ABSTRACT

Myelination of the nervous system is a critically important process for providing rapid conduction of nerve impulses and trophic support for axons in vertebrates. Within the central nervous system, myelin is produced by oligodendrocytes. The molecular regulation of CNS myelination is for the most part unknown, although several transcription factors like YY1, MRF, ZFP191, SOX10 etc have been identified as regulators of myelination. MeCP2 (Methyl CpG binding protein 2) is a multifunctional protein bind to methylated CpG, mutation of which cause a neurodevelopment disorder, Rett syndrome (RTT). Most of studies related to MeCP2 were primarily focused on role of MeCP2 in neuronal cells and its contribution to Rett syndrome. Recent studies have shown MeCP2 expression and function in glial cells. Since MeCP2 act as global transcriptional modulator, the present study hypothesizes that myelin genes may be transcriptional targets of MeCP2 in oligodendrocytes. The results show that MeCP2 negatively regulates expression of myelin related genes. Interestingly, myelin associated proteins myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG) which plays an important role in oligodendrocytes differentiation and myelin sheath formation were found to be induced in MeCP2 knock down oligodendrocytes. In addition, MeCP2 also regulates the Brain derived neurotrophic factor (BDNF) and YY1, a transcriptional regulator of oligodendrocytes differentiation, were also found to be dysregulated. MeCP2 directly binds to promoter of MBP, PLP and BDNF in oligodendrocytes. Further, oligodendrocytes precursor cells (OPCs) migration which is pre-requisite for myelination in the brain was found to be reduced in MeCP2 deficient condition. MeCP2 also regulates the morphological differentiation of oligodendrocytes. Besides, MeCP2 role in neurodevelopmental disorders, its importance in many cancers such as breast, colorectal, lung, liver, and prostate cancer is well studied. However, far too little attention has been given to the role of MeCP2 in glioma pathogenesis. Hence, we hypothesized that MeCP2 regulate the C6 glioma malignant behavior and related gene expression. The data indicate that MeCP2 inhibits C6 glioma proliferation, invasion, migration, adhesion, colony formation and sphere formation ability. MeCP2 is also shown to induce C6 glioma differentiation by inhibiting ERK activity and promoting the GFAP expression. Moreover, MeCP2 reduce the BDNF and FAK protein levels in C6 glioma. MeCP2 regulates GFAP and BDNF expression by directly binding to their promoter regions. These findings suggest that MeCP2 may play a crucial role in suppression of C6 glioma cancer progression. C6

glioma was found to retain the characteristic of glial precursor, express some oligodendrocyte and astrocytes marker genes including PLP, MAG and GFAP and therefore it was hypothesized that MeCP2 may also regulate the myelin gene expression in C6 glioma. Unlike oligodendrocytes, MeCP2 positively regulate the expression of myelin genes (MBP, PLP and MAG) in C6 glioma but does not bind to their promoters.

Overall, the findings from the present study conclusively reveal previously unknown role of MeCP2 in myelin gene regulation and glioma cancer.