CHAPTER 5

SUMMARY

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Myelination is a very important event for the proper functioning of the central nervous system and so the development of oligodendrocytes and myelination of axons is a highly regulated process and controlled by several intrinsic and extrinsic factors. The present study focused on MeCP2, a global transcriptional modulator, and its role in myelin genes regulation in the rat oligodendrocytes. Following the initial olig-2 dependent specification of oligodendrocyte lineage, subsequently, there are large numbers of transcription factors (Nkx2.2, Sox10, YY1, Tcf4) that are induced for the generation of mature and post mitotic oligodendrocytes. However, no information exists for the role of MeCP2 in the transcriptional regulation of CNS myelination. The data from the present study is the first report to conclusively demonstrate the role of MeCP2 to negatively regulate the major myelin (MBP, PLP, MOG and MOBP) and related proteins (BDNF and YY1) expression, which is essential for oligodendrocytes differentiation.

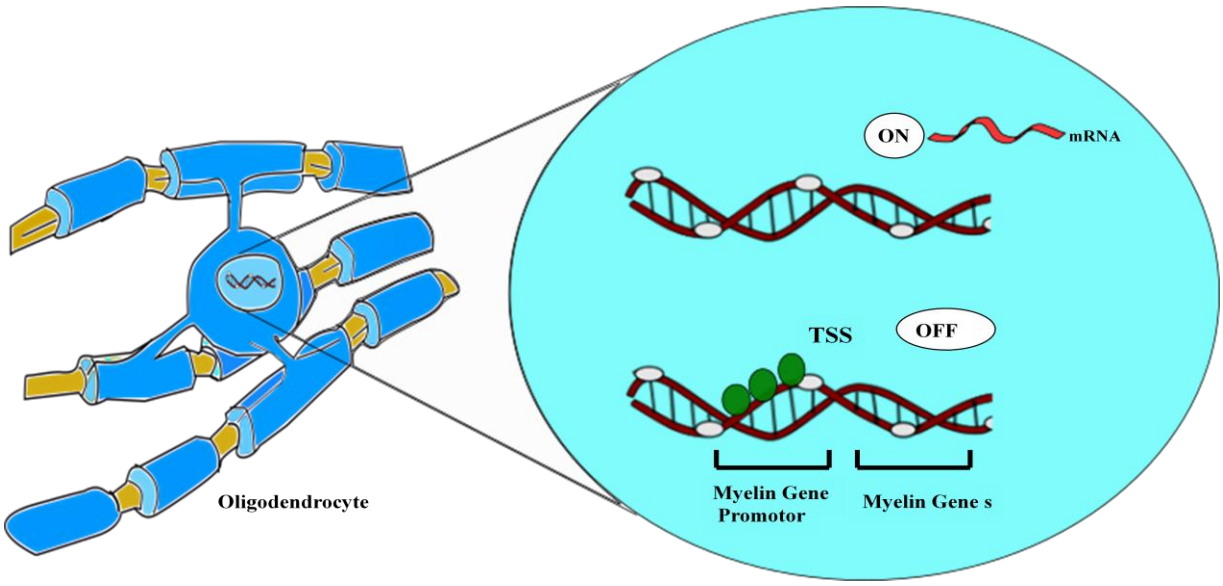

Figure 5.1: MeCP2 negatively regulate myelin gene expression in cultured rat oligodendrocytes

MeCP2 mediated direct regulation of gene expression require binding of MeCP2 to their promoter regions. In current study, it was confirmed that MeCP2 is recruited to promoter region of Myelin genes (MBP and PLP) and neurotrophin (BDNF). MBP and PLP are the major myelin

proteins that constitute 80% of myelin proteins. MBP and PLP proteins expression increase as oligodendrocytes mature and are essential for myelin compaction and integrity. Brain derived neurotrophin factor (BDNF) is target of MeCP2 in neurons, and involved in neuronal survival, differentiation and synaptic plasticity. Apart from that, the present study showed that BDNF is also involved in promotion of myelination and remyelination or myelin repair by oligodendrocytes. Therefore, the data from the current study shows that MeCP2 may affect myelination indirectly through the regulation of BDNF expression in oligodendrocytes.

Further, MeCP2 deficiency was found to reduce the migration of OPCs *in vitro* suggesting underlying aberrant epigenetic regulation of OPC migration involving the epigenetic regulator, MeCP2. Studies involving MeCP2 over expression in oligodendrocytes showed significant inhibition of the morphological differentiation which further confirms the function of MeCP2 as a regulator of oligodendrocyte differentiation.

Apart from its role in neurodevelopment disorders, MeCP2 has an important role in many cancers such as breast, colorectal, lung, liver, and prostate cancer. MeCP2 role in cancer is related to the epigenetic regulation of cancer-related genes that involve hypermethylation of gene promoters. However, MeCP2 function in glial cell derived cancer is not yet clearly known. In the present study, using C6 glioma as a model system it was clearly demonstrated that MeCP2 suppress glioma malignant phenotypes. MeCP2 inhibits C6 glioma tumorogenic characteristics such as proliferation, migration, invasion, adhesion and decrease the anchorage independent growth and sphere forming ability. MeCP2 is also shown to inhibit the ERK signaling which might be responsible for reduced proliferation, migration and invasion of C6 glioma. ERK signaling has been shown to involve in glioma proliferation, migration and invasion. Further, MeCP2 reduce the tumor behavior of C6 glioma by regulating the expression of GFAP, BDNF and FAK expression. Moreover, the present study also demonstrated that MeCP2 regulates the expression of GFAP and BDNF by directly binding to their promoter regions.

