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Review

Like a rolling histone: Epigenetic regulation of neural stem cells and brain development by factors controlling histone acetylation and methylation ☆

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ABSTRACT

Background: The development of the nervous system is a highly organized process involving the precise and coordinated timing of many complex events. These events require proper expression of genes promoting survival, differentiation, and maturation, but also repression of alternative cell fates and restriction of cell-type-specific gene expression.
Scope of the review: As the enzymes mediating post-translational histone acetylation and methylation are regulating higher order chromatin structure and controlling gene transcription, knowledge of the roles for these enzymes becomes crucial for understanding neural development and disease. The widespread expression and general biological roles for chromatin-modifying factors have hampered the studies of such enzymes in neural development, but in recent years, in vivo and in vitro studies have started to shed light on the various processes these enzymes regulate. In this review we summarize the implications of chromatin-modifying enzymes in neural development, with particular emphasis on enzymes regulating histone acetylation and methylation.
Major conclusions: Enzymes controlling histone acetylation and methylation are involved in the whole process of neural development, from controlling proliferation and undifferentiated, "poised", state of stem cells to promoting and inhibiting neurogenic and gliogenic pathways and neuronal survival as well as neurite outgrowth.
General significance: Aberrant enzymatic activities of histone acetyl transferases, deacetylases, and demethylases have been chemically and genetically associated with neural developmental disorders and cancer. Future studies may aim at linking the genetic and developmental studies to more in-depth biochemical characterization to provide a clearer picture of how to improve the diagnosis, prognosis, and treatment of such disorders. This article is part of a Special Issue entitled Biochemistry of Stem Cells.

1. Introduction

The control of transcription is crucial in cell differentiation and development of the nervous system. In the last decade, histone modifications have been shown to control many aspects of transcription including higher order chromatin structure and gene expression. The enzymes mediating post-translational histone modifications are therefore at the heart of development that requires precise control of gene expression patterns. The concept of the self-renewing, multipotent neural stem cells generating the main cell types of the nervous system has received a lot of attention and identification of adult neural stem cells residing in spinal cord and dentate gyrus has excitingly triggered a vision of enabling neural-replacement strategies solving severe disease situations, like spinal cord injuries or neurodegenerative diseases, by promoting a functional recovery (cf [1]). Characterizing epigenetic cell state regulation is essential in many aspects for normal development but also to understand developmental disorders. Importantly, epigenetic processes are also influenced by environmental cues like maternal behavior or prenatal stress and have shown to be central in influencing responses in the offspring [2,3]. From epigenetic studies it has become clear that histone-modifying enzymes control transcription both through their cell-type specific expression and their specific activity. Histones can be post-translationally modified in many ways, for example by acetylation, methylation, phosphorylation, ubiquitination, and sumoylation [4]. These modifications have profound effects on the local chromatin environment and the modifications can be regulated by active addition or removal. Hence, the enzymes regulating these modifications become focus of attention when dissecting the epigenetic mechanisms influencing neural stem cell state and fate and nervous system development. In this review we aim to present the implications of the specific enzymes with activities modulating acetylation, i.e. histone acetyl transferases and histone deacetylases, and methylation, i.e. histone methyl transferases and histone demethylases, of lysines of the histone tails identified to be involved in neural development. These findings have

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strong implications for the teratogenic effects of widely used medical substances, such as valproic acid, neurodevelopmental disorders including mental retardation, pediatric tumors of the nervous system, and predisposition for developing disease in adulthood.

2. Histone acetyl transferases (HATs)

Histones H3 and H4 can be acetylated on several lysines on their N-terminal tails and the acetylation level of histones in a promoter is positively correlated to an active transcription, but the enzymes that acetylate the histones in vivo are not well studied in a developmental context, not even in cellular systems. The fact that the substrate specificity of the HATs is fairly low when studied in vitro makes it difficult to couple specific acetylated residues to any single enzyme. Many of the HATs also acetylate non-histone proteins, which also complicate the interpretation of the phenotypes observed in acetyl transferase (AT) knock-out mice [5]. CBP and p300 are large, similar proteins that interact with many different transcription factors and are shown to have both AT activity as well as non-enzymatic functions where they act as scaffolds bringing the general transcriptional machinery and the DNA binding transcription factors together [6]. Mutations in either factor cause Rubinstein–Taybi syndrome, a disease in part characterized by mental retardation. One example of a non-enzymatic function of CBP is the finding that ES cells from CBP AT activity deficient mice surprisingly respond to bone morphogenetic protein 2 (BMP2) signaling by upregulating BMP-inducible genes to a similar if not higher level than wild type ES cells [5]. However, the AT activity of the enzymes is essential to mouse development since deficiency in AT activity is embryonic lethal [5]. Nevertheless, there are several studies linking HATs to neural development (Table 1, Fig. 1) even though knockouts of the whole protein do not differentiate between CBP/P300 activities on histone acetylation and other functions of the proteins. Mice mutant for CBP die around embryonic day (E) 12 with malformations of the central nervous system as a result of failure to close the dorsal tube cranially [7], which implicates CBP function during early neural development. Similar observations were made early in the p300 mutant mice [8]. In addition, neural lineage decision has been linked to functional CBP activity [9] and development of motor neurons in the spinal cord has been shown to be dependent on CBP through a synergistic interaction with retinoic acid receptor (RAR) and Neurogenin2 [10]. CBP and p300 can be modified post-translationally at several positions, and phosphorylation of CBP by atypical protein kinase Cζ controls the AT activity. This phosphorylation has been shown to be necessary for histone acetylation of neural promoters and neuronal differentiation [11]. Regeneration in response to injury is also related to development and nerve injury models have been used to study the formation of nerves. Thus, in an ocular nerve model of nerve damage, p300 overexpression was observed to promote axonal regeneration [12].

