Stress, Epigenetic Changes and Vulnerability to Psychiatric Disorders

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Exposure to early life stress (ELS) is an important factor for the vulnerability to psychiatric disorders, including major depression. Among other mechanisms, epigenetic changes, such as DNA methylation and miRNA expression, have emerged as a major mechanism through which adverse life experiences lead to the persistent changes in gene transcription that may sustain adult behavioral abnormalities.

With this respect, we performed DNA methylation analyses in adult rats exposed to stress during gestation (PNS), a model that is associated with persistent behavioral alterations relevant for psychiatric disorders and we performed cross-tissues and cross-species analyses to identify key players for the long-term effects produced by ELS [1, 2, 3]. As an example, using an epigenomic analysis, we found that a large number of genes was differentially methylated in the hippocampus and in the prefrontal cortex of male and female rats exposed to PNS. By focusing on genes that were modulated in the same direction, we identified miR-30a as being less methylated in PNS rats. One of the validated targets for miR30a is the neurotrophin BDNF, whose expression was indeed reduced as a consequence of the prenatal manipulation. Interestingly chronic treatment of PNS rats with lurasidone during adolescence was able to prevent the changes in miR30a and normalized the expression of the neurotrophin. We also performed transcriptomic and miRNomic analyses in the hippocampus of rats exposed to PNS. The mRNA-miRNAs combined analysis allowed the identification of a panel of 528 top-hit genes, which are involved in a number of pathways including Axonal Guidance, Glucocorticoid Receptor Signaling, TGF-beta Signaling, STAT3 Pathway, ILK Signaling and IL-8 signaling. We then overlapped these genes with those that were significantly modulated in the blood of subjects in association with childhood trauma. We found 16 genes modulated in the same direction, with a specific cluster involved in inflammatory processes and glucocorticoid functionality composed by Forkhead box protein O1 (FOXO1), Alpha-2-Macroglobulin (A2M) and Transforming Growth Factor Beta 1 (TGFB1). Interestingly, we were able to validate the role of these genes as potential mediator for the long-term effects of emotional abuse in two different clinical cohorts.

In summary, our experimental approach proved useful to identify genes and pathways that may mediate the long-term effects of ELS exposure. We suggest that epigenetic signatures following ELS exposure may contribute to the identification of systems that play a pivotal role for long-term brain dysfunction associated with mood disorders and may therefore be potential target for pharmacological intervention.

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