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HOT TOPICS

MicroRNAs as promising peripheral sensors of prefrontal cortex developmental trajectory and psychiatric risk

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Individual differences in psychiatric vulnerability in adolescence result from the complex interaction between genetic and environmental factors. In adolescence, prefrontal cortex (PFC) circuits are still undergoing major refinement, remaining quite sensitive to the surge in novel experiences and physiological changes occurring during this age. Identifying adolescent markers of mental illness susceptibility, that could inform about the impact of environmental challenges on PFC maturation, will help tailor preventive and therapeutic programs for each individual. Studies on epigenetic processes implicated in PFC function and development highlight microRNAs as promising predictive biomarkers.

MicroRNAs are small single-stranded noncoding RNAs that regulate gene expression of many messenger RNAs. They are secreted from cells into peripheral fluids, regulating gene expression at far away targets [1]. MicroRNAs do not degrade in heat or after prolonged storage, and are abundant and readily quantified in peripheral fluids, including blood, saliva, and urine. Parallel changes in microRNA levels in brain and blood have been reported, and distinct microRNAs have been shown to be dysregulated in postmortem PFC or plasma of psychiatric patients [2, 3]. We identified the microRNA miR-218 as a potent regulator of genes that are known to control adolescent PFC development and that have been found to be altered in psychiatric disorders of adolescent onset [4]. PFC miR-218 expression is reduced in adult depressed subjects who died by suicide as well as in adult male mice susceptible to chronic stress-induced social avoidance [4]. Downregulation or upregulation of miR-218 in adult PFC neurons leads to corresponding changes in miR-218 expression in blood, indicating that circulating microRNAs could be readouts of epigenetic events in the PFC [5]. Indeed, adult mice susceptible to stress also show reduced miR-218 levels in blood [5] and similar findings have been reported in aging individuals with major depressive disorder [reviewed in refs. 2, 3].

Expression of miR-218 in the mouse PFC increases from early adolescence to adulthood, with the same dynamic pattern observed in blood [6]. Using blood samples from adolescent male mice that were subjected to chronic stress in adulthood, we demonstrated that having elevated "adult-like" expression of circulating miR-218 in adolescence predicts vulnerability to stress-induced social avoidance in adulthood. Mice that had increased miR-218 levels in adolescence show stress-induced downregulation of circulating miR-218 in adulthood. Furthermore, reducing levels of miR-218 in the PFC of adolescent mice promotes resilience to chronic stress later in life [6]. These results, together with the adolescent switch in global microRNA expression occurring in the human PFC [reviewed in ref. 2], suggest that peripheral microRNAs may provide information about PFC developmental trajectories and predict psychiatric vulnerability.

Detecting susceptible youth, particularly now, when abrupt changes to their lifestyle have been imposed by the global pandemic, is urgently needed. A next step in our research is to conduct longitudinal noninvasive high-throughput analysis of microRNA profiles of peripheral fluids derived from cohorts of adolescents with or without a history of early adversity and/or clinical diagnosis of a psychiatric condition. Discovering objective longitudinal markers of psychiatric risk could help guide early diagnosis, treatment, and prognosis.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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