC (Ito et al., 1999; Fyodorov, Kadonaga, 2003; Kukimoto et al., 2004) and ToRC (Emelyanov et al., 2012) complexes as well as with the human RSF complex (Loyola et al., 2003). The catalytic subunit of each of these complexes belongs to the ISWI subfamily of the SNF2-like family of ATPases. ISWI by itself in conjunction with histone chaperone dNLP has a chromatin assembly activity (Khuong et al., 2017). Activity in an ATP-dependent chromatin assembly reaction was demonstrated for chromodomain-containing proteins of the CHD family: the *Drosophila*, yeast and mouse CHD1 protein (Robinson, Schultz, 2003; Lusser et al., 2005; Piatti et al., 2015) and human CHD2 (Liu et al., 2015). Unlike ACF, CHD1 cannot assemble chromatin containing the linker histone H1 (Lusser et al., 2005). Finally, the mammalian ATRX-DAXX complex catalyzes the deposition and remodeling of H3.3-containing nucleosomes (Drane et al., 2010; Lewis et al., 2010). ISWI and CHD1 remodelers share some structural and functional similarities (Narlikar et al., 2013; Clapier et al., 2017). Both ISWI and CHD1 proteins reposition nucleosomes to locations close to the center of short DNA fragments. The directionality and rate of nucleosome mobilization are determined in ISWI and CHD1 proteins by the SANT-SLIDE DNA binding domain (DBD), structurally similar between two proteins. DBD binds DNA at the nucleosomal entry site and in the adjacent linker anchoring the remodeler to the nucleosome. Although the N-terminal regions of ISWI and CHD1 are not related at the sequence level, they carry out similar functions. *Drosophila* ISWI protein contains two conserved regulatory regions, termed AutoN and NegC, which negatively regulate ATP hydrolysis (AutoN) or the coupling of ATP hydrolysis to DNA translocation (NegC). In CHD1 protein, a similar negative regulatory function is performed by the double chromodomain unit of the CHD1 remodeler, which can pack against the DNA-binding surface of the ATPase motor. Double chromodomains of mammalian CHD1 protein recognize the trimethylated histone H3

lysine 4, but chromodomains of yeast and *Drosophila* CHD1 and of mammalian CHD2 do not have such specificity. In yeast chromodomain mutations result in dissociation of Chd1 from chromatin. By contrast, in *Drosophila melanogaster* the chromodomains do not play an important role in its localization to chromatin; however, mutations in *Drosophila* CHD1 chromodomains negatively affect the chromatin assembly activities of CHD1 *in vitro* (Morettini et al., 2011). Similar biochemical characteristics probably determine the role of these two subfamilies of SNF2-type remodelers in chromatin assembly reaction as well as partial redundancy of these factors *in vivo*. The translocase domains of ATRX proteins have diverged from those of ISWI, and CHD1, suggesting another mechanism for histone exchange (Narlikar et al., 2013). The ATRX protein associates with the DAXX chaperone to couple chromatin dissociation with the reassembly of nucleosomes enriched for the histone variant H3.3 (Lewis et al., 2010).

Despite extensive biochemical characterization of ATP-dependent nucleosome loading and remodeling, it has remained unclear to what extent nucleosome assembly is an ATP-dependent process *in vivo*. We provided the first clear confirmation of the requirement of an ATP-utilizing motor protein (CHD1) in chromatin assembly *in vivo* (Konev et al., 2007). We generated *Chd1* null alleles and found that *Chd1* mutants are subviable but sterile. When maternal CHD1 is eliminated, the paternal genome does not undergo the first zygotic mitosis, leading to the development of haploid embryos. In contrast, CHD1 does not appear to affect the organization of maternal chromatin. It has been shown in *Drosophila* and mice that H3.3 is specifically present in the male pronucleus (Loppin et al., 2005; Torres-Padilla et al., 2006). Histones are deposited in decondensing sperm DNA by replication-independent mechanisms involving the HIRA chaperone complex, which use the histone variant H3.3, but not canonical H3 (Loppin et al., 2005; Orsi et al., 2013). Using the FLAG-tagged H3.3 transgene we demonstrated that, in contrast to wild-type animals, in Chd1-null embryos the H3.3-FLAG signal in the male pronucleus did not co-localize with the DNA and remained constrained to the nuclear periphery (Konev et al., 2007). We have found that CHD1 physically interacts with the H3.3-specific histone chaperone HIRA, which delivers histones H3.3-H4 to the male pronucleus. CHD1 is dispensable for protamine removal. This work established that CHD1 is a major factor in replacement histone metabolism and revealed a critical role for CHD1 in the genome-scale, replication-independent nucleosome assembly involving the histone variant H3.3. Thus, the molecular motor proteins, such as CHD1, function not only in remodeling of existing nucleosomes but also in *de novo* nucleosome assembly from DNA and histones *in vivo*.

