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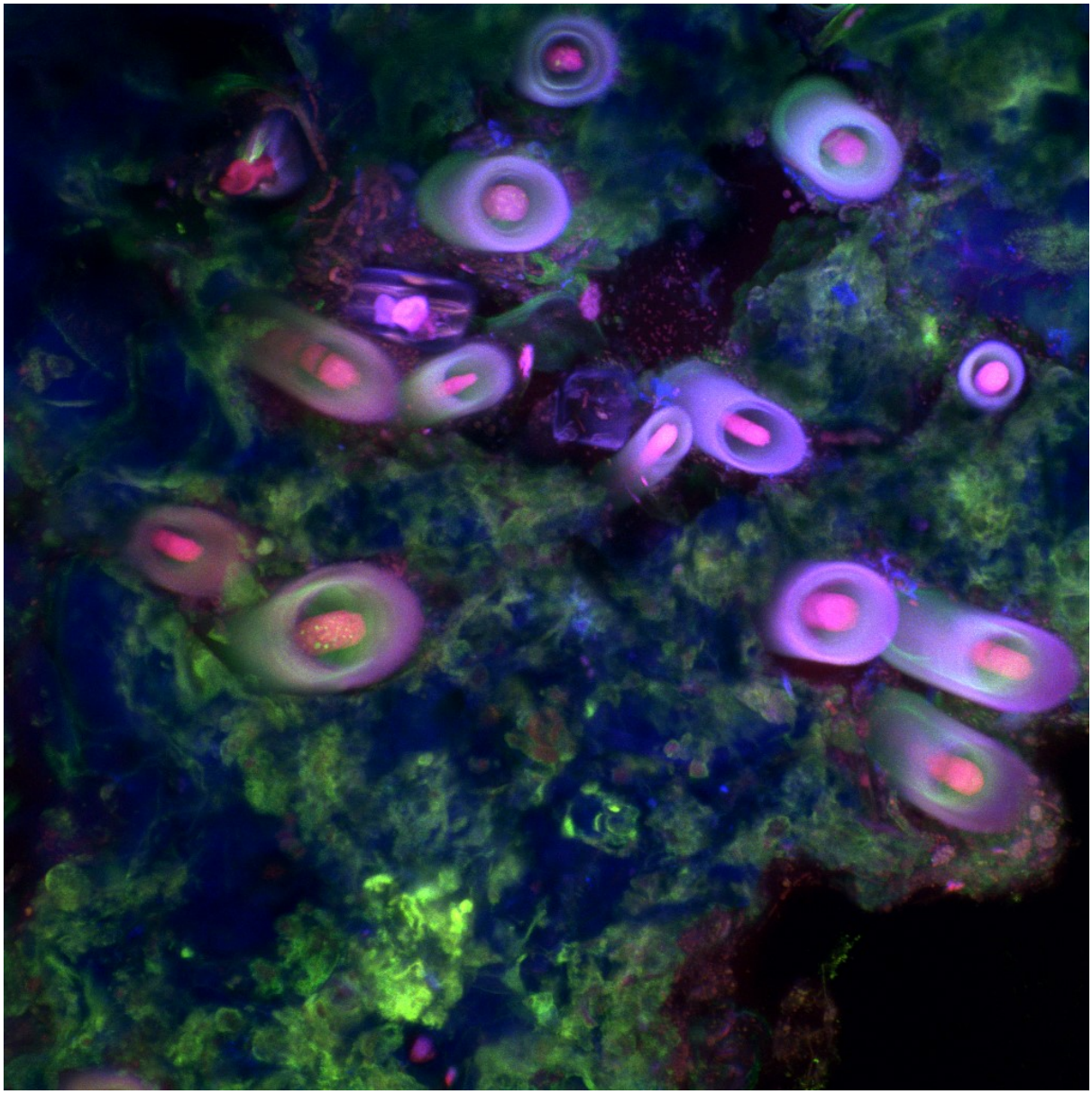
LVI SAIB Meeting – XV SAMIGE Meeting



