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The role of the methyl-CpG binding protein 2 (MECP2) in shaping vulnerability for psychopathology

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Exposure to trauma is a common experience worldwide, which may lead to multiple adverse consequences for physical and mental health, and is compulsory for the diagnosis of post-traumatic stress disorder (PTSD), a chronic mental disorder characterized by symptoms of persistent anxiety and hypervigilance. Considering the key role played by susceptibility in determining the outcome of traumatic experiences, and the well-documented contribution of epigenetic mechanisms in the establishment of interindividual differences in PTSD risk and resilience, this dissertation aimed at translationally addressing the potential contribution of the X-linked epigenetic regulator methyl-CpG binding protein 2 (MECP2) in shaping vulnerability to develop stress and trauma-related disorders.

With this goal, taking advantage of a transgenic mouse line, we evaluated whether disruptions in MeCP2 functionality may predispose to the onset of PTSD-like symptomatology in the aftermath of a traumatic event. Male mice constitutively expressing a hypofunctional form of MeCP2 protein and exposed to unescapable footshocks, displayed exaggerated fear and increased avoidance of trauma cues, overgeneralization of fear responses and altered circadian rhythms, mimicking the psychopathological symptoms experienced by patients. Also, traumatized mutants displayed peripheral alterations in gene expression mirroring patterns already evidenced in people suffering from PTSD. Interestingly, although mutant females displayed similar disruptions in fear memory compared to males, sex-dependent alterations in stress responsivity were evidenced among mutants, with females releasing lower and males higher levels of glucocorticoids compared to sex-matched wild type (wt) controls. At the brain level, a region- and sex- specific pattern of stress-related alterations in gene expression was found.

We also aimed at confirming that reduced MECP2 functionality was associated with increased stress vulnerability in human cohorts. This issue was addressed in two different studies. The first, including healthy participants, explored the link between blood *MECP2* expression and childhood adversities, and addressed its effect on symptoms of depression and anxiety, which could confer vulnerability to stress-related disorders. The second study focused on the evaluation of blood *MECP2* levels in PTSD patients and healthy traumatized and non-traumatized controls, with or without stress during childhood, and their correlation with the severity of PTSD symptomatology. In the first study we found that decreased *MECP2* expression was indirectly associated with increased depressed mood and trait anxiety in healthy participants, a correlation mediated by childhood stress and moderated by gender. In line with this, in the second study we observed that childhood stress mediated the association between decreased MECP2 expression and increased PTSD symptom severity in traumatized participants, especially among women, further corroborating a role for MECP2 downregulation in promoting trauma vulnerability. Interestingly, men traumatized at adulthood overexpressed MECP2, independently from the severity of childhood stress.

Overall, the present work presents strong evidence for the role of decreased MECP2 functionality in boosting susceptibility to develop PTSD in the aftermath of traumatic experiences, opening to the possibility that MECP2-related epigenetic pathways might be involved in the etiology of the disorder. Importantly, gender emerges as an important modulator of the association between MECP2 and PTSD susceptibility.