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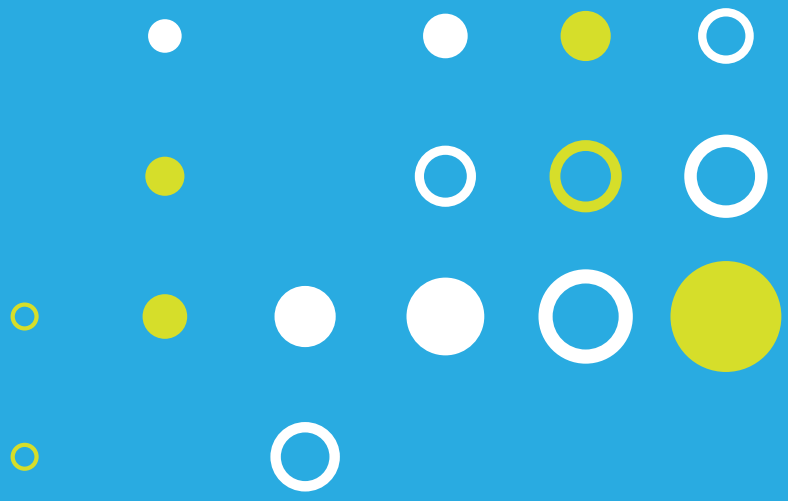

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CB-P09.

CORTICOSTERONE HALTS DIFFERENTIATION OF A NEURONAL CELL LINE VIA ACETYLCHOLINE RECEPTOR MODULATION

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In previous work we determined that prenatal stress affects the expression of α7 nicotinic acetylcholine receptor (α7-AChR) in the frontal cortex of adult rat offspring. The aim of the present study was to investigate whether corticosterone (CORT) affects the biology of AChRs. A neuronal cell line (CNh) derived from cerebral cortex and exhibiting a cholinergic phenotype was treated with CORT (1μM). Whole-cell voltage-clamp recordings showed functional AChR expression at the plasma membrane. Upon treatment with CORT, CNh cells expressed lower levels of α7-AChR (~60% of that in control cells). As a control, α4-AChR was found not to be affected. Morphometric analyses showed that CORT delayed the acquisition of the mature CNh cell phenotype. After 48 h in differentiation medium, cell cycle analysis using flow cytometry showed that control CNh cells were arrested in the G0/G1 phase (~65-70%), whereas cells grown in the presence of CORT remained undifferentiated (G0/G1<60%). Nicotine treatment affected the differentiation of CNh cells and exerted a synergistic effect together with CORT (G0/G1~40%, G2/M~55-60%). Transfection of CNh cells with GFP-tagged α7-AChR abolished the alterations in the cell cycle in CORT-treated cells. Thus, α7-AChR could act as a modulator of the differentiation of CNh cells and CORT, through this receptor, could impair the acquisition of a mature phenotype.

CB-P10.

MOLECULAR MOTORS AND THEIR ADAPTORS GOVERN STRESS GRANULE DYNAMICS AND COMPOSITION

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Stress granules (SGs) are discrete cytoplasmic ribonucleoparticles (RNPs) that store silenced mRNA and assemble transiently in response to cellular stress. SGs are highly dynamic, with mRNA and protein components shuttling in and out by mechanisms that involve mainly microtubule-based transport. Studies from our lab have shown that the molecular motors cytoplasmic dynein and kinesin-1 mediate SGs assembly and disassembly, respectively. However, the selective transport of target mRNA molecules and their associated proteins (RBPs) remains elusive. We speculated that molecular motor's adaptor proteins are responsible for such selection. Using Drosophila S2 cells together with RNAi technology and high-resolution confocal microscopy we found that Egalitarian (egl), but not Lisencephaly-1 (Lis1), two dynein adaptor proteins, are required for assembly of SGs. Conversely, Barentsz (Btz) and zipcode-binding protein (ZBP), adaptors of kinesin-1 are necessary for the timely dissolution of SGs. In addition, we observed that Fragile-X mental retardation protein (dFMRP) and Staufen-1, essential components of SGs are delivered by different adaptor proteins. Our data suggest that cargo-specific recruitment of adaptor proteins during SG formation is a key mechanism to maintain specificity in translation regulation during cellular stress.

CB-P11.

TYPICAL 2-CYS PEROXIREDOXINS REGULATE STRESS GRANULES FORMATION

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Stress granules (SGs) are cytoplasmic accretions that form transiently in all cell types undergoing acute stress. SGs contain mRNAs trapped in abortive translation initiation complexes and RNA-binding proteins involved in reprogramming mRNA translation and decay, and are linked to pathogenic protein aggregates (Thomas *et al*., Cell Sig 2011). SG assembly and disassembly depends on: I) destabilization of polysomes (Thomas *et al*., MBoC 2005, JCS 2009). II) Retrograde transport by dynein and bicaudal (Loschi *et al*., JCS 2009, III)Aggregation through specific proteins, IV) Disolution and dispersion mediated by stress-induced chaperones and kinesin (Loschi *et al*., JCS 2009; Thomas *et al*., CS 2011).

In a high-throughput RNAi-screen in Drosophila S2R+ cells we identified 32 positive regulators and 15 inhibitors of SG formation (Perez-Pepe *et al,* PLoS ONE 2012). In addition, we investigated the role of the typical 2-Cys Peroxiredoxins (2C-Prx), which are peroxidases with stress-regulated chaperone and kinase activities. In addition, 2C-Prxs bind RNA and associate to ribosomes under normal conditions. We find that 2C-Prxs facilitate SG formation upon oxidative stress induction. Both reduced and overoxidized Prxs are excluded from SGs. Collectively, these results suggest that Prx peroxidase or chaperone activities are involved in SG regulation.

CB-P12.

c-FOS-ACTIVATED SYNTHESIS OF NUCLEAR PTDINS(4,5)P_2 PROMOTES GLOBAL TRANSCRIPTIONAL CHANGES

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In addition to the canonical activity of c-Fos as a transcription factor, we previously showed that cytoplasmic c-Fos activates phospholipid synthesis by an AP-1independent mechanism. For this, c-Fos associates with particular enzymes of the pathway of synthesis of lipids at the endoplasmic reticulum. Since lipid synthesis has been shown to occur in the nucleus, and different phospholipids have been assigned transcription regulatory functions, herein we examine if c-Fos acts as a regulator of phospholipid synthesis also in the nucleus. We also examine if c-Fos is able to modulate transcription through its phospholipid synthesis activator capacity.

In vitro and *in culture* studies showed nuclear-localized c-Fos associated with and activating Phosphatidyl Inositol-4-phosphate 5 Kinase, but not Type III β Phosphatidyl Inositol 4 Kinase, thus promoting Phosphatidyl Inositol-4,5-bisphosphate [PtdIns(4,5)P_2] formation. c-Fos promoted increased PtdIns(4,5)P_2 formation promotes AP-1-independent transcriptional changes.

The regulatory transcriptional functions of c-Fos can now be extended to its capacity to activate phospholipid synthesis. We propose c-Fos as a key regulator of nuclear polyphosphoinositides synthesis in response to growth signals and hypothesize that both c-Fos-AP-1 independent and c-Fos-AP-1 dependent mechanisms will work coordinately when a cell re-enters the cell cycle.