SAIB-SAMIGE Joint Meeting 2020 – *Online*

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LVI Annual Meeting
Argentine Society for Biochemistry and Molecular Biology
(SAIB)

XV Annual Meeting
Argentinean Society for General Microbiology
(SAMIGE)

SAIB-SAMIGE – Online
Joint Meeting 2020

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ST-C02-11
INEFFICIENT RESOLUTION OF UNDER-REPLICATED DNA IN MITOSIS TRIGGERS GENOMIC INSTABILITY

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The S phase is the period of the cell cycle in which genomes are entirely duplicated. But in organisms with gigabase-sized genomes, such as humans, cells routinely enter the G2 phase with stretches of under-replicated DNA (URDNA). Such DNA regions can be duplicated in mitosis by a specialized DNA replication pathway known as mitotic DNA synthesis (MiDAS). Failure to replicate UR-DNA during mitosis results in aberrant chromosome segregation, which subsequently leads to genomic instability. Genomic instability is defined as a persistent and high rate of mutations and is a hallmark of cancer; it contributes to intratumoral genetic heterogeneity, which implies the risk of developing resistance to oncologic treatments. Thus, elucidating the mechanisms that trigger genomic instability is of utmost importance to cancer research. Herein, we show that downregulation of Checkpoint Kinase 1 (Chk1), a key mediator of the S-phase checkpoint and whose inhibitors are undergoing clinical evaluation across a variety of cancers, induces UR-DNA and MiDAS. But in apparent contrast with the idea that MiDAS completes DNA duplication and hence safeguards genomic stability, our data show that MiDAS in Chk1-deficient cells induces chromosome mis-segregation. Importantly, we unveil the molecular basis of aberrant MiDAS. Upon Chk1 loss, mitotic DNA replication intermediates in mitosis stall due to nucleotide shortage. Stalled DNA replication intermediates are then cleaved by the structure-specific endonuclease Mus81-Eme1, and these mitotic DSBs culminate in chromosome mis-segregation. Intriguingly, both MiDAS abrogation, Mus81-Eme1 down-regulation and MiDAS upregulation by nucleosides revert the genomic instability caused by Chk1 depletion. Such observation indicates that genomic instability is the consequence of incomplete duplication of UR-DNA by MiDAS. Our work unveils a novel molecular pathway leading to genomic instability in cancer cells. Given the interest in avoiding genomic instability during oncologic treatments, our study provides tools to develop novel anti-cancer strategies.

ST-C03-63
14-3-3 AND HIPPO PATHWAY PROTEINS UPREGULATION DURING ADIPOGENESIS OF 3T3-L1 CELLS INDUCTION WITH GLP-1 ANALOGS

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3T3-L1 cells undergo a complex roadmap of signals to differentiate into fat cells. The exact mechanism for the coordination of these signals remains elusive, although 14-3-3 proteins could be key players. In our laboratory, we examined how the combination of different adipogenic differentiation drugs affects the expression of the Hippo kinase pathway genes, as well as the expression of specific 14-3-3 paralogs. We achieve adipocyte differentiation in vitro by adding an adipogenic differentiation medium (ADM) that includes Dulbecco's modified Eagle's medium, 10% fetal bovine serum, synthetic drugs (dexamethasone, IBMX, rosiglitazone), and peptide hormones (insulin). We performed qPCR experiments to measure the gene expression of 14-3-3 and the most important proteins of the Hippo pathway on days 3 and 7 of adipogenic differentiation. We have determined that the conditions which most promoted adipogenic differentiation (evidenced as a larger number and size of lipid droplets) showed higher levels of Hippo pathway proteins and both 14-3-3 gamma and beta isoforms on day 7. These effects were especially evident when IBMX was replaced by GLP-1 in the ADM. These results confirm previous qPCR data obtained under similar experimental conditions. The main question is whether such increased expression is related to the effects of differentiation inducers (glucocorticoids, thiazolidinediones, incretins, or insulin) during early or late adipogenesis. We also would like to determine if the differentiation and the observed increased expression correlate with the activation of the Hippo pathway.

