GENE EXPRESSION CHANGES IN PREFRONTAL CORTEX OF SOCIAL DEFEAT STRESSED MICE REVEAL NEW POTENTIAL DRUG TARGETS FOR TREATMENT OF MOOD DISORDERS

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INTRODUCTION

Despite high prevalence and harm mood disorders remains poorly understood. Animal experimental models of brain disorders represent a valuable tool in refining the existing and developing new, neuropsychiatric theories. Since stress is the most common risk factor contributing to the onset and progression of mood disorders, animal models often use various forms of stressors to induce depression-like behaviors. Social defeat stress model (also known as sensory contact model) can be briefly characterized as repeated exposure to variety of cues from more aggressive mice that evokes depression- and anxiety-like behavior, social avoidance, sleep disturbance, weight loss and anhedonia. Despite being relatively high valid and effective exact pathological mechanism of this model remains poorly understood. Here we apply RNA sequencing to study gene expression changes in prefrontal cortex on different stages of social defeat stress modeling and use topological analyses of resulting molecular pathways to investigate potential drug targets for therapy of mood disorders.

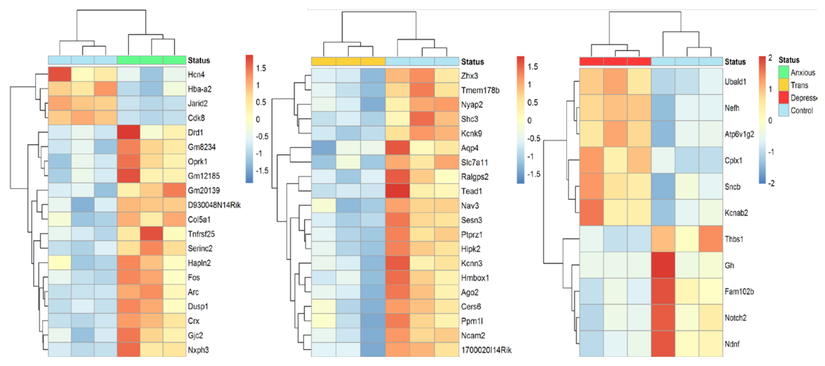

Figure 1
Heatmaps comparing top 20 or all genes found to be differentially expressed in anxious (left), transitional (center) and depressed (right) groups. Data represented as rlog normalized values minus mean of rlog normalized value of gene across all samples and then scaled for each row.

METHODS

Standard sensory contact protocol for social defeat stress modeling on 9 C57BL/6J strain mice was conducted. Briefly, each animal was placed in cage with different dominant aggressive mice equipped with cage lid that was removed for 10 minutes each day. As a result 4 groups (n=3) were used: anxious (defeated for 10 days), transitional (15), depressed (20) and control (was housed alone for 5 days). RNA sequencing was performed on HiSeq1500 with standard protocols for extraction, library preparation, quality check and sequencing. Differential expression (DE) was analyzed by environment R. Protein-protein interaction (PPI) network was constructed with these genes in String data-base and analyzed for nodes degrees in Cytoscape.

RESULTS

Were identified 189 upregulated and 80 downregulated uniqely DE genes in anxious, 2 upregulated and 39 downregulated in transitional and 6 upregulated and 5 downregulated in depressed groups (Figure 1). Top 20 nodes in constructed from DE genes PPI network are Rhou, Fgfr3, Epha, Prkca, Map2k1, Plk3, Hpcal4, Ptprz1, Rab11b, Fn1, Hdac9, Nipbl, Ptpru, Ppm1l, Camk2d, Limk1, Snca, Islr , Notch2 , Trib1 (Figure 2).

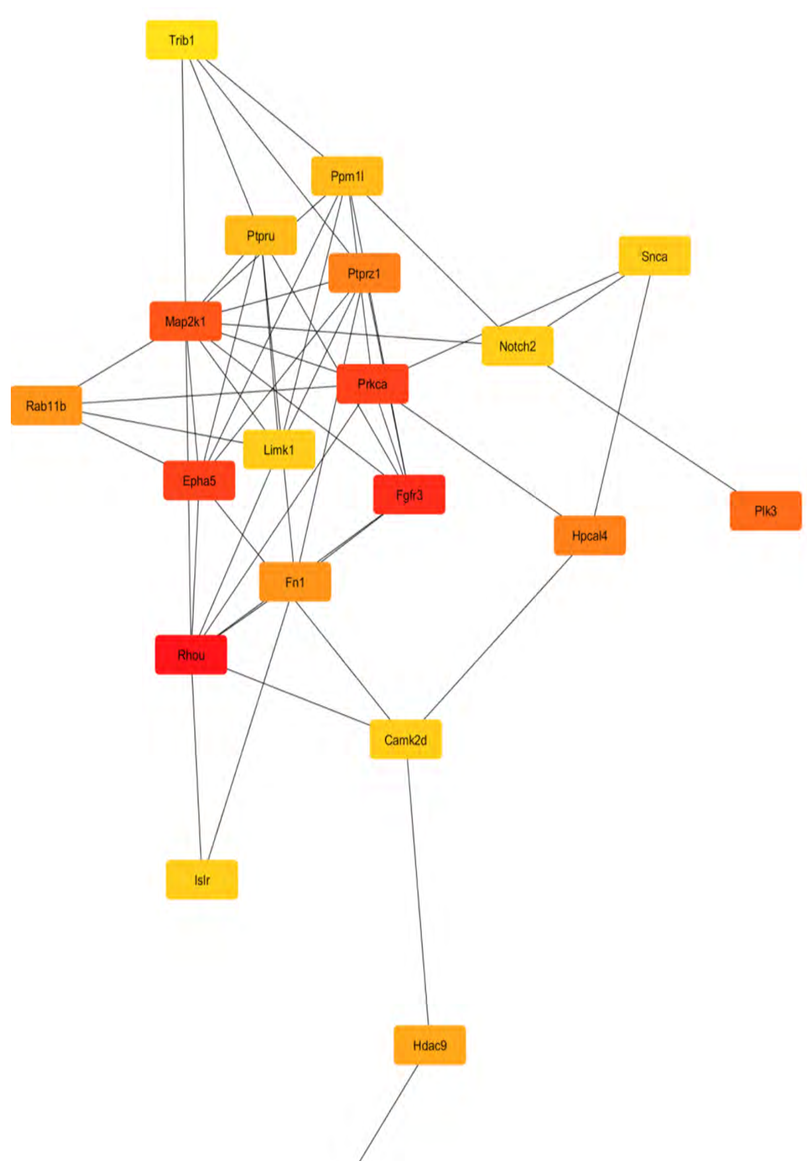

Figure 2
Top 20 nodes based on their degree and their connections to each other based on overall differentially expressed genes in PPI String network. Color of node represent its rank (most red is #1 and most yellow #20).

CONCLUSIONS

study shows that social defeat stressed modeling in mice leads to changes in expression of genes associated with main signaling pathways, neurotransmitter systems, ions homeostasis, astrocytes function, apoptosis, adhesion and immune response and propose potential drug targets for treatment of associated with this model conditions.

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