C6 glioma retains characteristic of glial precursor and also expresses some oligodendrocyte and astrocytes genes including PLP, MAG and GFAP. Hence, the present study was undertaken to study the differential MeCP2 regulation of myelin genes expression in oligodendrocytes and C6 glioma. Myelin genes expression were studied in C6 glioma and found that in contrast to oligodendrocytes, MeCP2 positively regulate the myelin genes (MBP, PLP and MAG) expression in C6 glioma. Unlike oligodendrocytes, MeCP2 does not bind to promoter regions of

MBP and PLP genes which suggest that MeCP2 differentially regulates its target genes in different cell types.

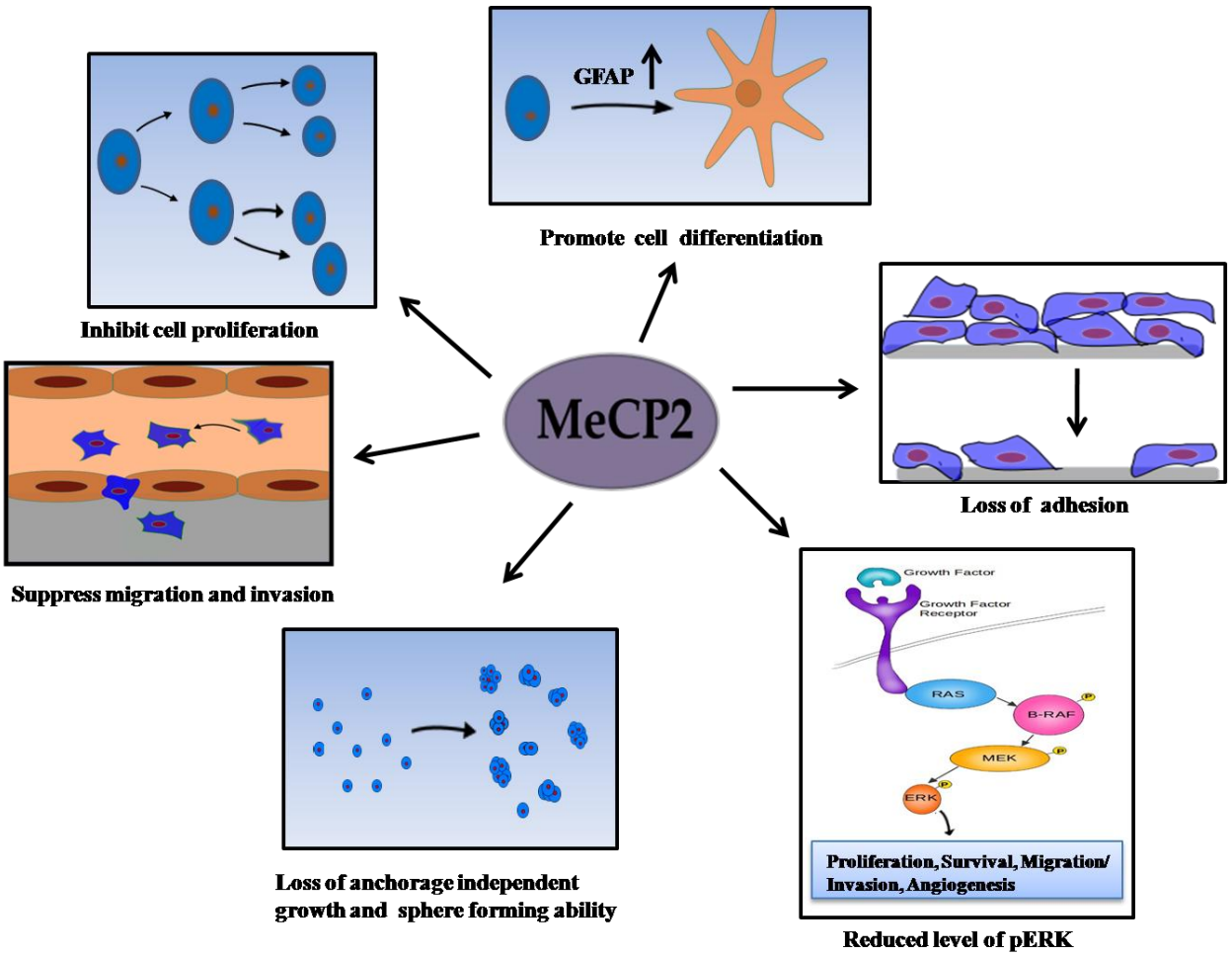

Figure 5.2: MeCP2 inhibits the malignant phenotypes of C6 glioma.

Thus, findings of the present study demonstrated that MeCP2 acts as a negative transcriptional regulator of major myelin proteins required for proper oligodendrocyte differentiation and myelination. Further, MeCP2 regulates the glioma malignant phenotypes which suggest that MeCP2 could be as therapeutic for glioma treatment.