CHAPTER 6

SUMMARY

SUMMARY

Over the last decade, emerging studies have transformed the understanding of the role of astrocytes in the CNS from being submissive supporters of neurons and other glial cells to crucial players in the brain. Recently, the role of astrocytes in myelination has garnered interest and suggested critical functions of astrocytes which directly or indirectly regulate myelination. The current study focused on a global transcriptional regulator, MeCP2, in the regulation of astrocyte mediated myelination. The presence and involvement of MeCP2 in glial cells especially astrocytes has been widely studied with respect to numerous functions such as impaired dendritic arborisation and dysregulation of many of crucial astrocytic genes. However, no information exists on the role of astrocytic MeCP2 in regulation of myelination. The data from the current study is the first preliminary observation which suggests of the involvement of astrocytes and astrocytic MeCP2 in regulating central nervous system myelination.

MeCP2 deficiency in astrocytes was found to regulate myelination promoting and inhibitory factors such as CNTF, LIF, PDGF and CXCL10. These factors have been extensively studied for their crucial roles in myelination. The positive regulation of myelination promoting factors- CNTF and LIF and the negative regulation of myelination inhibiting factors- PDGF and CXCL10 by astrocytic MeCP2 is convincing of its involvement in myelination. Unlike neurons and oligodendrocytes, astrocytes are not directly involved in the cellular milieu of myelination. However, they are producers of various secreted factors that can either promote or impede myelination and also regulate myelin pathology. The astrocyte secretome finds potential avenues as investigative or therapeutic agents for CNS conditions. In the present study, the astrocyte secretome exhibited comparable variation in MeCP2 deficient condition compared to control. Neurotrophin- BDNF, widely studied MeCP2 target gene, was one principle secreted astrocytic factor with considerable modulation in response to MeCP2 deficiency.

The diverse range of factors generated by astrocytes also coordinate complex responses in other cell types such as oligodendrocytes, neurons as well as neighbouring astrocytes that influence myelination collectively. Deficiency of MeCP2 in astrocytes was found to inhibit OPC survival, proliferation and oligodendrocyte differentiation which ultimately hamper myelination. Additionally, astrocytic MeCP2

also influences neuronal survival and disrupts normal neuronal dendritic morphology thus leading to improper myelination.

Involvement of MeCP2 was also evident in the establishment of axo-glial interactions as an initial event of myelination. Astrocytic MeCP2 influences axo-glial interaction molecules present on neurons such as Caspr and Nrg1 while their corresponding oligodendroglial molecules, such as Notch and NF155, were not affected. However, oligodendrocyte MeCP2 modulates the oligodendroglial molecules independently which suggests differential regulation of MeCP2 targets in different cell types. The present study is unique to establish a triple *in-vitro* culture of astrocytes-DRG neurons-oligodendrocytes to study myelination. This triple culture is an attempt to mimic the *in vivo* environment of myelination to its closest possibility. Modulation of astrocytic MeCP2 in these triple cultures leads to the positive regulation of major myelin genes and proteins (MBP and PLP) as well as total myelin protein.

The findings of the current study validated the role of astrocytic MeCP2 in influencing central nervous system myelination by regulating various facets of astrocytes, oligodendrocytes and neuronal cells along with an impact on axo-glial interactions and myelination.

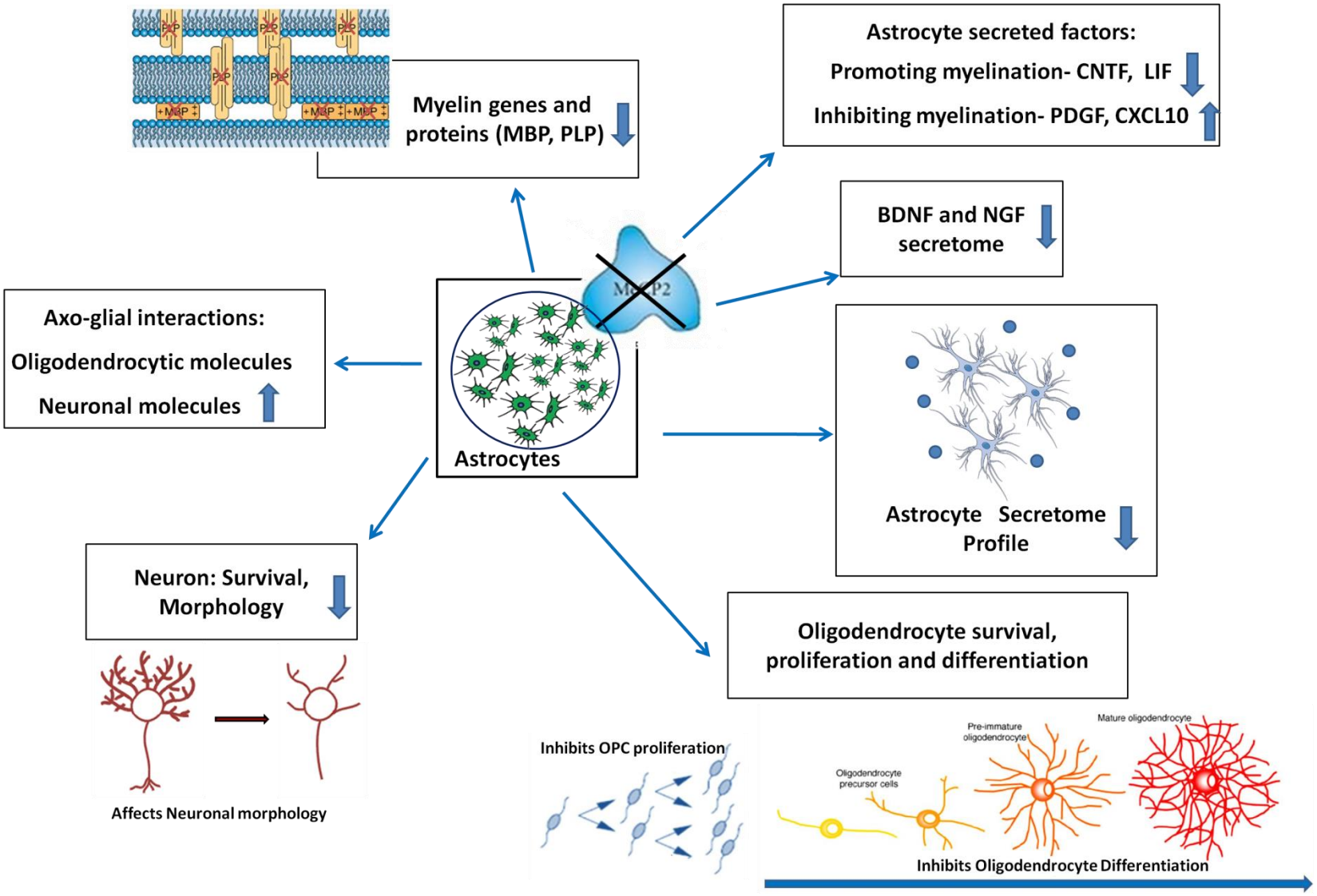

Figure 6.1: Involvement of astrocytic MeCP2 in regulating CNS myelination