Apart from neurogenesis, HATs have also been implicated in astrocytic differentiation. Neural stem cell differentiation into astrocytes has been shown to be dependent on synergistic signaling between leukemia inhibitory factor (LIF) and BMP2 [13]. These signals are coordinated by p300 acting as a bridge between STAT3 and Smad1 representing the downstream signals in the LIF and BMP2 signaling cascades [13]. CBP and p300 have also been implicated in astrocytic differentiation in differentiating Ntera2 cells, where CBP and p300 are recruited directly to the astrocytic marker glial fibrillary acidic protein (GFAP) promoter and facilitate transcription [14].

In several of these studies, CBP/p300 has been suggested to act as signaling hubs that integrate the activity of several transcriptional activators from different signaling pathways [10,13] and it is important to note that this seems to be a general role for CBP and p300 in neural development. In addition to the CBP and p300 studies the Gcn5 HAT has also been implicated in neural development since mice with a point mutation in the HAT domain of Gcn5 show neural tube closure effects [15]. More studies on other HATs than CBP and p300 in neural stem cells and brain development will be of interest to increase the understanding for specific roles of histone acetylation in these events.

Table 1
Histone modifying enzymes involved in neural development. References for the table: [7,10–15,21,22,24–27,31–34,36,40,47,49,51–54,66,67,69,70].

Function	Enzyme	Effect on neural development	References
HAT	CBP	Required for neuronal development	Tanaka, 2000; Lee, 2009; Wang, 2010
	P300	Required for astrocyte development, promotes axonal regeneration	Cheng, 2011; Nakashima, 1999; Gaub, 2011
	GCN5	HAT activity needed for neural tube closure	Bu, 2007
HDAC	HDAC1	Blocks premature differentiation of NSCs, required for oligodendrocyte differentiation	Ye, 2009; Jacob, 2011; Chen, 2011; Akhtar, 2009
	HDAC2	Blocks premature differentiation of NSC, required for oligodendrocyte differentiation	Ye, 2009; Jacob, 2011; Chen, 2011; Akhtar, 2009
	HDAC1-3	VPA stimulates neurogenesis, inhibits oligodendrocyte differentiation	Hsieh, 2004; Laeng 2004
	HDAC5	Promotes neural stem cell proliferation	Sun, 2007
	HDAC9	Regulates dendritic growth	Sugo, 2010
	Sirt1	Influences neuronal differentiation	Zhang, 2011; Prozorovski, 2008; Wallenborg, 2009
DNMT	DNMT1	Required for neural cell viability	Fan, 2001
	DNMT3a	Required for neuromuscular junction	Nguyen, 2007
HMT	Mll1	Controls neurogenesis	Lim, 2009
	G9a	Prevents misexpression of neural genes, required for neurogenesis	Roopra, 2004
	Ezh2	Controls neural stem cell state, prevents premature differentiation	Rai, 2010 Pereira, 2010
HDM	LSD1	Controls neural stem cell proliferation	Sun, 2010
	Jarid2a	Control repression of pluripotency genes during neural differentiation	Schmitz, 2011
	JMJD3	Promotes neuronal differentiation	Jepsen, 2007
	KDM7	Required for neural development	Tsukada, 2010
	Jarid1c/SMCX	Required for neuronal survival and dendrite development	Iwase, 2007

3. Histone deacetylases (HDACs)

HDACs are generally divided into four classes. Class I HDACs (HDAC1, 2, 3 and 8) are most closely related to the yeast transcriptional regulator Rpd3 and are sensitive to the HDAC inhibitor Valproic acid (VPA) that is clinically widely used to treat epilepsy and bipolar disorder [16]. Class II HDACs (HDAC4, 5, 6, 7, 9 AND 10) share domains that have similarities in the yeast deacetylase HDA1. Common HDAC inhibitors, such as Trichostatin A (TSA), block HAT activities from both class I and class II HDACs. Class III HDACs are also called sirtuins after the founding member Sir2 in yeast. These are NAD + dependent enzymes and at least a subset of these can be activated by the well-studied and discussed polyphenol resveratrol. Class IV only contains one HDAC (HDAC 11) and has characteristics of both class I and Class II HDACs. The expression of HDAC 11 is cytoplasmic which suggest a non-histone deacetylation function (for extensive review on HDACs, please see [17]).

4. Effects of chemical inhibitors of HDACs

As HAT activity is affecting neural differentiation it is not surprising that also HDAC activity, which counteracts histone acetylation, can affect neural differentiation. Many studies have used chemical means of inhibiting HDAC activity in different systems. In neuronal cells, the histone deacetylase inhibitors TSA and sodium butyrate were observed