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CELL SIGNALING 5

(1503) A NOVEL LINK BETWEEN CELLULAR STRESS AND NEURODEGENERATION

Marcelo Pérez-Pepe, Leticia Inés Larotonda, Pablo La Spina, Maximiliano J Katz, Ana Fernández-Álvarez, Pablo Wappner, Graciela Lidia Boccaccio
Fundación Instituto Leloir

Cellular stress is a common feature in diverse pathologies, including cancer and neurodegeneration. Several stress factors, including oxidants and unfolded proteins trigger a global translational shut down, while the translation of protective proteins is facilitated. Quite recently, independent work from several labs including ours indicates that mRNAs that aren't translated during the stress response form large cytoplasmic aggregates termed Stress Granules (SGs). SG formation is conserved in mammalian, insects, yeasts, trypanosomes and plants. SGs are transient and highly dynamic and their contribution to the stress-induced translational reprogramming or to cell survival remains unknown. Understanding SG composition and dynamics will help to unveil their regulation and relevance.

To identify the signaling pathways that regulate SG formation and dissolution we performed a loss-of-function screen in Drosophila cells. We developed BUHO, a MATLAB script for image analysis and we identified 21 positive and 16 negative modulators of SG dynamics (Z-Score > 2). We decided to focus on Leucine Rich Repeat Kinase (dLRRK), given that mutations in the human homolog hLRRK2 are causative of Parkinson disease, which has not been linked to SG formation previously. We found that the knock down of dLRRK or hLRRK2 enhances SG formation. Experiments in human cell lines and fly brains indicate that LRRK dysfunction leads to the accumulation of ubiquitinated protein and provokes proteotoxic stress ($p<0.01$, two-way ANOVA). This work provides a novel link between the stress response regulation and Parkinson disease.

Keywords: stress granules, proteasome, proteotoxic stress, neurodegeneration, high-throughput image analysis

(605) PHOSPHOLIPASE D SIGNALING MODULATES THE INFLAMMATORY RESPONSE DURING 6-OH DOPAMINE (6-OHDA)-INDUCED NEUROTOXICITY

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Parkinson's disease (PD) is the second most common neurodegenerative disorder related with aging. The death of dopaminergic neurons triggered by oxidative stress and mitochondrial dysfunction is one pathognomonic characteristic of PD patients.

Neuronal exposure to 6-OH dopamine (6-OHDA), a hydroxylated analogue of dopamine, constitutes a very useful strategy for studying the molecular events associated with neuronal death in PD. Our aim in this study was to characterize the role of phospholipase D (PLD) signaling during 6-OHDA-induced neurotoxicity. The exposure to 6-OHDA (50 and 75 μM) induced an increase in reactive oxygen species ($p<0.05$) and lactate dehydrogenase release ($p<0.05$) along with a decrease in mitochondrial viability ($p< 0.001$) in human neuroblastoma IMR-32 cells. We also observed by immunocytochemistry ($p<0.05$) and subcellular fractionation followed by Western blot ($p<0.01$) the nuclear translocation of NF-κB p65 subunit ($p<0.01$) in the presence of 6-OHDA (50 μM). NF-κB nuclear localization was also accompanied by an increase of IkB phosphorylation ($p<0.05$) as well as COX-2 mRNA levels (determined by RT-qPCR, $p<0.001$). On the other hand, pharmacological inhibition of PLD1 (EVJ, 5μM) and PLD2 (APV, 5 μM) was able to prevent the decrease in cell viability triggered by 6-OHDA ($p < 0.01$; $p<0.001$). In line with this, pharmacological inhibition of PLD1 with EVJ inhibited NF-κB p65 subunit nuclear translocation ($p < 0.001$).

Our results indicate that oxidative stress induced by 6-OHDA triggers an inflammatory response that involves NF-κB activation and COX-2 upregulation. Moreover, we also demonstrate here that phosphatidic acid signaling elicited by PLD modulates the inflammatory response associated with neuronal injury.

Keywords: neurotoxicity, phosphatidic acid, oxidative stress, inflammation, 6-OHDA

(1337) MAPK/JNK PATHWAYS AND THE MOLECULAR CHAPERONE HSP90 ARE INVOLVED IN IMMUNOPHILIN-DEPENDENT NEURODIFFERENTIATION

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In nervous cells, cellular differentiation occurs through various eliciting agents such as retinoic acid. Our laboratory has previously demonstrated that the immunophilin-ligand FK506 is a good neurotrophic factor. In this study, it was evaluated the possible signaling cascade involved in such process. N2a mouse neuroblastoma cells were stimulated with 1 μM FK506 or 1 μM retinoic acid (for comparative purposes). Using neurite length as a differentiation parameter, FK506 showed as a stronger neurodifferentiation inducer. Then, cells were treated with different inhibitors. It was found that after inhibiting ERK1/2 activation (MAPK pathway) with the MEK inhibitor PD98059, cells showed shorter neurites, suggesting that this pathway is involved in FK506 action. JNK pathway was also involved since the inhibitor SP600125 exhibited similar inhibitory action as the MEK1 inhibitor. Nonetheless, SP600125 also showed an increasing number of neurites per cell. In previous works of our laboratory, where the role of molecular chaperones was analyzed, it was suggested the involvement of Hsp90 ATPase activity in neuronal differentiation, whereas other work in the literature reported inhibitory action. Due to this discrepancy, the requirement of Hsp90 biological activity for the neurodifferentiation process was tested using radicicol, a known Hsp90 ATPase activity inhibitor. Cells showed even longer neurites than those treated with FK506, and also showed more varicosities (usually seen in mature neurons). Taking together, these observations suggest that the MAPK and JNK pathways mediate FK506-dependent differentiation, and that the inhibition of Hsp90 activity is also a positive regulatory mechanism.

Keywords: pathway signaling; neuronal differentiation; FK506; hsp90

(394) EXPLORING CRHR2α SIGNALING AND TRAFFICKING IN A HIPPOCAMPAL CELLULAR CONTEXT

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The corticotropin-releasing hormone (CRH) system orchestrates the response and adaptation to stress, acting on the hypothalamic-pituitary-adrenal axis and in different brain regions. A large body of evidence points to dysregulation of CRH system signaling as causally linked to anxiety and depressive disorders. There are two different G-protein-coupled receptors (GPCRs), CRHR1 and CRHR2, encoded by different genes which display different localization and ligand preferences. We are particularly interested in the alpha splicing isoform (CRHR2α) given that it is the most important in the brain. CRHR2α has a pseudo signal peptide which gives this receptor specific trafficking and signaling characteristics. We are exploring the signaling pathways activated by CRHRs in order to identify mechanisms involved in CRH and its related peptides action in the brain. Given that previous results showed specific CRH actions *in vivo* in particular limbic structures such as hippocampus, we perform our studies in HT22 cells, a mouse hippocampal neuronal cell line widely used as a neuronal model. We generated stable clones expressing CRHR1 and CRHR2α in HT22 cells to explore the mechanisms involved in the signaling cascade and trafficking of each receptor. We used CRH and UCNs as ligands for each receptor to assess whether different signaling pathways are activated depending