Prenatal inflammation and altered neurodevelopment: the role of MeCP2

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Infection/inflammation during pregnancy is a frequent occurrence, carrying important risks for the offspring. Neurodevelopmental disorders – and in particular autism – are known to result from inflammatory alterations in the maternal immune system during pregnancy, but information about the molecular processes affected are still lacking. Interestingly, either MeCP2 reductions or increases result in synapse dysfunctions and indeed MeCP2 loss- or gain-of-function leads to severe neurodevelopmental disorders, including autism spectrum disorder, Angelman’s syndrome and learning disabilities (1,2). However, it is still unknown whether non-genetic factors, such as inflammation, impact MeCP2 expression.

By exploiting a genetic mouse model lacking IL-1R8, an IL-1β negative modulator, we recently found that hyperactivation of IL-1β signaling results in the up-regulation of MeCP2, leading to impairment in synaptic transmission and plasticity (3). Furthermore, we have preliminary results indicating that IL-6 produces instead reductions of MeCP2 expression. These data are very relevant, since i) optimal MeCP2 levels are required for a proper synapse function (4); ii) altered dosage of MeCP2 results in various disease phenotypes (5); iii) maternal immune activation (MIA), resulting in cytokine dysregulation, results in delayed GABA-switch and higher susceptibility to seizures (6) and affects the risk and/or severity of a variety of neurodevelopmental disorders (7). Based on these data, my future aims are i) to investigate the processes by which immune activation regulates MeCP2, a key player in brain development, and ii) to modulate the immune response as a possible strategy for normalizing MeCP2 levels in neurodevelopmental diseases.

References:

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