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Epigenetic alchemy for cell fate conversion

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Recent progress in neural stem cell research shows that a number of extrinsic factors and intracellular mechanisms, including epigenetic modifications, are involved in the self-renewal of neural stem cells and in neuronal and glial differentiation. Remarkably, there is increasing evidence that the remodeling of chromatin structure and the alteration of epigenetic marks, including histone methylation and acetylation and DNA methylation, can cause committed cells to convert from one fate to another, and such converted cells are functional when transplanted *in vivo*. Thus, epigenetic research might generate the alchemy required to convert any non-neural stem cells into functional neural stem cells, which are few and difficult to extract from the adult central nervous system.

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Introduction

Everyone wishes that all cells or tissues that are lost as a result of injury or illness could be readily regenerated. Recent progress in medical research might help us to realize this goal. Stem cells, which give rise to many types of cells and function in tissue homeostasis, have been found in many adult tissues and are thought to be possibly the best cell source for regenerative medicine. Because the number of tissue-specific stem cells in the adult central nervous system (CNS) is very small and the number of stem cells donors is very limited, there is an increasing demand to find an alternative source of stem cells.

During the past decade, a number of studies have shown that adult stem cells, which were thought to be lineage-restricted, can acquire a broad developmental potential and give rise to cells characteristic of other organs [1,2]. For example, when transplanted into various sites *in vivo*, adult neural stem cells (NSCs) can give rise to blood cells, skeletal muscle cells, endothelial cells and other cell types [1–3], and bone marrow stromal cells can transdifferentiate into neurons and glia [4]. However, given that some of these results have been either difficult to reproduce or shown to be misinterpretations of other phenomena, such as cell-fusion, the extent of adult stem cell plasticity is still uncertain.

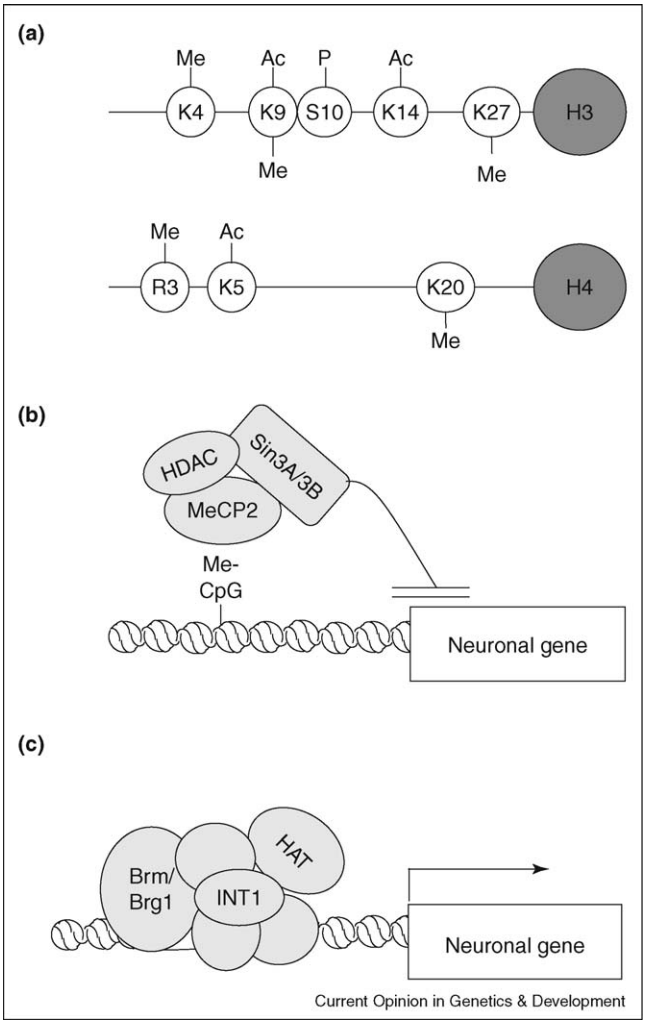
Recent advances in epigenetics suggest that cell fates can be reset by the alteration of epigenetic marks or the histone code, and that such converted cells are functional when transplanted *in vivo*. These remarkable findings suggest that epigenetics might provide an important new technology for improving regenerative medicine. In this review, I focus on new findings and the insights they give us into the roles of epigenetic processes in neural cell-fate conversion.

Histone modification and neural differentiation

A number of histone modifications, including acetylation, methylation, phosphorylation, ubiquitination, sumoylation and ADP-ribosylation, regulate gene expression and chromatin structure [5,6]. For example, when a gene is transcriptionally active, histone H3 is acetylated at lysines 9 and 14, dimethylated or trimethylated at lysine 4, and phosphorylated at serine 10 (Figure 1a). By contrast, histone H3K9 is dimethylated or trimethylated in inactive chromatin. Histone H4 is acetylated at K5 and methylated at K3 in active chromatin, whereas histone H4 sumoylation is connected with transcriptional repression, because the sumoylated H4 recruits histone deacetylases (HDACs) and heterochromatin protein 1, which are transcription repressors [7]. These histone modifications are regulated by specific enzymes: histone acetyltransferases (HATs), HDACs, histone methyltransferases (HMTs), kinases, the E1–E3 ubiquitinating enzyme complex, deubiquitinating enzymes, SUMO-activating and -conjugating enzymes, and poly-ADP-ribose polymerase [5,6].