Nevertheless, the results of the further studies of the ISWI- and CHD1-type remodelers' role in chromatin assembly *in vivo* are somewhat controversial. In yeasts *Saccharomyces cerevisiae* Iswi complexes (yeasts have two ISWI proteins: Isw1p and Isw2p) and Chd1 have partially redundant roles in nucleosome assembly and positioning (Xella et al., 2006; Gkikopoulos et al., 2011; Smolle et al., 2012; Yadav, Whitehouse, 2016). While individual *isw1*, *isw2* and *chd1* mutants are viable, only the *isw1 isw2 chd1* triple mutant combination results in severe growth defects as well as in wide-spread disruption of nucleosome positioning throughout the yeast genome (Vary et al., 2003; Gkikopoulos et al., 2011). Very similar results were obtained for the fission yeast *Schizosaccharomyces pombe*, which lacks ISWI-type remodelers, but has two CHD1-type ATPases, Hrp1 and Hrp3 (Hennig et al., 2012; Pointner et al., 2012). It was shown that *de novo* nucleosome assembly after DNA replication is altered in yeast *S. cerevisiae* mutants lacking histone chaperones (CAF-1) or chromatin remodelers Isw1 and Chd1 (Yadav, Whitehouse, 2016). ATP-dependent chromatin-remodeling enzymes Isw1 and Chd1 collaborate with histone chaperones to assemble and remodel nucleosomes as they are loaded behind a replication fork, allowing for rapid organization of chromatin during S phase. Chd1 is known to associate with elongating RNAPII through interaction with the PAF complex and other RNAPII-associated proteins (Simic et al., 2003). Some evidence has suggested a role for Chd1 in replication-independent histone exchange or assembly in the process of active transcription (Radman-Livaja et al., 2012; Smolle et al., 2012). Genome-wide analysis of H3 histone exchange in *S. cerevisiae* Chd1-deficient strains has shown that promoter and 5′ histone turnover are slower in *chd1Δ* cells, while maximal H3 replacement is instead observed at the 3′ ends of genes (Radman-Livaja et al., 2012). Thus, Chd1 accelerates H3 replacement at the 5′ ends of genes, while protecting the 3′ ends of genes from excessive H3 turnover, and specifically stabilizes nucleosomes over the 3′ ends of longer genes. Studies of H3 histone turnover in an Isw1b and Chd1 double mutant revealed that these chromatin remodeling factors both prevent co-transcriptional trans-histone exchange at largely overlapping, yet somewhat distinct groups of genes (Smolle et al., 2012). It is proposed, that yeast Isw1 and Chd1 may prevent histone exchange and promote chromatin integrity at lowly and highly transcribed genes respectively: Isw1 in the form of the Isw1b complex by remodeling nucleosomes that were retained on the DNA in spite of transcription, and Chd1 by reassembling nucleosomes in cis in the wake of RNAPII (Smolle et al., 2012). Still, it is clear that nucleosomes can be assembled without both Isw1b and Chd1. Analyses of nucleosome organization in the wild-type H2BK123A strain, incapable to monoubiquitinate histone H2B on Lys 123, and the *chd1Δ* strain indicate that in the absence of H2B monoubiquitination or Chd1, genes that are positively regulated by histone H2B monoubiquitination or Chd1 fail to adequately assemble nucleosomes +2, +3, and +4 in coding regions (Lee et al., 2012).

We have shown that in *Drosophila* CHD1 functions in H3.3 deposition during later stages of embryonic development, possibly in a processes associated with transcription (Konev et al., 2007). Analyses of polytene chromosomes revealed that the null mutations in *Drosophila Chd1* cause a decondensation of the male X chromosome, similar to that observed for the *ISWI* mutations (Konev et al., 2016). An effect of *Chd1* null mutations is increased by deficiency of one of two genes encoding the histone variant H3.3, *His3.3B*, suggesting that the role of CHD1 in the male X chromosome organization can be mediated by CHD1 activity in H3.3 histone deposition and exchange.

Mammals have two orthologs of yeast and *Drosophila* CHD1, Chd1 and Chd2. It was shown that in muscle development, transcriptional activation of the myogenic transcription factor MyoD is mediated by replication-independent histone

deposition (Yang et al., 2011). In this process, HIRA and Asf1a, but not CHD1 or Asf1b, mediate H3.3 incorporation in the promoter and the critical upstream regulatory regions of the *MyoD* gene. However, MyoD interacts with Chd2 and recruits it to downstream myogenic gene promoters, but not to housekeeping or silent gene promoters both in myoblasts and in differentiated cells (Harada et al., 2012). Genome-wide analysis of endogenous H3.3 incorporation demonstrates that knockdown of Chd2 prevents H3.3 deposition at differentiation-dependent, but not housekeeping, genes and inhibits myogenic gene activation. Thus, MyoD determines cell fate and facilitates differentiation-dependent gene expression through Chd2-dependent deposition of H3.3 at myogenic loci prior to differentiation (Harada et al., 2012). Chd2 is also required to maintain the differentiation potential of mouse embryonic stem cells (ESC). Chd2-depleted ESCs showed suppressed expression of developmentally regulated genes upon differentiation and alterations in the nucleosome occupancy of the histone variant H3.3 for developmentally regulated genes (Semba et al., 2017). Chd1 is also essential for open chromatin and pluripotency of embryonic stem cells, and for somatic cell reprogramming; downregulation of Chd1 leads to accumulation of heterochromatin (Gaspar-Maia et al., 2009). It is not known yet, whether or not effects of Chd1 in ESC are associated with changes in histone deposition. Analyses of genome-wide nucleosome specificity and function of chromatin remodelers in ES cells revealed that, while Chd1 is present near the 5′ ends of genes, the Chd2-nucleosome enrichment pattern encompassed the entire transcription unit and shared a high correlation with H3K36me3 (de Dieuleveult et al., 2016). This is consistent with how yeast Chd1 works, and thus yeast Chd1 may be functionally equivalent rather to mammalian Chd2.

