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Review

Epigenetics in NG2 glia cells

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ABSTRACT

The interplay of transcription and epigenetic marks is essential for oligodendrocyte progenitor cell (OPC) proliferation and differentiation during development. Here, we review the recent advances in this field and highlight mechanisms of transcriptional repression and activation involved in OPC proliferation, differentiation and plasticity. We also describe how dysregulation of these epigenetic events may affect demyelinating disorders, and consider potential ways to manipulate NG2 cell behavior through modulation of the epigenome.

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Contents

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1. Introduction

NG2 glial cells are traditionally defined as oligodendrocyte progenitor cells (OPC) receiving synaptic inputs and with the ability to respond to a variety of extracellular stimuli by proliferating, migrating, differentiating or modulating brain homeostasis and plasticity (Barres et al., 1994a; Demerens et al., 1996; Fannon et al., 2015; Hernandez and Casaccia, in press; Nishiyama et al., 1999; Pringle et al., 1992; Raff et al., 1983; Tsai et al., 2009; Wake et al., 2011). These biological responses result from the integration of environmental signals with the intrinsic properties of the cells. The latter ones might evolve with age as progenitors in the neonatal period show different responsiveness than their adult counterparts, in terms of their biological properties, including fate-choice decisions, proliferation, migration or differentiation rates (Chari et al., 2003; Windrem et al., 2004; Wolswijk and Noble, 1989; Young et al., 2013). It is likely that these changes result from modifications of the epigenetic landscape over time.

Among well-defined epigenetic mechanisms this review will discuss: DNA methylation, chromatin modifications and remodeling and non-coding RNA.

DNA methylation is the only known epigenetic modification that directly modifies DNA components, by adding a methyl group at the C-5 position of cytosine residues at CpG dinucleotides (Eden and Cedar, 1994). This reaction is catalyzed by: the DNA maintenance methyltransferase DNMT1, which is responsible for the faithful transmission of DNA methylation from mother to daughter cells during replication and by the *de novo* methyltransferases DNMT3A and DNMT3B for the establishment of new methylation marks (Goll and Bestor, 2005; Lei et al., 1996; Okano et al., 1998). These enzymes are expressed in the CNS, where the DNA methylation level is higher than in any other tissues (Ono et al., 1993; Tawa et al., 1990). They have been shown to regulate survival and differentiation of neurons and astrocytes, while their role in the NG2 cells has not been thoroughly investigated (Fan et al., 2001; Noguchi et al., 2015; Takizawa et al., 2001; Wu et al., 2012b). DNA methylation at promoter regions is mainly associated with transcriptional repression, either by directly preventing the access of transcription factors to their binding sequence or by recruiting cofactors that modulate the chromatin environment (Schübeler, 2015; Smith and Meissner, 2013). Another modification of the DNA is the oxidation of 5-methylcytosine to 5-hydroxymethylcytosine (5-hmC) by the recently identified ten-eleven translocation (TET) enzymes, which are dynamically expressed in the oligodendroglial lineage (Branco et al., 2012; Tahiliani et al., 2009; Zhao et al., 2014). The low levels of 5-hmC initially found in the genome of embryonic stem cells led to the hypothesis that 5-hmC was only a short-lived intermediate associated with the removal of methyl groups from cytosine residues (Tahiliani et al., 2009). However, the abundance of 5-hmC in euchromatic regions, especially in the brain, suggests that it might also be an important epigenetic regulator of gene expression (Ficz et al., 2011; Münzel et al., 2010; Szulwach et al., 2011; Szwagierczak et al., 2010). Hydroxymethylation is characteristically enriched at gene bodies and transcription starting sites, where it has been associated with transcriptional activation and alternative splicing (Feng et al., 2015; Szulwach et al., 2011). In both human and mouse embryonic stem cells, hydroxymethylation enrichment at binding sites of pluripotency-associated transcription factors has been linked to regulation of cell lineage choice and differentiation (Ficz et al., 2011).

Histones H2A, H2B, H3 or H4 are protein components of the nucleosome, which defines the basic unit of chromatin. They can be subject to post-translational modifications including methylation, acetylation, sumoylation, phosphorylation, citrullination, ubiquitination, proline isomerization and ADP-ribosylation (Kouzarides, 2007). Addition or removal of these groups at specific amino acid residues on the tails of the histones, can either activate or repress gene expression (Jenuwein and Allis, 2001; Strahl and Allis, 2000). For example, acetylation of lysine 27 in histone H3 (H3K27ac) at active enhancers has been associated with transcriptional activation, whereas acetyl group removal by histone deacetylases (HDACs) is mainly linked to gene repression (Creyghton et al., 2010; Rada-Iglesias et al., 2011). Histone methylation marks, catalyzed by lysine-specific histone methyltransferase and arginine-specific histone methyltransferases, are also divided in two categories: methylation of lysine 4 in histone H3 (H3K4me1), usually enriched at enhancers, and dimethylation of arginine 3 in histone H4 (H4R3me2) are active histone marks, while trimethylation of lysines 9 or 27 in H3 (H3K9me3 and H3K27me3) are repressive marks, usually enriched in silenced genes (Di Lorenzo and Bedford, 2011; Mikkelsen et al., 2007; Shilatifard, 2006).

In addition to histone modifications, chromatin structure can also been rearranged by ATP-dependent chromatin remodelers that are characterized by nucleosomal sliding activity (Sohn et al., 2007). The SWI/SNF complex has first been identified in yeast, and several members of this family, including BRG1 (or SMARCA4) and BRM (or SMARCA2), have later been described in mammalian cells and also in NG2 cells (Bischof et al., 2015; Hargreaves and Crabtree, 2011; Ho and Crabtree, 2010; Yu et al., 2013). Chromatin remodeling has been associated to both activation and repression of gene expression (Clapier and Cairns, 2009).

Recently described non-coding RNA are another epigenetic mechanisms regulating gene expression, notably during brain development (Derrien et al., 2012; Qureshi and Mehler, 2012) and in neurological disorders (Esteller, 2011). In this family, the 20–25 nucleotide-long micro-RNAs (miRNA), which are processed by RNA polymerase II and DICER, can form a complex with Argonaute to induce mRNA silencing or