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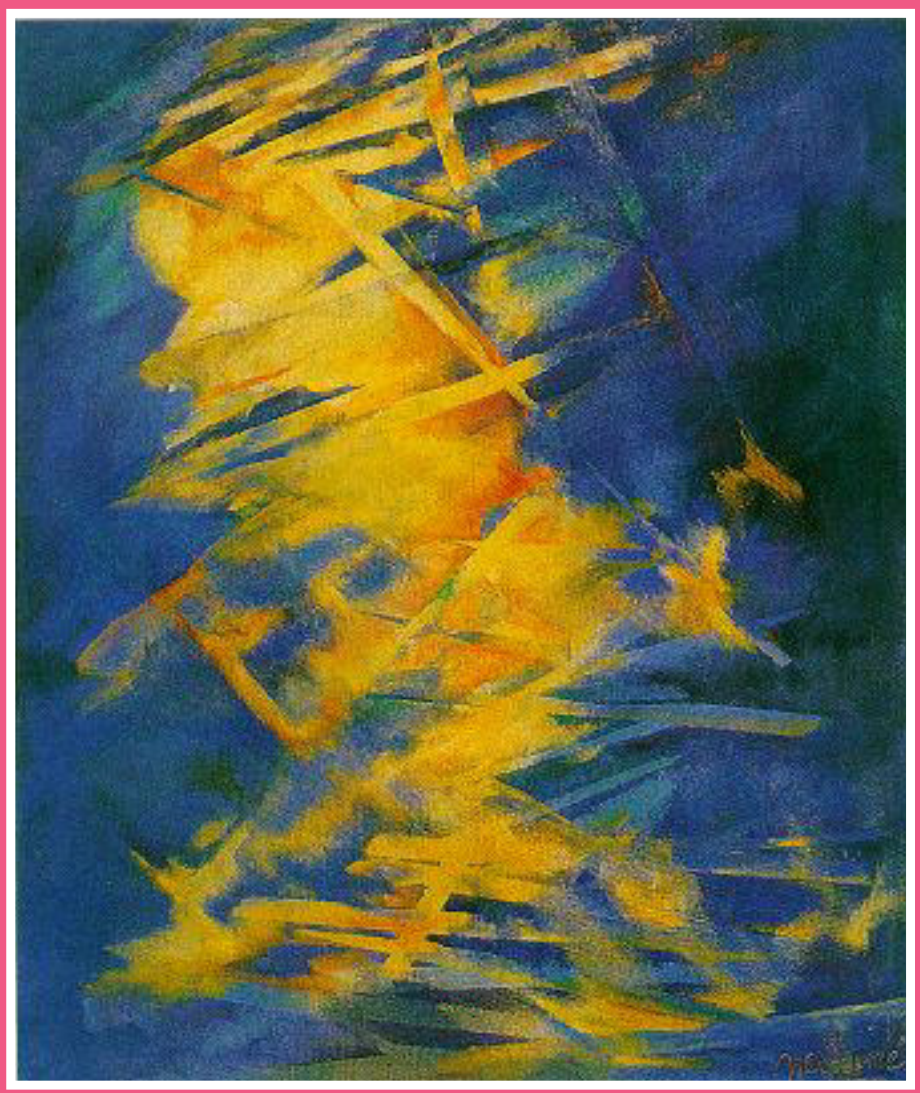

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sana J. Pasquaré
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Lipids in nuclei are membrane components as well as signaling molecules with a potential role in regulating gene transcription. Former studies from our lab demonstrated an active nuclear glycerolipid metabolism in the central nervous system. We detected diacylglycerol lipase, monoacylglycerol lipase, and lysophosphate phosphatase enzymatic activities, which are responsible for maintaining the levels of endocannabinoid 2-arachidonoyl-glycerol (2-AG), a bioactive lipid mediator. The endocannabinoid system is a cellular signaling mechanism with a protective role in many pathophysiological processes, especially in the nervous system. 2-AG activates CB1 and CB2 GPCR receptors and triggers different signaling cascades, modulating intracellular Ca^{2+} levels, ERK1/2 phosphorylation, and other second messengers. Different studies have reported that CB1 is expressed not only in plasma membrane but also in intracellular compartments where they also seem to be functional. Therefore, the aim of this work was to study CB1 expression and function in isolated nuclei from rat cerebral cortex (CC). To this end, CC from Wistar rats were dissected, homogenized and highly purified nuclei (CCN) were isolated on a sucrose-density ultracentrifugation. CB1 protein expression was observed in CCN as well as in isolated cerebellum nuclei by Western Blot, which was confirmed by immunocytochemistry. In order to evaluate if CB1 is functional, CCN were incubated at 37 °C with a CB1 agonist (WIN 55-212-2) and ERK1/2 and Akt signaling cascades were studied by Western Blot. Interestingly, it was observed that ERK1/2 phosphorylation increased in nuclei treated with WIN 5 μM for 30 min with respect to controls ($p<0.01$) while no changes were seen in Akt phosphorylation. Taken together, these results demonstrate that CB1 has also a nuclear localization in the cerebral cortex where it could have a potential role in chromatin regulation and gene expression.