ISWI protein is a catalytic subunit of four complexes, capable to assemble extended, periodic arrays of nucleosomes *in vitro*: ACF, CHRAC, Torch and RSF. In *Drosophila*, *ISWI* is an essential gene, and loss of ISWI function results in global structural alteration of the chromosomes, specifically the male X-chromosome (Deuring et al., 2000). It was found that ISWI is involved in the incorporation of the linker histone H1 into chromatin *in vivo* (Corona et al., 2007; Siriaco et al., 2009). Our work had shown that ISWI is unable to substitute for CHD1 in the deposition of H3.3 (Konev et al., 2007). However, at fertilization, maternal ISWI targets the paternal genome and drives its repackaging into de-condensed nucleosomal chromatin (Doyen et al., 2015). In embryos from *ISWI*^{1} mothers, the male pronucleus remained abnormally condensed, but core histones were deposited efficiently onto the condensed paternal genome in the absence of ISWI. These observations suggest that ISWI is not required for the incorporation of histones into the male pronucleus but is crucial for the formation of an open chromatin structure. As in the case of *Chd1* mutants (Konev et al., 2007; Podhraski et al., 2010), failure of proper transition from sperm chromatin to nucleosomal chromatin in *iswi* mutant embryos is followed by mitotic defects, aneuploidy, and haploid embryonic divisions (Doyen et al., 2015). ACF (ATP-utilizing chromatin assembly and remodeling factor) (Ito et al., 1999; Fyodorov, Kadonaga, 2003) and CHRAC (chromatin-accessibility-complex) (Kukimoto et al., 2004) contain one common subunit, termed Acf1, which stimulates and modulates the intrinsic chromatin assembly and remodeling activities of ISWI (Ito et al., 1999; Eberharter et al., 2001; Fyodorov, Kadonaga, 2002). In addition, CHRAC comprises two small, developmentally regulated subunits (CHRAC14, CHRAC16) which facilitate nucleosome sliding (Corona et al., 2000; Hartlepp et al., 2005). Expression of the signature subunit ACF1 is restricted during embryonic development, but remains high in primordial germ cells. Therefore, we explored roles for ACF1 during *Drosophila* oogenesis (Borner et al., 2016). We have isolated the novel loss – of function allele *Acf1(7)* which leads to defective egg chambers and their elimination through apoptosis. Two-fold overexpression of CHRAC (ACF1 and CHRAC-16) leads to increased apoptosis and packaging defects in egg chambers. Thus, finely tuned CHRAC levels are required for proper oogenesis. The mutant *acf1* fly line displays defects in heterochromatic silencing and exhibits reduced ATP-dependent chromatin assembly activity in embryonic cell extracts (Fyodorov et al., 2004). ACF/CHRAC contribute to establishing the repressive ground state of chromatin through organization of regular nucleosome arrays (Scacchetti et al., 2018). Surprisingly, despite the fact that ACF is the first discovered ATP-dependent chromatin assembly complex, direct evidence of its role in chromatin assembly *in vivo* is lacking. The human two-subunit complex RSF (Remodeling and Spacing Factor) contains, in addition to the ISWI homolog hSNFH, the p325 (Rsf-1) polypeptide, which is similar but not homologous to *Drosophila* Acf1 (Loyola et al., 2003). In *Drosophila* RSF contributes to histone H2Av replacement in the pathway of silent chromatin formation (Hanai et al., 2008).

We described a novel, evolutionarily conserved, ISWI-containing complex, ToRC (Toutatis-containing chromatin remodeling complex), which consist of ISWI, Toutatis/TIP5 and the transcriptional corepressor CtBP (Emelyanov et al., 2012). Toutatis (Tou) is the *Drosophila* ortholog of TIP5, a large subunit of a nucleolar-specific, SNF2H-containing chromatin remodeling factor, NoRC (Strohner et al., 2001). Tou exhibits strong similarity to Acf1 and shares with it a number of domains that are important for the chromatin assembly activity of ACF. ToRC facilitates ATP-dependent nucleosome assembly *in vitro* and all three subunits are required for its maximal biochemical activity. By contrast with NoRC, the ToRC complex is excluded from the nucleolus. ToRC tethering to its nuclear targets is dependent on the transcriptional corepressor CtBP. ToRC is involved in CtBP-mediated regulation of transcription by RNA polymerase II *in vivo*. However, native C-terminally truncated Toutatis isoforms do not associate with CtBP and localize predominantly to the nucleolus. Thus, Toutatis forms two alternative complexes, ToRC and dNoRC, comprising of Tou and ISWI, that have differential distribution and can participate in distinct aspects of nuclear DNA metabolism. It is remained to be determined whether or not ToRC or NoRC is involved in histone incorporation *in vivo*.

ATRX is a chromatin remodeler that together with its chaperone DAXX in mammalian cells deposits the histone variant H3.3 in pericentric and telomeric regions (Drane et al., 2010; Goldberg et al., 2010; Lewis et al., 2010; Wong et al., 2010). We performed biochemical and genetic analyses of the *Drosophila melanogaster* ortholog of ATRX (Xnp) (Emelyanov et al., 2010). *Drosophila* ATRX is expressed

throughout development in two isoforms, p185 and p125, which form distinct multisubunit complexes in fly embryos. The ATRX185 complex comprises p185 and heterochromatin protein HP1a. Consistently, ATRX185 but not ATRX125 in polytene chromosomes is highly concentrated in the pericentric beta-heterochromatin of the X chromosome, where it is required for HP1a deposition. The loss-of-function allele of the *Drosophila* ATRX/Xnp gene is semilethal and alleles of the ATRX/XNP gene that do not express p185 are strong suppressors of position effect variegation. In another study it was shown that the ATRX/XNP focus near the heterochromatin of the X chromosome corresponds to an unusual decondensed satellite DNA block, and both active genes and the XNP focus are sites of ongoing H3 to H3.3 nucleosome replacement (Schneiderman et al., 2009). Using an inducible system that produces nucleosome-depleted chromatin at the Hsp70 genes in *Drosophila* it was found that the ATRX/XNP chromatin remodeler and the Hira histone chaperone independently bind nucleosome-depleted chromatin (Schneiderman et al., 2012). H3.3 deposition assays reveal that Xnp and Hira are required for efficient nucleosome replacement, and double-mutants are lethal. Thus, the function of ATRX in H3.3 deposition is conserved in evolution.

