

Abstract

Mutations in the gene coding for the methyl-CpG binding protein 2 (*MECP2*) cause a severe form of mental retardation known as Rett syndrome. Almost exclusively girls are affected by this disease. The first mutations in the X-chromosomal gene *MECP2* have been described in 1999, but the molecular mechanisms underlying the disorder are still unknown. *MECP2* can act as a transcriptional repressor and only two neuronal target genes (*Bdnf* and *Dlx5*) have been identified so far. While *MECP2* is expressed ubiquitously, the phenotype of the disease is primarily neuronal. This suggests that *MECP2* has an important function in the brain, whereas, in peripheral tissues, loss of function of *MECP2* might be compensated by functionally redundant proteins.

To find proteins that could potentially mediate such a compensation, two strategies were applied. In a first project, a bioinformatics approach was used to find additional polypeptides that contain an methyl-CpG binding domain (MBD), the domain of *MECP2* which binds to methylated CpGs. Six new such proteins could be detected and were studied for their expression and domain structure.

A second project aimed at identifying proteins with an overall amino acid similarity to *MECP2*. Such proteins could point to additional, so far unknown functions of *MECP2*. Two proteins were identified by database screens and their properties are discussed in this thesis. The structure of one of them, the neurofilament NEFH, suggests that *MECP2* has an elongated shape.

To elucidate the target genes of *MECP2* in the brain, chromatin immunoprecipitation (ChIP) was established and combined with a cDNA microarray approach. An animal model for Rett syndrome was used for this analysis. The microarray experiment showed, that *Mecp2*-null animals differentially express several genes that are induced during stress response by glucocorticoids. Increased levels of mRNAs for plasma glucocorticoid-inducible kinase 1 (*Sgk*) and FK506-binding protein 51 (*Fkbp5*) were observed. Immunohistochemistry revealed, that in mouse brains *Mecp2* and *Fkbp5* as well as *Sgk* are expressed in the same cells. These results suggests a modulating function of *MECP2* in gene expression regulation rather than a total repression since the transcriptional repressor *MECP2* and its target genes are expressed in the same cells..

In *Fkbp5*, three MECP2-binding regions could be determined by CHIP. One of the regions is also a target site for the glucocorticoid receptor (GR). Therefore a model can be proposed in which MECP2 and GR compete for a binding site in *Fkbp5* and regulate its transcription. In Rett patients this regulation would be disturbed due to the loss of function of MECP2 leading to a constant overexpression of glucocorticoid pathway downstream targets and potentially to several features of the Rett syndrome phenotype.