PhD in Cellular and Molecular Neuroscience

Early roles played by MeCP2 during neocortex maturation: novel insights in the etiology of Rett Syndrome

Rett syndrome (RTT) is a genetic pediatric neurological disorder representing one of the most common causes of severe mental retardation in girls worldwide. After an initial phase lasting 6 to 18 months during which no apparent signs of the pathology are yet overt, RTT patients present regression of motor and cognitive skills; RTT affected females typically develop autistic features, breathing disturbances, seizures and severe intellectual disability. Roughly 90% of RTT cases are ascribable to mutations affecting MECP2, an X-linked gene that is one of the major actors in epigenetics. MeCP2 binds methylated CpG dinucleotides thereby affecting chromatin structure and transcription; however, so far only a few direct targets of MeCP2 action have been discovered, while the research on RTT has not yet produced solid therapies for a pathology that, currently, hardly has any. This proposal finds its rationale in the preliminary data we gathered suggesting that a delay in the maturation rate of MeCP2 null neurons is evident even at early (or the earliest) stages of development thus leading MeCP2 null neuron to be less able to respond to external stimuli compared to wt neurons. This clearly implies that at least part of the dysfunctions affecting the MeCP2 neuronal network in adulthood can ideally be traced back to early embryonic phases of maturation. The main goal of this project is to verify the existence of a causative link between early embryonic maturation delay and the later development of the neuronal defects that typically arise during postnatal life.

This proposal is divided in two tasks. At first, exploiting morphological, functional and transcriptional approaches, we will produce a detailed analysis of the defects displayed by the MeCP2 null cortex at different stages of maturation. These information will be then used as readouts for the purposes described in the second task. In the second task of this project we will verify whether the impairments displayed by the MeCP2 null animals can be rescued by acting at different time points on the intrinsic responsiveness of MeCP2 null neurons. To produce such rescue, we will reduce the threshold by which null samples (differentiated neurons produced from in vitro cultured neuroprogenitors, primary neuronal cultures produced from embryonic cortexes, ex utero cultivated organotypic cortical slices and postnatal pups) can be intrinsically excited by treating with Ampakines, compounds that are able to enhance neuronal responses mediated by AMPA receptors. The responsiveness to external stimuli is in fact known to be one of the major forces driving differentiation and maturation of any neuronal network. To be noticed, the two tasks are here described in an order only for sake of clarity, as they will be developed simultaneously, so that the entire bulk of data will be produced and analyzed within the time frame of the graduate school program. Besides a detailed histological and transcriptional analysis, both the aims here described will be developed in tight connection with functional Calcium imaging and electrophysiological assessment thanks to our partners at the Humanitas Clinical and Research Center (Rozzano). We believe this approach will shed new light on basic mechanisms of neuronal maturation that have been largely neglected so far in the etiology of RTT syndrome. The comprehension of the roles played by MeCP2 during maturation could open a completely new field for RTT research by highlighting the molecular pathways that are responsible for the RTT like symptoms displayed by mice. Nonetheless, such studies will possibly produce translational insights as well; our data could in fact help developing new therapies modulating upstream maturation mechanisms and unlocking the ability of MeCP2 mutant cells to completely acquire their final, established fate.

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