ATP-dependent chromatin assembly and remodeling factors have also been implicated in the maintenance of centromeric chromatin, which is epigenetically specified in most eukaryotes by the centromere-specific histone H3 variant, CENP-A. Human RSF1 localizes to centromeres and promotes the stable association of CENP-A with centromeres (Perpelescu et al., 2009). Tethering RSF1 to an ectopic non-centromeric alphoid DNA array is sufficient to stimulate histone exchange, and this reaction was coupled with new H3.3 or CENP-A assembly (Ohzeki et al., 2016). CHD1 was found to stimulate the deposition of CENP-A at centromeres in fission yeast and humans (Walfridsson et al., 2005; Okada et al., 2009), however, it is dispensable for CID (*Drosophila* CENP-A) deposition in flies (Podhraski et al., 2010).

Chromatin dynamics plays a very important role during DNA repair (Hauer, Gasser, 2017). ATRX-deficient cells exhibit a defect in repairing exogenously induced DNA double-strand breaks (DSBs) by homologous recombination (HR) (Juhasz et al., 2018). DAXX- and H3.3-depleted cells exhibit identical HR defects as ATRX-depleted cells, and both ATRX and DAXX function to deposit H3.3 during DNA repair synthesis. This suggests that ATRX facilitates the chromatin reconstitution required for extended DNA repair synthesis and sister chromatid exchange during HR (Elbakry et al., 2018; Juhasz et al., 2018). Human CHD2 plays a crucial role in regulating non-homologous end-joining (NHEJ), a dominant DSB repair pathway in human cells (Luijsterburg et al., 2016). This mechanism is initiated by DNA damage-associated poly(ADP-ribose) polymerase 1 (PARP1), which recruits CHD2 through a poly(ADP-ribose)-binding domain; CHD2 in turn triggers rapid deposition of histone variant H3.3 at sites of DNA damage. PARP1, CHD2, and H3.3 regulate the assembly of NHEJ complexes at broken chromosomes to promote efficient DNA repair (Luijsterburg et al., 2016). Targeted disruption of the CHD1 gene in human cells leads to a defect in DSB repair via homologous recombination, resulting in hypersensitivity to ionizing radiation and in increased error-prone NHEJ repair for DSB repair (Kari et al., 2016; Shenoy et al., 2017; Zhou et al., 2018). We have shown that null mutations of *Drosophila Chd1* cause hypersensitivity to ionizing radiation at the third instar larval stage, suggesting that *Drosophila* CHD1 is also involved in DSB repair. Considering that *Drosophila* has only a single ortholog of human CHD1 and CHD2, it will be interesting to determine which of the two major pathways of DSB repair is affected and whether or not this effect is associated with the role of fly CHD1 in H3.3 deposition.

Conclusion

The studies of *in vivo* functions of ATP-dependent chromatin assembly and remodeling factors clearly demonstrated that these factors do participate in nucleosome assembly and histone exchange *in vivo*. Most of the evidence concerning the role of ATP-dependent chromatin assembly and remodeling factors in the process of chromatin assembly *in vivo* was obtained for recombination independent assembly processes, involving histone variants such as H3.3. Yet it was shown that ATP-dependent chromatin-remodeling enzymes Isw1 and Chd1 in collaboration with histone chaperones assemble and remodel nucleosomes as they are loaded behind a replication fork (Yadav, Whitehouse, 2016), suggesting a common mechanism for both types for chromatin assembly. Their role is especially prominent in the processes of large-scale chromatin reorganization, for example during male pronucleus formation or DNA repair. Analysis of effects of individual factors is hampered by a high level of redundancy in the function of ATP-dependent chromatin assembly and remodeling factors. Interpretations of the role of chromatin remodelers in chromatin assembly *in vivo* is further complicated by the fact that mutations in the ATP-dependent chromatin assembly and remodeling factors, such as Chd1, may affect the distribution of histone modifications known to affect nucleosome stability (Lee J.S. et al., 2012; Radman-Livaja et al., 2012; Lee Y. et al., 2017). Together, ATP-dependent chromatin assembly and remodeling factors, histone chaperones and chromatin modifying enzymes form a "chromatin integrity network" to ensure proper maintenance and propagation of the chromatin landscape as well as regulation of genetic processes. All identified ATP-dependent chromatin assembly factors are linked to cancer. Thus, dissecting a chromatin integrity network should not only provide further insight into the fundamental organization of the eukaryotic genome but also contribute to human health.

References

Borner K., Jain D., Vazquez-Pianzola P., Vengadasalam S., Steffen N., Fyodorov D.V., Tomancak P., Konev A., Suter B., Becker P.B. A role for tuned levels of nucleosome remodeler subunit ACF1 during *Drosophila* oogenesis. Dev. Biol. 2016;411(2):217-230. DOI 10.1016/j.ydbio.2016.01.039.

Clapier C.R., Iwasa J., Cairns B.R., Peterson C.L. Mechanisms of action and regulation of ATP-dependent chromatin-remodelling complexes. Nat. Rev. Mol. Cell. Biol. 2017;18(7):407-422. DOI 10.1038/nrm.2017.26.

Corona D.F., Eberharter A., Budde A., Deuring R., Ferrari S., Varga-Weisz P., Wilm M., Tamkun J., Becker P.B. Two histone fold proteins, CHRAC-14 and CHRAC-16, are developmentally regulated subunits of chromatin accessibility complex (CHRAC). EMBO J. 2000;19(12):3049-3059. DOI 10.1093/emboj/19.12.3049.

Corona D.F., Siriaco G., Armstrong J.A., Snarskaya N., McClymont S.A., Scott M.P., Tamkun J.W. ISWI regulates higher-order chromatin structure and histone H1 assembly *in vivo*. PLoS Biol. 2007;5(9):e232. DOI 10.1371/journal.pbio.0050232.

de Dieuleveult M., Yen K., Hmitou I., Depaux A., Boussouar F., Bou Dargham D., Jounier S., Humbertclaude H., Ribierre F., Baulard C., Farrell N.P., Park B., Keime C., Carriere L., Berlivet S., Gut M., Gut I., Werner M., Deleuze J.F., Olaso R., Aude J.C., Chantalat S., Pugh B.F., Gerard M. Genome-wide nucleosome specificity and function of chromatin remodellers in ES cells. Nature. 2016; 530(7588):113-116. DOI 10.1038/nature16505.

