Network analysis of hippocampal tissue proteomic data suggesting roles for CDC37 in long-term memory formation

Guilherme de Araujo Juvenal[1], Henning Ulrich[1]

[1.] USP, Universidade de São Paulo, R. da Reitoria, 374 - Butantã, São Paulo - SP, 05508-220;

Human memory is characterized as a higher cognitive process responsible for classifying, encoding, storing, and retrieving information. Protein synthesis in the hippocampus and the dynamic interaction between them are fundamental for forming long-term memory (LTM). In this work, proteomic data were used to construct and analyze protein interaction networks to select targets and mechanisms fundamental to LTM. Six proteomic datasets of hippocampal tissue from organisms with some type of impairment (MI) or focus (HM) on the memory formation process were used. Networks were constructed, and the interactions were weighted with the quantification of proteins. The sum of closeness and betweenness (*wSI*) was calculated for each protein in the network. The datasets within the same class are similar to each other and dissimilar when compared between classes. This indicates that the modeling distinguishes the two systems. Using the average wSI fold change (FC), the p-value, and outlier identification methodologies as guides, 32 proteins with high variability between MI and HM (target proteins) were selected. These proteins were subjected to Reactome and Gene Ontology, and their pathways and cellular components (CC) were enriched. Six of the nine pathways with the lowest fold change (FC) (-0.76) are related to the neurotransmitter release cycle. On the other hand, the pathway with the highest increase in *wSI* in MI was the caspase-mediated cleavage of cytoskeletal proteins. Eighty percent of the enriched CCs with a negative FC refer to the synaptic region. This shows that the proteins with significant variations are focused on a region highly related to LTM. For each selected target protein, perturbation analysis was performed by deletion of interactors or protein interactions within the networks. Four perturbations were significant regarding the progression of *wSI* in target proteins towards MI and five regarding the progression towards HM. The cell division cycle protein 37 (CDC37) is present in three of the four perturbations that possibly cause memory impairment. CDC37 is a co-chaperone that recruits proteins complexing with the heat shock protein 90 (HSP90). We investigated whether the HSP90/CDC37 interaction and subsequent decoupling of the complex between CDC37 and the target proteins STX1A, THAP7, or LRRK2 compromise memory. Disruption of the HSP90/CDC37 complex by celastrol and the specific inhibition of CDC37 activation by 4,5,6,7-tetrabromobenzotriazole (TBB) were performed to evaluate our hypothesis. The HT-22 mouse hippocampal cell line was differentiated along 48 h with NeuroBasal medium containing 1% L-Glutamine, 1% penicillin-streptomycin, and 1x N2 supplement. Treatment of differentiated cells with celastrol resulted in decreased expression of CDC37 and LRRK2, while TBB treatment led to increased LRRK2 and THAP7 expression. Additionally, the effects of these treatments were studied in the SAMP8 mouse model of premature aging and dementia. Animals with 60 and 90 days of age were subjected to the passive avoidance test and contextual fear conditioning. A memory improvement was observed in animals treated with celastrol. The results indicate that the interaction between CDC37 and its interacting proteins is important for LTM, which may be used to mitigate cognitive impairment in neurodegenerative conditions.

Agradecimentos: Grants and fellowships by FAPESP, CAPES, and CNPq.