Keywords: CB1, nuclei, cerebral cortex

(1487) INSULIN SIGNALING EFFECTS ON 2-ARACHIDONOYLGLYCEROL HYDROLYSIS IN SYNAPTIC TERMINALS EXPOSED TO AMYLOID BETA OLIGOMERS

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2-arachidonoylglycerol (2-AG) behaves as a neuroprotective agent in Alzheimer's disease (AD). Aβ oligomers (OAβ) are responsible for the synaptic dysfunction observed in AD and were shown to disrupt the synaptosomal membrane and to diminish 2-AG availability. Insulin (Ins) is involved in synaptic plasticity and its signaling was shown to be downregulated in AD. OAβ can bind to insulin receptor (IR) and can, therefore, be internalized into neurons, while Ins prevents this binding and thus its neurotoxicity. Here, we aimed to study Ins preincubation effects on 2-AG hydrolysis in cerebral cortex synaptosomes (Syn) exposed to OAβ. To this end, Syn were isolated by differential centrifugation, purified in ficoll gradients, and preincubated with 10 μM LY294002 (phosphatidylinositol-3-kinase -PI3K- inhibitor) or 100 μM genistein (tyrosine kinase -TK- Inhibitor) for 10 min, and subsequently incubated with 0.2 mM vanadate (protein-tyrosine phosphatase inhibitor), 100 nM Ins, or 0.2 mM vanadate plus 100 nM Ins, for 30 min. Syn were then incubated for 10 min with or without 0.1 μM OAβ, and for 20 min with [^{3}H]monoacylglycerol, to assay 2-AG hydrolysis. It was observed that Ins and vanadate -either separately or coincubated- decreased 2-AG hydrolysis ($p<0.01$), and that their effect was not seen if Syn were preincubated with LY ($p>0.05$). On the other hand, in the presence of OAβ, while Ins and vanadate failed to alter 2-AG hydrolysis ($p>0.05$), LY increased this activity ($p<0.001$). However, the presence of Ins plus vanadate after incubation with LY could restore the activity ($p<0.001$) to basal levels in Syn treated with OAβ. Additionally, the presence of genistein previous to OAβ did not change the activity ($p>0.05$). Our results show a regulation of 2-AG hydrolysis by Ins, possibly decreasing its availability via IR and involving PI3K pathway, which is abolished by OAβ. The effect of OAβ appears to be independent of TK receptors and to involve PI3K activity.

Keywords: Insulin, 2-arachidonoylglycerol, Synaptic terminals, Amyloid β oligomers

ONCOLOGY-ONCOIMMUNOLOGY 9

(120) **ABERRANT MIRNAS EXPRESSION PROFILE INDUCED BY METABOLIC SYNDROME IN THE MAMMARY GLAND MIGHT BE CRITICAL FOR BREAST CARCINOGENESIS.**

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Abstract: Breast cancer (BrCa) is the most common malignant neoplasm and the leading cause of cancer female death in the world, excluding skin cancers. Metabolic Syndrome (MeS) is a risk factor for BrCa that and increase its aggressiveness and metastasis. Recently, we generated a MeS experimental model by chronically feeding mice with a high fat diet which induced alterations in the mammary glands such as an increase of postnatal development and prominent duct patterns. These ducts showed high expression of CtBP1, a tumor suppressor gene that is activated by low NAD+/NADH ratio. Moreover, we found that CtBP1 and MeS increased breast tumor growth and progression modulating the expression of 42 miRNAs involved in cell proliferation and tumor progression. The aim of this work was to identify the miRNA expression profile induced by MeS in normal mammary glands.

We selected a panel of miRNAs obtained from the miRNA microarray analysis to determine expression levels in samples of mammary tissue from mice with MeS or control using RT-qPCR stem loop metodology: miR-378a-3p, miR-146a-5p, miR-223-3p, miR-381-5p, miR-433-3p, miR-194-1-5p.We found that MeS significantly repressed the expression of miR-194-1-5p while induced miR-433-3p in mammary tissue. Using the bioinformatics tool ChemiRs, that integrates the information of ten miRNAs databases, we analyzed the molecular pathways modulated by these miRNAs. We found that miR-194-1-5p and miR-433-3p are involved in several molecular pathways including cancer, metabolism, developmental biology, adherent junction and apoptosis. Finally, evaluating microarray datasets from cBioPortal, we demonstrated that miR-194-1-5p presented DNA amplification in 20 % of BrCa patients.

Altogether, these results suggest that MeS induces an aberrant miRNA expression profile that could be critical in breast carcinogenesis.

Keywords: Breast carcinogenesis, metabolic syndrome, miRNAs

(1318) **N-TERMINAL DOMAIN OF cFOS AND FRA1: A NOVEL APPROACH TO INHIBIT BREAST TUMOR PROGRESSION**

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Breast cancer is the most common type of cancer and the leading cause of cancer death in women worldwide. Although early detection has improved survival, in less developed countries most cases are diagnosed at late stages when available therapies are not efficient. Highly proliferating breast tumor cells require high rates of phospholipid (pl) synthesis to support membrane biogenesis for their exacerbated growth. Both Fra-1 and c-Fos are overexpressed in breast tumors, contrasting with their undetectable levels in normal tissue and both promote pl synthesis by activating rate limiting enzymes such as CDP-DAG synthase (CDS) through a physical association with the activated enzyme. We have previously demonstrated that the basic domain of both Fra1 and cFos are involved in the activation of CDS whereas the N-terminal domain of Fra1/cFos physically associates with CDS. Herein we demonstrate using *in culture* experiments, that both N-terminal domains together inhibit the proliferation of the breast tumor cell line MDA-MB-231.