Deuring R., Fanti L., Armstrong J.A., Sarte M., Papoulas O., Prestel M., Daubresse G., Verardo M., Moseley S.L., Berloco M., Tsukiyama T., Wu C., Pimpinelli S., Tamkun J.W. The ISWI chromatin-remodeling protein is required for gene expression and the maintenance of higher order chromatin structure *in vivo*. Mol. Cell. 2000;5(2):355-365.

Doyen C.M., Chalkley G.E., Voets O., Bezstarosti K., Demmers J.A., Moshkin Y.M., Verrijzer C.P. A Testis-specific chaperone and the chromatin remodeler ISWI mediate repackaging of the paternal genome. Cell Rep. 2015;13(7):1310-1318. DOI 10.1016/j.celrep.2015.10.010.

Drane P., Ouararhni K., Depaux A., Shuaib M., Hamiche A. The death-associated protein DAXX is a novel histone chaperone involved in the replication-independent deposition of H3.3. Genes Dev. 2010; 13(7):1310-1318. DOI 10.1101/gad.566910.

Eberharter A., Ferrari S., Langst G., Straub T., Imhof A., Varga-Weisz P., Wilm M., Becker P.B. Acf1, the largest subunit of CHRAC, regulates ISWI-induced nucleosome remodelling. EMBO J. 2001; 20(14):3781-3788.

Elbakry A., Juhasz S., Mathes A., Lobrich M. DNA repair synthesis and histone deposition partner during homologous recombination. Mol. Cell. Oncol. 2018;5(5):e1511210. DOI 10.1080/23723556.2018.1511210.

Elsasser S.J., Huang H., Lewis P.W., Chin J.W., Allis C.D., Patel D.J. DAXX envelops a histone H3.3-H4 dimer for H3.3-specific recognition. Nature. 2012;491(7425):560-565. DOI 10.1038/nature11608.

Emelyanov A.V., Konev A.Y., Vershilova E., Fyodorov D.V. Protein complex of *Drosophila* ATRX/XNP and HP1a is required for the formation of pericentric beta-heterochromatin *in vivo*. J. Biol. Chem. 2010;285(20):15027-15037. DOI 10.1074/jbc.M109.064790.

Emelyanov A.V., Vershilova E., Ignatyeva M.A., Pokrovsky D.K., Lu X., Konev A.Y., Fyodorov D.V. Identification and characterization of ToRC, a novel ISWI-containing ATP-dependent chromatin assembly complex. Genes Dev. 2012;26(6):603-614. DOI 10.1101/gad.180604.111.

Fei J., Torigoe S.E., Brown C.R., Khuong M.T., Kassavetis G.A., Boeger H., Kadonaga J.T. The prenucleosome, a stable conformational isomer of the nucleosome. Genes Dev. 2015;29(24):2563-2575. DOI 10.1101/gad.272633.115.

Fyodorov D.V., Blower M.D., Karpen G.H., Kadonaga J.T. Acf1 confers unique activities to ACF/CHRAC and promotes the formation rather than disruption of chromatin *in vivo*. Genes Dev. 2004;18(2):170-183.

Fyodorov D.V., Kadonaga J.T. Binding of Acf1 to DNA involves a WAC motif and is important for ACF-mediated chromatin assembly. Mol. Cell. Biol. 2002;22(18):6344-6353.

Fyodorov D.V., Kadonaga J.T. Chromatin assembly *in vitro* with purified recombinant ACF and NAP-1. Methods Enzymol. 2003;371: 499-515.

Gaspar-Maia A., Alajem A., Polesso F., Sridharan R., Mason M.J., Heidersbach A., Ramalho-Santos J., McManus M.T., Plath K., Meshorer E., Ramalho-Santos M. Chd1 regulates open chromatin and pluripotency of embryonic stem cells. Nature. 2009;460(7257):863-868. DOI 10.1038/nature08212.

Gkikopoulos T., Schofield P., Singh V., Pinskaya M., Mellor J., Smolle M., Workman J.L., Barton G.J., Owen-Hughes T. A role for Snf2-related nucleosome-spacing enzymes in genome-wide nucleosome organization. Science. 2011;333(6050):1758-1760. DOI 10.1126/science.1206097.

Goldberg A.D., Banaszynski L.A., Noh K.M., Lewis P.W., Elsaesser S.J., Stadler S., Dewell S., Law M., Guo X., Li X., Wen D., Chapgier A., DeKelver R.C., Miller J.C., Lee Y.L., Boydston E.A., Holmes M.C., Gregory P.D., Greally J.M., Rafii S., Yang C., Scambler P.J., Garrick D., Gibbons R.J., Higgs D.R., Cristea I.M., Urnov F.D., Zheng D., Allis C.D. Distinct factors control histone variant H3.3 localization at specific genomic regions. Cell. 2010; 140(5):678-691. DOI 10.1016/j.cell.2010.01.003.

Hammond C.M., Stromme C.B., Huang H., Patel D.J., Groth A. Histone chaperone networks shaping chromatin function. Nat. Rev. Mol. Cell. Biol. 2017;18(3):141-158. DOI 10.1038/nrm.2016.159.

Hanai K., Furuhashi H., Yamamoto T., Akasaka K., Hirose S. RSF governs silent chromatin formation via histone H2Av replacement. PLoS Genet. 2008;4(2):e1000011. DOI 10.1371/journal.pgen.1000011.

Harada A., Okada S., Konno D., Odawara J., Yoshimi T., Yoshimura S., Kumamaru H., Saiwai H., Tsubota T., Kurumizaka H., Akashi K., Tachibana T., Imbalzano A.N., Ohkawa Y. Chd2 interacts with H3.3 to determine myogenic cell fate. EMBO J. 2012;31(13):2994-3007. DOI 10.1038/emboj.2012.136.

