Review

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Histone variants and cellular plasticity

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The broad diversity of cell types within vertebrates arises from a unique genetic blueprint by combining intrinsic cellular information with developmental and other extrinsic signals. Lying at the interface between cellular signals and the DNA is the chromatin, a dynamic nucleoprotein complex that helps to mediate gene regulation. The most basic subunit of chromatin, the nucleosome, consists of DNA wrapped around histones, a set of proteins that play crucial roles as scaffolding molecules and regulators of gene expression. Growing evidence indicates that canonical histones are commonly replaced by protein variants before and during cellular transitions. We highlight exciting new results suggesting that histone variants are essential players in the control of cellular plasticity during development and in the adult nervous system.

Histone variants are unique modifiers of chromatin

Since the groundbreaking discovery of a distinct isoform of histone H3 in calf thymus [1], numerous histone variants have been discovered in eukaryotes [2,3]. Histone variants are non-allelic isoforms of the canonical histone proteins H1, H2A, H2B, H3, and H4 [3] (see Glossary). Whereas canonical histones are generally produced in coordination with DNA replication from mRNAs containing short 3′ stem-loop tails [4], many variants are translated from mRNAs with conventional poly-A tails outside S-phase and are incorporated into the chromatin, often with the help of special chaperones [5]. The synthesis of histone variants outside S-phase and in specific tissues enables them to perform specialized functions such as DNA repair (H2A.X) [6], conversion of chromatin to nucleoprotamine during spermatogenesis (testis-specific histone H2B, TSH2B) [7], and kinetochore assembly (centromere protein A; CENP-A) [8]. Moreover, exciting new studies have revealed prominent roles for a subset of histone variants in regulating cellular plasticity, broadly defined as the capacity of a cell to undergo changes in its structural or functional properties.

Biochemical and structural alterations to chromatin are associated with an ever-expanding array of histone PTMs (Box 1) [9,10]. One might therefore wonder what additional features can be provided by the replacement of canonical histones with histone variants. Clearly, canonical histones are insufficient to sustain life in metazoans, perhaps owing to the evolution of specific developmental and physiological processes in these organisms, which may require unique chromatin landscapes for specialized gene expression programs. At a biochemical level, some variants, such as macroH2A and H2A.Z, have highly-divergent polypeptide sequences, which enable major changes in chromatin structure and function [11]. Other variants, such as H3.3, provide more subtle differences that can nevertheless cause crucial changes in post-translational modifiability [12] as well as in interactions with chaperones [13] and chromatin 'readers' [14]. In addition to increasing functional diversity, histone variants also offer a means to reduce it. For example, the transient removal of H3.3 from the maternal genome following fertilization may enable the global resetting of pre-existing PTMs to create a totipotent embryo [15]. Whether histone variants provide additional but so far uncovered functions is an exciting question.

Despite decades of study, the functions and expression patterns of many vertebrate histone variants remain poorly defined owing to high levels of sequence identity between

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Glossary

Bivalent chromatin: region of chromatin that contains both activating and repressive modifications, and is thus silent but poised for potential future activation.
Embryonic stem cell (ESC): cell derived from the inner cell mass of a blastocyst (an early-stage embryo) that is pluripotent and can be grown indefinitely in culture.
Heterotypic nucleosome: nucleosome that contains one copy of a particular histone variant and one copy of a canonical histone from the same family.
Histone post-translational modification (PTM): covalent chemical modification of a histone protein that affects its structure and function.
Histones: five families of positively charged proteins (H1, H2A, H2B, H3, and H4) that package DNA into nucleosomes within eukaryotic cell nuclei and play central roles in regulating gene expression.
Histone variant: non-allelic isoform of a canonical histone protein.
Homotypic nucleosome: nucleosome that contains two copies of a particular histone variant.
Hybrid nucleosome: nucleosome that contains multiple distinct histone variants.
Multipotency: the ability of a cell to divide and produce more than one differentiated cell type.
Neuronal activity: electrical and chemical signaling that occurs upon activation of neuronal receptors.
Nuclear reprogramming: process in which a differentiated cell is converted to pluripotency.
Nucleosome: the basic unit of chromatin in eukaryotes, consisting of DNA wrapped around an octamer of histone proteins (two subunits from each of the H2A, H2B, H3, and H4 families).
Pluripotency: the ability of a cell to divide and produce all of the differentiated cell types in an organism.
S-phase: phase ('synthesis') of the cell cycle in which DNA is replicated and packaged largely with canonical histones.
Somatic cell nuclear transfer (SCNT): process in which the nucleus from a differentiated cell is reprogrammed following transfer to an oocyte.

