Abstract

Epigenetic programming is the process through which an environmental stimulus during development alters the gene expression by changing the epigenetic marks (e.g., DNA methylation, histone modifications, etc.) to produce a persistent phenotypic effect. MeCP2 is a multifaceted protein as it functions as a transcriptional repressor or activator via binding to methylated CpGs in the promoters and nearby regions of target genes. The X chromosome linked MECP2 gene is associated with several neurological disorders, like Rett syndrome etc. MeCP2 undergoes various post-translational modifications (PTMs), such as phosphorylation, ubiquitination, acetylation, and sumoylation. Recent studies have shown that phosphorylation has extremely important effects on the modulation of MeCP2 function. Accumulated evidences suggest that MeCP2 could be phosphorylated at multiple sites, of which the well-documented MeCP2 phosphorylation sites are S421 and S80; phosphorylation of which modulates the transcription in opposite manners leading to gene silencing or activation. However, to date, most studies have reported pMeCP2s exclusively in neurons. The study is mainly focused on the regulation of MeCP2 phosphorylation in glial cells of CNS mainly oligodendrocytes and astrocytes. There is large number of developmental stimuli which affects the overall development of these glial cells in CNS. However, no information exists for these factors regulating MeCP2 phosphorylation in glial cells. The data from the present study is the first report to conclusively demonstrate the involvement of growth factor (BDNF) and ECM (LN) in MeCP2 phosphorylation, which is essential for proper development of the glial cells of CNS. In addition to this, the study reported for the first time that the reactive astrocytes after LPS exposure show the upregulation of MeCP2 phosphorylation thereby affecting its sub-cellular localization. Importantly, the study showed that, although MeCP2 is expressed in all the cells of CNS, it appears that pS421MeCP2 is not expressed in OLGs. This is probably since the phosphorylation of MeCP2 is dependent on both the cell type and the stimuli and thus each cell will not consist of all possible modifications. Moreover, it was found that BDNF increased the pS421MeCP2 expression levels in astrocytes. The results showed that upon BDNF treatment, the pS421MeCP2 was localized into the nuclei from the cytoplasm. Moreover immunocytochemistry results demonstrated the sub-nuclear localization of pS421MeCP2 in the BDNF treated astrocytes and it was shown to be associated with the euchromatin region. By inhibiting

the CamKII signaling, there was a decrease in the level of pS421MeCP2 and the association of pS421MeCP2 with the euchromatin also decreased drastically. MeCP2 not only play a role in neurodevelopmental disorders but it has been a substantial epigenetic regulator in many cancers like prostrate, lung, liver, breast cancers etc. However, there are no reports on MeCP2 phosphorylation in this glial cell derived cancer. In the current work, increased levels of pS80MeCP2 and pS421MeCP2 were observed when C6 glioma cell line was treated with BDNF and this phosphorylation was mediated by TrkB receptor. In conclusion, MeCP2 in glial cells is functionally regulated by stimuli mediated phosphorylation which would allow MeCP2 to bind to distinct sites with an effect on chromatin affinity through sub-cellular localization thereby providing regulatory specificity during CNS myelination.