Hartlepp K.F., Fernandez-Tornero C., Eberharter A., Grune T., Muller C.W., Becker P.B. The histone fold subunits of *Drosophila* CHRAC facilitate nucleosome sliding through dynamic DNA interactions. Mol. Cell. Biol. 2005;25(22):9886-9896.

Hauer M.H., Gasser S.M. Chromatin and nucleosome dynamics in DNA damage and repair. Genes Dev. 2017;31(22):2204-2221. DOI 10.1101/gad.307702.117.

Haushalter K.A., Kadonaga J.T. Chromatin assembly by DNA-translocating motors. Nat. Rev. Mol. Cell. Biol. 2003;4(8):613-620.

Henikoff S., Ahmad K. Assembly of variant histones into chromatin. Annu. Rev. Cell Dev. Biol. 2005;21:133-153.

Hennig B.P., Bendrin K., Zhou Y., Fischer T. Chd1 chromatin remodelers maintain nucleosome organization and repress cryptic transcription. EMBO Rep. 2012;13(11):997-1003. DOI 10.1038/embor.2012.146.

Ito T., Bulger M., Pazin M.J., Kobayashi R., Kadonaga J.T. ACF, an ISWI-containing and ATP-utilizing chromatin assembly and remodeling factor. Cell. 1997;90(1):145-155.

Ito T., Levenstein M.E., Fyodorov D.V., Kutach A.K., Kobayashi R., Kadonaga J.T. ACF consists of two subunits, Acf1 and ISWI, that function cooperatively in the ATP-dependent catalysis of chromatin assembly. Genes Dev. 1999;15;13(12):1529-1539.

Juhasz S., Elbakry A., Mathes A., Lobrich M. ATRX promotes DNA repair synthesis and sister chromatid exchange during homologous recombination. Mol. Cell. 2018;71(1):11-24 e7. DOI 10.1016/j.molcel.2018.05.014.

Kari V., Mansour W.Y., Raul S.K., Baumgart S.J., Mund A., Grade M., Sirma H., Simon R., Will H., Dobbelstein M., Dikomey E., Johnsen S.A. Loss of CHD1 causes DNA repair defects and enhances prostate cancer therapeutic responsiveness. EMBO Rep. 2016; 19(10):pii: e46783. DOI 10.15252/embr.201846783.

Khuong M.T., Fei J., Cruz-Becerra G., Kadonaga J.T. A simple and versatile system for the ATP-dependent assembly of chromatin. J. Biol. Chem. 2017;292(47):19478-19490. DOI 10.1074/jbc.M117.815365.

Konev A.Y., Tiutiunnik A.A., Baranovskaya I.L. The influence of the *Chd1* chromatin assembly and remodeling factor mutations on *Drosophila* polythene chromosome organization. Tsitologiia. 2016; 58(4):281-284. (in Russian)

Konev A.Y., Tribus M., Park S.Y., Podhraski V., Lim C.Y., Emelyanov A.V., Vershilova E., Pirrotta V., Kadonaga J.T., Lusser A., Fyodorov D.V. CHD1 motor protein is required for deposition of histone variant H3.3 into chromatin *in vivo*. Science. 2007;317(5841): 1087-1090.

Krude T., Keller C. Chromatin assembly during S phase: contributions from histone deposition, DNA replication and the cell division cycle. Cell. Mol. Life Sci. 2001;58(5-6):665-672.

Kukimoto I., Elderkin S., Grimaldi M., Oelgeschlager T., Varga-Weisz P.D. The histone-fold protein complex CHRAC-15/17 en-

hances nucleosome sliding and assembly mediated by ACF. Mol. Cell. 2004;13(2):265-277.

Lee J.S., Garrett A.S., Yen K., Takahashi Y.H., Hu D., Jackson J., Seidel C., Pugh B.F., Shilatifard A. Codependency of H2B monoubiquitination and nucleosome reassembly on Chd1. Genes Dev. 2012; 26(9):914-919. DOI 10.1101/gad.186841.112.

Lee Y., Park D., Iyer V.R. The ATP-dependent chromatin remodeler Chd1 is recruited by transcription elongation factors and maintains H3K4me3/H3K36me3 domains at actively transcribed and spliced genes. Nucleic Acids Res. 2017;45(12):7180-7190. DOI 10.1093/nar/gkx321.

Lewis P.W., Elsaesser S.J., Noh K.M., Stadler S.C., Allis C.D. Daxx is an H3.3-specific histone chaperone and cooperates with ATRX in replication-independent chromatin assembly at telomeres. Proc. Natl. Acad. Sci. USA. 2010;107(32):14075-14080. DOI 10.1073/pnas.1008850107.

Liu J.C., Ferreira C.G., Yusufzai T. Human CHD2 is a chromatin assembly ATPase regulated by its chromo- and DNA-binding domains. J. Biol. Chem. 2015;290(1):25-34. DOI 10.1074/jbc.M114.609156.

Loppin B., Bonnefoy E., Anselme C., Laurencon A., Karr T.L., Couble P. The histone H3.3 chaperone HIRA is essential for chromatin assembly in the male pronucleus. Nature. 2005;4437(7063):1386-1390.

Loyola A., Huang J.Y., LeRoy G., Hu S., Wang Y.H., Donnelly R.J., Lane W.S., Lee S.C., Reinberg D. Functional analysis of the subunits of the chromatin assembly factor RSF. Mol. Cell. Biol. 2003; 23(19):6759-6768.

Luijsterburg M.S., de Krijger I., Wiegant W.W., Shah R.G., Smeenk G., de Groot A.J., Pines A., Vertegaal A.C., Jacobs J.J., Shah G.M., van Attikum H. PARP1 links CHD2-mediated chromatin expansion and H3.3 deposition to DNA repair by non-homologous end-joining. Mol. Cell. 2016;61(4):547-562. DOI 10.1016/j.molcel.2016.01.019.

