Circuit-wide Transcriptional Profiling Reveals Brain Region-Specific Gene Networks Regulating Depression Susceptibility

Neuron; June 2016

Bagot RC, Cates HM, Purushothaman I, Lorsch ZS, Walker DM, Wang J, Huang X, Schlüter OM, Maze I, Peña CJ, Heller EA, Issler O, Wang M, Song WM, Stein JL, Liu X, Doyle MA, Scobie KN, Sun HS, Neve RL, Geschwind D, Dong Y, Shen L, Zhang B, Nestler EJ.

Objective –Depression is a neurological disorder that is the result of complex interactions between social, psychological and neurological factors. Antidepressants unfortunately lead to remission in only half of the patient population as a result of which depression constitutes a substantial global health burden. Perhaps this is because research done to discover drugs for depression has focused on single genes and on single areas of the brain instead of the interplay between genes and between brain regions.

A recent study sought to change this paradigm by investigating the genetic profile of four areas of the brain that have been implicated in depression - nucleus accumbens, ventral hippocampus, prefrontal cortex and the amygdala in mice. They chose a model of depressive behavior known as chronic social defeat stress (CSDS). In this model, a ten day-long exposure of mice to a stressful experience divides mice into two groups – those that are depression-susceptible and those that are depression-resilient. In the current paper, this CSDS model was used, and comprehensive genomic analysis of the four brain areas were done at three time points to capture a complete picture of changes in the depressed mouse brain. Control mice i.e. those that had never been exposed to CSDS were also used. RNA sequencing was done to investigate genome-wide transcriptional profile.

Results – RNA sequencing was done in brain tissue of mice exposed to CSDS, and distinct differences in transcriptional profiles were found in depression-susceptible vs. depression-resilient mice. A few novel genes like *Sdk1, Dkk1 and Neurod2* that cpnfer susceptibility to depression were identified. Out of these, the *Dkk1* gene was identified in the ventral hippocampus as a depression-susceptible gene. Using viral vectors to overexpress *Dkk1*, the scientists found a large number of other genes were also overexpressed when *Dkk1* was overexpressed. This probably means that *Dkk1* is a 'hub' gene and a possible target for discovery of future antidepressants. Overexpression of *Dkk1* also was associated with an increase in excitability in the ventral hippocampus, pointing towards a potential mechanism of how *Dkk1* might confer a depressive phenotype.

Interpretation – Numerous studies that have investigated transcriptional profiles of genomes in depression have been done; however, they have looked either at single genes or at one structure of the brain. The current study provides insight into multiple genes in four areas of the brain that have been implicated in depression. Moreover, the scientists also did functional studies for genes that hadn't been tested before and that were responsible for depression-susceptible behavior. This massive undertaking gives us new groups of genes/ transcriptional networks to focus on to come up with better therapies for depression.

As the author mention, all experiments in this manuscript were done in male mice. Sex differences in depressive phenotype have been documented; so it would be worthwhile to see how and whether this would differ in female mice.

Link to the paper – **Free access** - no