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Effects of chronic social stress on the expression of carcinogenesis-associated and apoptosis-associated genes in the hypothalamus of mice

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Motivation and Aim: Chronic social stress leads to a mixed anxiety/depression disorder that is accompanied by psychogenic immunodeficiency and—as shown previously- by the stimulation of oncogenesis in mice. Undoubtedly, the hypothalamus is involved in the pathophysiology of psychoemotional disorders and the related immune pathologies and cancers. In this brain region of male mice with severe depressive symptoms, we aimed to identify differentially expressed genes (DEGs) encoding proteins related to mechanisms of carcinogenesis and apoptosis.

Materials and Methods: To induce a mixed anxiety/depression disorder in male mice, the model of chronic social conflict was used, which causes a pronounced depressive state as a result of the chronic social defeat stress under the influence of 20-day agonistic interactions in animals. For comparison, male mice with positive fighting experience in the same model were analyzed. Transcriptomes of the hypothalamus in animals with the alternative social experiences (aggression and defeat) were sequenced at the Genoanalytica (http://genoanalytica.ru/, Moscow, Russia). For the analysis, the genes were selected that participate in the mechanisms underlying apoptosis and carcinogenesis according to databases (http://deathbase.org and https://webs.iiitd.edu.in/raghava/apocand/browse.php).

Results:

The expression of genes *Casp2*, *Foxp2*, *Opa1*, and *Tnfrsf22* changed in the aggressive mice but not in the depressed ones. In the depressed mice, genes *Arc*, *Bax*, *Nosip*, *Alkbh7*, *Mapk3*, and *Foxp2* showed higher expression, whereas genes *Casp2*, *Casp8*, *Stk17b*, *Anxa1*, and *Pycard* manifested lower expression compared to the aggressive animals.

Furthermore, there were 26 genes (*Aifm1*, *Ak2*, *Akt2*, *Anxa1*, *Bcl2l13*, *Bnip3*, *Casp8*, *Ccar1*, *Cldn5*, *Cldn12*, *Cyld*, *Dpf2*, *Fastkd2*, *Mcl1*, *Nol3*, *Nol4*, *Nomo1*, *Nos1*, *Nos3*, *Pdcd5*, *Ppargc1b*, *Pycard*, *Sfrp1*, *Siva1*, *Stk17b*, and *Tnfrsf8*) whose expression changed only in the depressed mice. In the correlation analysis expression of eight genes (*Akt1*, *Bag6*, *Foxp4*, *Mapk3*, *Mapk8*, *Nol3*, *Pdcd10*, and *Xiap*) most strongly correlated with the expression of other genes in the mouse groups (control, aggressive, and depressed animals), (R > 0.950, Fig. 1).

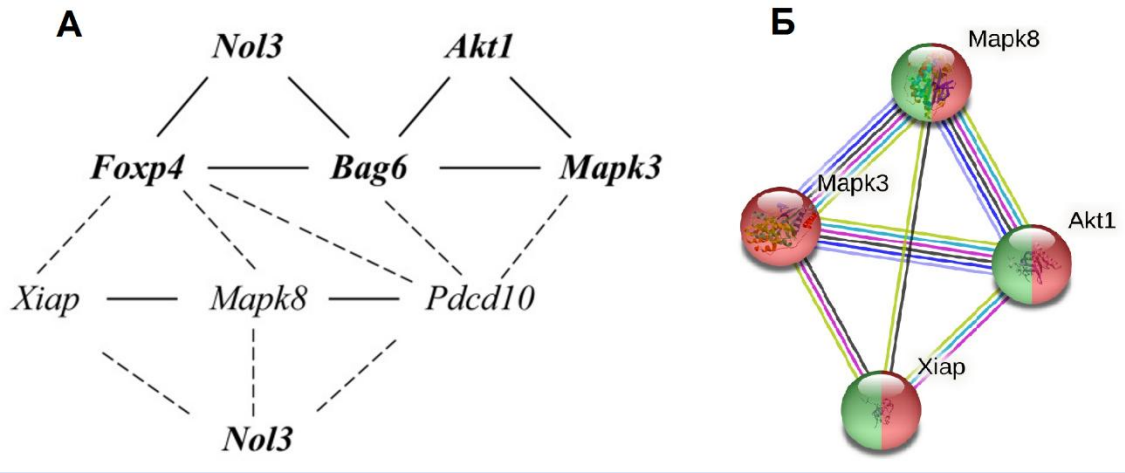

Figure 1А. Correlation relationships of the functional activity of the DEG. "---": negative correlation; "—": positive correlation; the regular font indicates decreased expression, and the bold font denotes enhanced expression. *Nol3* is shown twice to visualize both positive and negative correlations.
1Б. The largest number of relationships, according to the STRING database (string-db.org), was found for the genes *Akt1*, *Mapk3*, *Mapk8*, *Xiap*. Gene annotation color coding (GO): red - apoptotic process (GO:0006915; FDR < 1.06e-05), green - negative regulation of apoptotic process (GO:0043066; FDR < 0.00025).

Conclusion:

In male mice with alternative social experiences (aggression and defeats), there are similar changes in the hypothalamic mRNA expression of oncogenesis and apoptosis genes. It is possible the similar changes is a consequence of long-term stress exposure.

Probably, it is genes *Akt1*, *Bag6*, *Foxp4*, *Mapk3*, *Mapk8*, *Nol3*, *Pdcd10*, and *Xiap* that mostly ensure the coordination of neurotranscriptomic changes in the hypothalamus, and the leading role apparently belongs to *Mapk3*, the expression of which differs between the mice with the opposite types of social experience. Further research on the participation of these genes and their products in the consequences of chronic social stress may be useful for the development of pharmacological therapies of psychosomatic pathologies.

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