Lusser A., Urwin D.L., Kadonaga J.T. Distinct activities of CHD1 and ACF in ATP-dependent chromatin assembly. Nat. Struct. Mol. Biol. 2005;12(2):160-166.

Morettini S., Podhraski V., Lusser A. ATP-dependent chromatin remodeling enzymes and their various roles in cell cycle control. Front. Biosci. 2008;13:5522-5532.

Morettini S., Tribus M., Zeilner A., Sebald J., Campo-Fernandez B., Scheran G., Worle H., Podhraski V., Fyodorov D.V., Lusser A. The chromodomains of CHD1 are critical for enzymatic activity but less important for chromatin localization. Nucleic Acids Res. 2011; 39(8):3103-3115. DOI 10.1093/nar/gkq1298.

Narlikar G.J., Sundaramoorthy R., Owen-Hughes T. Mechanisms and functions of ATP-dependent chromatin-remodeling enzymes. Cell. 2013;54(3):490-503. DOI 10.1016/j.cell.2013.07.011.

Ohzeki J., Shono N., Otake K., Martins N.M., Kugou K., Kimura H., Nagase T., Larionov V., Earnshaw W.C., Masumoto H. KAT7/HBO1/MYST2 regulates CENP-A chromatin assembly by antagonizing Suv39h1-mediated centromere inactivation. Dev. Cell. 2016; 37(5):413-427. DOI 10.1016/j.devcel.2016.05.006.

Okada M., Okawa K., Isobe T., Fukagawa T. CENP-H-containing complex facilitates centromere deposition of CENP-A in cooperation with FACT and CHD1. Mol. Biol. Cell. 2009;20(18):3986-3995. DOI 10.1091/mbc.E09-01-0065.

Orsi G.A., Algazeery A., Meyer R.E., Capri M., Sapey-Triomphe L.M., Horard B., Gruffat H., Couble P., Ait-Ahmed O., Loppin B. *Drosophila* Yemanuclein and HIRA cooperate for de novo assembly of H3.3-containing nucleosomes in the male pronucleus. PLoS Genet. 2013;9(2):e1003285. DOI 10.1371/journal.pgen.1003285.

Perpelescu M., Nozaki N., Obuse C., Yang H., Yoda K. Active establishment of centromeric CENP-A chromatin by RSF complex. J. Cell Biol. 2009;185(3):397-407. DOI 10.1083/jcb.200903088.

Piatti P., Lim C.Y., Nat R., Villunger A., Geley S., Shue Y.T., Soratroi C., Moser M., Lusser A. Embryonic stem cell differentiation requires full length Chd1. Sci. Rep. 2015;5:8007. DOI 10.1038/srep0800.

Podhraski V., Campo-Fernandez B., Worle H., Piatti P., Niederegger H., Bock G., Fyodorov D.V., Lusser A. CenH3/CID incorporation is not dependent on the chromatin assembly factor CHD1 in *Drosophila*. PLoS One. 2010;5(4):e10120. DOI 10.1371/journal.pone.0010120.

Pointner J., Persson J., Prasad P., Norman-Axelsson U., Stralfors A., Khorosjutina O., Krietenstein N., Svensson J.P., Ekwall K., Korber P. CHD1 remodelers regulate nucleosome spacing *in vitro* and align nucleosomal arrays over gene coding regions in *S. pombe*. EMBO J. 2012;31(23):4388-4403. DOI 10.1038/emboj.2012.289.

Radman-Livaja M., Quan T.K., Valenzuela L., Armstrong J.A., van Welsem T., Kim T., Lee L.J., Buratowski S., van Leeuwen F., Rando O.J., Hartzog G.A. A key role for Chd1 in histone H3 dynamics at the 3′ ends of long genes in yeast. PLoS Genet. 2012;8(7):e1002811. DOI 10.1371/journal.pgen.1002811.

Robinson K.M., Schultz M.C. Replication-independent assembly of nucleosome arrays in a novel yeast chromatin reconstitution system involves antisilencing factor Asf1p and chromodomain protein Chd1p. Mol. Cell. Biol. 2003;23(22):7937-7946.

Scacchetti A., Brueckner L., Jain D., Schauer T., Zhang X., Schnorrer F., van Steensel B., Straub T., Becker P.B. CHRAC/ACF contribute to the repressive ground state of chromatin. Life Sci. Alliance. 2018;1(1):e201800024. DOI 10.26508/lsa.201800024.

Schneiderman J.I., Orsi G.A., Hughes K.T., Loppin B., Ahmad K. Nucleosome-depleted chromatin gaps recruit assembly factors for the H3.3 histone variant. Proc. Natl. Acad. Sci. USA. 2012;109(48): 19721-19726. DOI 10.1073/pnas.1206629109.

Schneiderman J.I., Sakai A., Goldstein S., Ahmad K. The XNP remodeler targets dynamic chromatin in *Drosophila*. Proc. Natl. Acad. Sci. USA. 2009;106(34):14472-14477. DOI 10.1073/pnas. 0905816106.

Semba Y., Harada A., Maehara K., Oki S., Meno C., Ueda J., Yamagata K., Suzuki A., Onimaru M., Nogami J., Okada S., Akashi K., Ohkawa Y. Chd2 regulates chromatin for proper gene expression toward differentiation in mouse embryonic stem cells. Nucleic Acids Res. 2017;6;45(15):8758-8772. DOI 10.1093/nar/gkx475.

Serra-Cardona A., Zhang Z. Replication-coupled nucleosome assembly in the passage of epigenetic information and cell identity. Trends Biochem. Sci. 2018;43(2):136-148. DOI 10.1016/j.tibs.2017.12.003.