Box 1. Histone PTMs

Histones are subject to a wide array of PTMs (Table I) that are generated and removed by specific modifiers which are precisely regulated in their genomic localization and activity (reviewed in [10,110]). To date, only a fraction of known PTMs have been analyzed with respect to their genomic localization, and fewer still are understood on a functional level. Of the PTMs that have been analyzed extensively, most appear to be enriched within specific gene regions. Moreover, PTM enrichment is strongly correlated with the transcriptional status of a gene. In some cases, PTMs are known to influence chromatin structure directly and/or through recruitment of effector molecules, and knockouts of PTM modifiers or effectors have revealed severe developmental defects. Despite our incomplete understanding of PTMs, it is clear that they play pivotal roles in organizing chromatin and regulating gene expression during development and throughout life.

Table I. PTMs discussed in this review

PTM	Genomic localization	Functional association(s)
H3K4me3	Promoter regions of active and poised genes	Transcriptional activation or poising in active or bivalent domains, respectively; catalyzed by enzymes of the trithorax group: MLL1–4, SETD1A, and SETD1B
H3K27me3	Promoter regions of silent and poised genes; large heterochromatin blocks	Transcriptional repression or poising in silent or bivalent domains, respectively; catalyzed by the polycomb repressive complex 2 (PRC2), which contains EZH2 (or EZH1), SUZ12, and EED
H3K9me3	Constitutive heterochromatin	Transcriptional repression
acH2A.Z	Promoter regions of active and poised genes[a]	Transcriptional activation or poising in active or bivalent domains, respectively
H2A.Zub1	Promoter regions of poised genes[a]	Transcriptional repression or poising in silent or bivalent domains, respectively; modified by the Ring1B component of PRC1 [37,111]
H2BK5me1	Bodies of active genes, especially those with metabolic roles; enhancers; telomeres[b]	Transcriptional elongation
H2BK5ac	Promoter regions of active genes[b]	Transcriptional activation

[a]Based on analysis of ESCs and neural progenitor cells [37].

[b]Based on analysis of $CD4^+$ T cells [105,112].

histone species. Major advances in high-resolution and quantitative chromatin analysis [16,17], combined with loss of function analysis [18,19], have expanded inroads for the study of chromatin. In particular, advances have revealed that a set of vertebrate histone variants play crucial roles in developmental transitions [20], when cells lose plasticity and acquire defined and stable identities [21]. In addition, crucial roles have emerged for histone variants during cellular transitions that occur throughout life, particularly in the nervous system, where the modulation of gene expression drives experience-dependent cellular changes [22,23]. We review recent studies of the roles played by histone variants in regulating cellular plasticity during early development and within the nervous system.

Histone variants are key regulators of developmental plasticity

Programmed differentiation, which begins at the earliest stages of development in the totipotent zygote and pluripotent embryonic stem cells (ESCs) [24], and continues throughout development and into adulthood [25], involves the coordinated activation of lineage-specific genes and the stable repression of genes underlying developmental multipotency. The balance between stem cell self-renewal and differentiation, as well as the process of differentiation itself, are tightly controlled at the level of chromatin [26]. Investigations of these processes have historically focused on the functions of transcription factors and PTMs. However, intriguing recent evidence indicates that crucial aspects of developmental plasticity in the early embryo may be regulated by histone variants.

TH2A and TH2B help to establish developmental plasticity in the early embryo

Histone variants TH2A and TH2B, which differ from canonical H2A and H2B by 15 and 16 amino acids, respectively [2], were first identified in testis tissue [27,28]. Unexpectedly, high levels of these variants were also recently found in oocytes and zygotes, with decreasing levels observed as differentiation proceeds to the blastocyst stage [29] (Figure 1). Interestingly, oocytes derived from TH2A/TH2B knockout mice showed a significantly reduced ability to reach the blastocyst stage following fertilization compared to wild-type counterparts, as well as defects in paternal genome activation [29]. These observations, together with findings that endogenous levels of TH2A and TH2B increase dramatically during 'reprogramming' of somatic cells to a pluripotent state, suggest that TH2A and TH2B might play a role in the induction of pluripotency [29]. Indeed, coexpression of TH2A and TH2B, together with the oocyte-specific histone chaperone NPM (nucleophosmin), enhanced the efficiency of reprogramming mouse embryonic fibroblasts (MEFs) 18-fold [29]. Moreover, reprogramming efficiency was reduced sixfold in MEFs obtained from TH2A/TH2B knockout mice, further evidence that endogenous TH2A and TH2B facilitate the induction of pluripotency [29].

How do TH2A and TH2B facilitate reprogramming? DNase I sensitivity assays revealed that expression of the variants during reprogramming promotes an open chromatin structure [29], a hallmark of pluripotency [30]. Further, chromatin localization experiments showed that the variants are distributed widely throughout the genome of MEFs undergoing reprogramming, suggesting