ABSTRACT
Epigenetic Regulation Of Neuronal Maturation: The effect of MeCP2 and MicroRNAs on the maturation of hippocampal neurons.

Dendrites and the dendritic spines of neurons play key roles in the connectivity of the brain and have been recognized as the locus of long-term synaptic plasticity, which is correlated with learning and memory. The development of dendrites and spines in the mammalian central nervous system is a complex process that requires specific molecular events over a period of time. It has been shown that specific molecules are needed not only at the spine’s point of contact, but also at a distance, providing signals that initiate a cascade of events leading to synapse formation. The specific molecules that act to signal neuronal differentiation, dendritic morphology, and synaptogenesis are tightly regulated by genetic and epigenetic programs. It has been shown that the dendritic spine structure and distribution are altered in many diseases, including many forms of mental retardation (MR) such as Rett syndrome, and can also be potentiated by neuronal activities and an enriched environment. Because dendritic spine pathologies are found in many types of MR, it has been proposed that an inability to form normal spines leads to the cognitive and motor deficits that are characteristic of MR. Epigenetic mechanisms, including DNA methylation, chromatin remodeling, and the noncoding RNA-mediated process, have profound regulatory roles in mammalian gene expression. My dissertation research focused on two aspects of epigenetic mechanisms, MeCP2-DNA methylation pathway and noncoding microRNAs that regulate the development and maturation of dendrites and spines. It is well known that Rett Syndrome, a severe postnatal childhood neurological disorder is mostly caused by mutations in the MECP2 gene. My studies focused on the role of MeCP2-mediated epigenetic regulation in postnatal brain development in a MeCP2-deficient mouse model. I found that, while MeCP2 was not critical for the production of immature neurons in the dentate gyrus (DG) of the hippocampus, the newly generated neurons exhibited profound deficits in neuronal maturation, including delayed transition into a more mature stage, altered expression of presynaptic proteins, and reduced dendritic spine density. Furthermore, I found that cultured neurons and brains lacking MeCP2 exhibited altered expression of microRNAs. My studies demonstrate that one brain-enriched microRNA, miR-137, has a significant role in regulating neuronal maturation by translational regulation of Mind bomb1. Despite extensive efforts to understand the molecular regulation of dendrite and spine development, epigenetic and non-coding RNA pathways have only recently been considered. In this thesis, I will first summarize the literature on epigenetic mechanisms that regulate the development and maturation of dendrites and spines, and discuss some general methodologies as well as recent technological advances in biology and neurosciences. I will then present my own data to show how epigenetic alterations could result in the morphological and phenotypic abnormalities that are a fundamental characteristic MR, such as Rett syndrome.