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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 [1] that is accompanied by psychogenic immunodeficiency and – as shown previously [2] – by the stimulation of oncogenic processes 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 [1] was used, which causes a pronounced depressive state as a result of the chronic social defeat stress in animals under the influence of 20-day agonistic interactions. For comparison, male mice with positive fighting experience in the same model were analyzed. Hypothalamus transcriptomes of the animals with the opposite social experiences (aggression and defeat) were sequenced at the multi-access center 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: In the comparison of the aggressive with depressed animals, analysis of the RNA-Seq data revealed similar expression changes for numerous DEGs (related to carcinogenesis and apoptosis) as compared with the control group (no agonistic interactions). Almost all genes whose expression changed under the influence of positive fighting experience showed expression changes in the depressed mice (under the influence of chronic social stress). The number of DEGs and the magnitude of expression changes were lower in the aggressive than in the depressed mice. For instance, in the aggressive mice, there were 40 DEGs; among them, 27 genes (68 %) were upregulated and 13 genes (32 %) downregulated. In the depressed animals, there were 62 DEGs, of which 39 genes (63 %) were upregulated and 23 genes (37 %) downregulated.
The expression of genes *Casp2*, *Foxp2*, *Opa1*, and *Tnfrsf22* changed in the aggressive mice but not in the depressed ones (encoded proteins are Caspase2, Forkhead Box p2, Mitochondrial Dynamin-like GTPase Tumor Necrosis Factor Receptor Superfamily Member 22 respectively). Compared to the aggressive animals, in the depressed mice, genes *Arc*, *Bax*, and *Nosip* (coding for regulatory molecules), *Alkbh7* and *Mapk3* (encoding protein enzymes), and *Foxp2* (coding for a transcription factor) showed higher expression, whereas genes *Casp2*, *Casp8*, and *Stk17b* (involved in the regulation of

apoptotic processes) and *Anxa1* and *Pycard* (encoding regulatory proteins) manifested lower expression.

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 a correlation analysis of gene expression in the mouse groups (control, aggressive, and depressed animals), expression of eight genes (*Akt1*, *Bag6*, *Foxp4*, *Mapk3*, *Mapk8*, *Nol3*, *Pdcd10*, and *Xiap*) most strongly correlated with the expression of other genes (R > 0.950, Fig. 1).

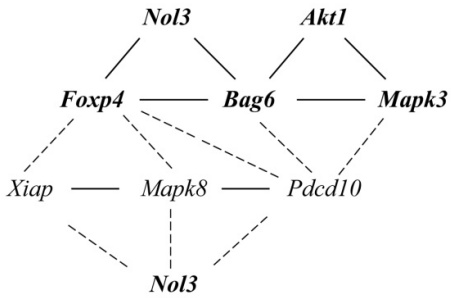

Fig. 1. Correlations of functional activity among the genes contributing to the correlation among carcinogenic and apoptotic processes. "---": negative correlation; "—": positive correlation; the regular font indicates decreased expression, and the bold font denotes enhanced expression. *Nol3* is shown twice to visualize both positive and negative correlations

Conclusion: In male mice with opposite social experiences (aggression and defeats), there are similar changes in the hypothalamic mRNA expression of oncogenesis and apoptosis genes. It is possible that this pattern is a consequence of long-term stress exposure, albeit differing between the defeated and aggressive males. As demonstrated earlier [1, 2], in aggressive animals, subsequent metastasis induced by tumor cell injection is significantly less pronounced than metastasis in depressed animals. Therefore, it is likely that the genes – whose expression stayed unchanged in the aggressive males under the influence of the agonistic interactions – encode hypothalamic proteins that serve as tumor suppressors. 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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