Shenoy T.R., Boysen G., Wang M.Y., Xu Q.Z., Guo W., Koh F.M., Wang C., Zhang L.Z., Wang Y., Gil V., Aziz S., Christova R., Rodrigues D.N., Crespo M., Rescigno P., Tunariu N., Riisnaes R., Zafeiriou Z., Flohr P., Yuan W., Knight E., Swain A., Ramalho-Santos M., Xu D.Y., de Bono J., Wu H. CHD1 loss sensitizes prostate cancer to DNA damaging therapy by promoting error-prone double-strand break repair. Ann. Oncol. 2017;28(7):1495-1507. DOI 10.1093/annonc/mdx165.

Simic R., Lindstrom D.L., Tran H.G., Roinick K.L., Costa P.J., Johnson A.D., Hartzog G.A., Arndt K.M. Chromatin remodeling protein Chd1 interacts with transcription elongation factors and localizes to transcribed genes. EMBO J. 2003;22(8):1846-1856.

Siriaco G., Deuring R., Chioda M., Becker P.B., Tamkun J.W. *Drosophila* ISWI regulates the association of histone H1 with interphase chromosomes *in vivo*. Genetics. 2009;182(3):661-669. DOI 10.1534/genetics.109.10205.

Smolle M., Venkatesh S., Gogol M.M., Li H., Zhang Y., Florens L., Washburn M.P., Workman J.L. Chromatin remodelers Isw1 and Chd1 maintain chromatin structure during transcription by preventing histone exchange. Nat. Struct. Mol. Biol. 2012;19(9):884-892. DOI 10.1038/nsmb.2312.

Strohner R., Nemeth A., Jansa P., Hofmann-Rohrer U., Santoro R., Langst G., Grummt I. NoRC-a novel member of mammalian ISWI-containing chromatin remodeling machines. EMBO J. 2001;20(17): 4892-4900.

Tagami H., Ray-Gallet D., Almouzni G., Nakatani Y. Histone H3.1 and H3.3 complexes mediate nucleosome assembly pathways dependent or independent of DNA synthesis. Cell. 2004;1116(1):51-61.

Torigoe S.E., Patel A., Khuong M.T., Bowman G.D., Kadonaga J.T. ATP-dependent chromatin assembly is functionally distinct from chromatin remodeling. Elife. 2013;2:e00863. DOI 10.7554/eLife.00863.

Torigoe S.E., Urwin D.L., Ishii H., Smith D.E., Kadonaga J.T. Identification of a rapidly formed nonnucleosomal histone-DNA inter-

mediate that is converted into chromatin by ACF. Mol. Cell. 2011; 43(4):638-648. DOI 10.1016/j.molcel.2011.07.017.

Torres-Padilla M.E., Bannister A.J., Hurd P.J., Kouzarides T., Zernicka-Goetz M. Dynamic distribution of the replacement histone variant H3.3 in the mouse oocyte and preimplantation embryos. Int. J. Dev. Biol. 2006;50(5):455-461.

Tyler J.K. Chromatin assembly. Cooperation between histone chaperones and ATP-dependent nucleosome remodeling machines. Eur. J. Biochem. 2002;269(9):2268-2274.

Vary J.C. Jr., Gangaraju V.K., Qin J., Landel C.C., Kooperberg C., Bartholomew B., Tsukiyama T. Yeast Isw1p forms two separable complexes *in vivo*. Mol. Cell. Biol. 2003;23(1):80-91.

Venkatesh S., Workman J.L. Histone exchange, chromatin structure and the regulation of transcription. Nat. Rev. Mol. Cell Biol. 2015; 16(3):178-189. DOI 10.1038/nrm3941.

Vincent J.A., Kwong T.J., Tsukiyama T. ATP-dependent chromatin remodeling shapes the DNA replication landscape. Nat. Struct. Mol. Biol. 2008;15(5):477-484. DOI 10.1038/nsmb.1419.

Walfridsson J., Bjerling P., Thalen M., Yoo E.J., Park S.D., Ekwall K. The CHD remodeling factor Hrp1 stimulates CENP-A loading to centromeres. Nucleic Acids Res. 2005;33(9):2868-2879.

Wong L.H., McGhie J.D., Sim M., Anderson M.A., Ahn S., Hannan R.D., George A.J., Morgan K.A., Mann J.R., Choo K.H. ATRX interacts with H3.3 in maintaining telomere structural integrity in pluripotent embryonic stem cells. Genome Res. 2010;20(3):351-360. DOI 10.1101/gr.101477.109.

Xella B., Goding C., Agricola E., Di Mauro E., Caserta M. The ISWI and CHD1 chromatin remodelling activities influence ADH2 expression and chromatin organization. Mol. Microbiol. 2006;59(5): 1531-1541.

Yadav T., Whitehouse I. Replication-coupled nucleosome assembly and positioning by ATP-dependent chromatin-remodeling enzymes. Cell Rep. 2016;15(4):715-723. DOI 10.1016/j.celrep.2016.03.059.

Yang J.H., Song Y., Seol J.H., Park J.Y., Yang Y.J., Han J.W., Youn H.D., Cho E.J. Myogenic transcriptional activation of MyoD mediated by replication-independent histone deposition. Proc. Natl. Acad. Sci. USA. 2011;108(1):85-90. DOI 10.1073/pnas.1009830108.

Zhou J., Li J., Serafim R.B., Ketchum S., Ferreira C.G., Liu J.C., Coe K.A., Price B.D., Yusufzai T. Human CHD1 is required for early DNA-damage signaling and is uniquely regulated by its N terminus. Nucleic Acids Res. 2018;46(8):3891-3905. DOI 10.1093/nar/gky128.

Acknowledgements. This work was partially supported by RFBR, grant 15-04-99583.

Conflict of interest. The authors declare no conflict of interest.

Received November 22, 2018. Revised December 25, 2018. Accepted December 25, 2018.