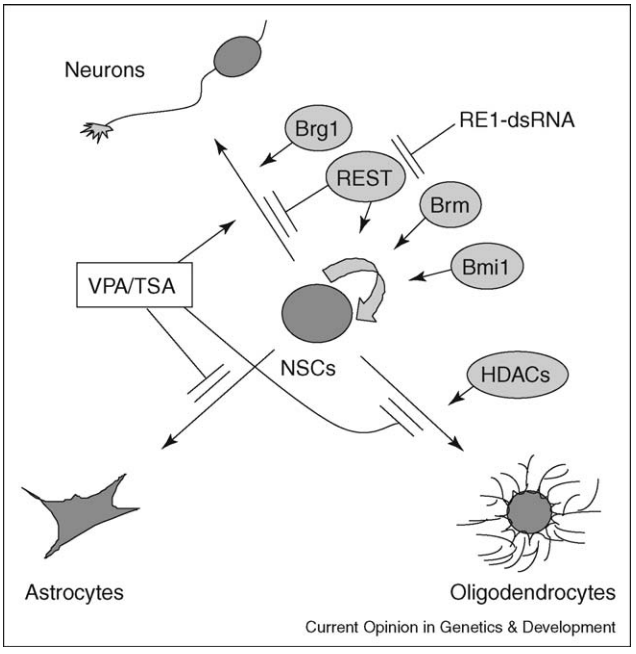
Many lines of evidence have shown that histone modifications are involved in neuronal and glial differentiation (Figure 2). Two HDAC inhibitors, valproic acid and Trichostatin A, prompt the differentiation of hippocampal neural progenitor cells into neurons, but they prevent their differentiation into oligodendrocytes and astrocytes [8•]. HDAC activity is essential during a specific temporal window for oligodendrocyte differentiation [9,10•]. Analysis of P19 cells during neuronal differentiation revealed enhanced trimethylation of histone H3K4 in the *synapsin* promoter [11•]. The differentiation of cortical progenitor cells into astrocytes is accompanied by the induction of histone H3K4 methylation and the suppression of histone

Figure 1



Epigenetic mechanisms involved in neural development. **(a)** Histone H3 and H4 are acetylated (Ac), methylated (Me) and/or phosphorylated (P) in active (upper letters) and inactive (lower letters) chromatin. **(b)** Methyl-CpG-binding domain (MBD) protein (MeCP2) binds to a methylated CpG site in the promoter of neuronal genes and recruits the repressor complex that contains histone deacetylase (HDAC) and Sin3A/3B. **(c)** An SWI/SNF chromatin-remodeling complex containing Brm or Brg1, histone acetyltransferase (HAT) and INT1 activates neural gene expression.

Figure 2



Roles of epigenetic factors in neural differentiation. The defining characteristics of NSCs, self-renewal and multipotency, are maintained by epigenetic factors, including the Polycomb factor Bmi1, Brm and REST. Neuronal differentiation is regulated by Brg1 and RE1 double-stranded RNA, which blocks REST activity. Histone acetylation induces neuronal differentiation but inhibits both astrocyte and oligodendrocyte differentiation. Consistent with this, HDAC activity is required for oligodendrocyte differentiation.

H3K9 methylation in the *gfap* promoter [12•]. In embryonic neuroepithelial progenitor cells, histone H3 in the promoter of *sox2*, which is essential for the proliferation and the maintenance of NSCs, is in its active form, with K4 methylation and K9 acetylation; whereas, during NSC differentiation, histone H3 is altered to its inactive form by K4 demethylation and K9 deacetylation and dimethylation [13•].

Non-coding RNA and neural differentiation

Recent studies have demonstrated that small non-coding RNAs, including microRNAs (miRNAs) and small interfering RNAs, inhibit gene expression at various steps, including transcription, translation of target mRNAs, and heterochromatin formation of the target genes [14]. There is accumulating evidence that non-coding RNAs are involved in neural development [15]. Repressor element 1 (RE1)-silencing transcription factor (REST; also known as neuron-restrictive silencing factor [NRSF]) is a crucial factor in neuronal development: REST can repress the expression of neuronal genes by binding to an RE1 consensus binding site and subsequently recruiting a transcriptional repressor complex, which contains HDACs, mSin3, Co-REST, methyl-CpG-binding domain (MBD) protein (MeCP2), and the H3K9 HMTs G9a and SUV39 [16–18]. Kuwabara *et al.* [19••] showed that a non-coding double-stranded RNA matching the RE1 consensus binding site is expressed during neuronal differentiation and activates neuron-specific genes that have undergone certain histone modifications (Figure 2) [19••]. Given that a number of miRNAs, including miR124 and miR128 in neurons, and miR23, miR26 and miR29 in astrocytes, are expressed in the developing brain, it is of great interest to analyze their functions in CNS development [20].