ST-C04-210
PHOSPHOLIPASE D (PLD) 1 AND 2 EXPRESSION IN ABC CELLS, A NEW RETINAL PIGMENT EPITHELIUM CELL LINE

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The retinal pigment epithelium (RPE) plays critical roles in the correct function of the neural retina and photoreceptor survival. Classical phospholipases D (PLD1 and 2) hydrolyze phosphatidylcholine (PC) to generate phosphatidic acid (PA) and choline. PA can be further dephosphorylated to diacylglycerol (DAG) by lipid phosphate phosphatases (LPPs). DAG and PA, as bioactive lipids, can modulate the activity of various proteins involved in cell signaling events, such as protein kinases C and the mTOR (mammalian target of rapamycin) complex, among others. Our previous studies demonstrated for the first time the participation of classical PLDs in the inflammatory response and in the autophagic process of RPE (ARPE-19 and D407) cells exposed to lipopolysaccharide (LPS). The aim of the present work was to study PLD1 and PLD2 expression in a new human RPE cell line (ABC cells), spontaneously arisen from a primary RPE cell culture. Western blot assays (WB) show that both classical PLDs are expressed in ABC cells. Using PLD1 and PLD2 siRNA, we were able to partially decrease the expression

of PLD1 (by 42%) and PLD2 (by30 %). Since PLD-generated PA activates mTORC1, the main inhibitor of autophagy initiation, we wanted to study the effect of classical PLDs silencing on mTOR activation. For this purpose, WB assays were performed in order to study the mTOR downstream effector S6 kinase (S6K) activation (phosphorylation) in ABC cells transfected with PLD1 and PLD2 siRNA. Our results show that in ABC cells transfected with PLD1 and PLD2 siRNA S6K activation is reduced by 34%. This result is in accordance with the increased autophagic process induced by PLD1 and PLD2 pharmacological inhibitors, previously observed in D407 RPE cells. Since it was previously demonstrated that the PLD pathway can modulate the phagocytic process in macrophages, we wanted to evaluate the effect of PLD1 and PLD2 silencing on the photoreceptor outer segment (POS) phagocytic process in ABC cells. With this aim, ABC cells were incubated with POS for 16 h, and total (bound + internal) and internalized POS were measured by WB using an anti-rhodopsin antibody. Under basal conditions, PLD1 and PLD2 silencing seem not to significantly affect POS phagocytosis by ABC cells. In conclusion, our results demonstrate the expression of classical PLD isoforms in a new RPE cell line and their role in the modulation of the mTOR/S6K pathway. Further experiments are needed to fully elucidate the role of classical PLDs in the phagocytic process of ABC RPE cells exposed to inflammatory conditions. The results presented herein, together with our previous findings, contribute to the knowledge of the molecular basis of retinal inflammatory and degenerative diseases, such as diabetic retinopathy, aged-related macular degeneration and endophthalmitis, among others.

BIOTECHNOLOGY

BT-C01-27
THE ROLE OF ENGINEERED BACTERIAL OUTER MEMBRANE VESICLES IN CONFERRING PROTECTIVE IMMUNITY AGAINST CHAGAS DISEASE

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The limited protective immunity induced by most of the vaccine candidates evaluated so far for Chagas disease demands the development of novel strategies able to trigger a broader and longer immunity. Thanks to their potent built-in adjuvanticity, bacterial outer membrane vesicles (OMVs) represent an attractive vaccine platform for many diseases. Among their several beneficial characteristics, we could mention the simplicity in their production process as well as the possibility of being genetically engineered. In this study, we investigated, in a mouse model, the protective capacity of recombinant OMVs expressing different *Trypanosoma cruzi* antigens. Initially, we would like to highlight the success in expressing, for the first time, trypanosomatid antigens in bacterial OMVs. Engineered OMVs elicited high anti-OMVs and specific antigen antibodies when administered in mice after three separate doses. The humoral phenotype obtained from serum samples was balanced between a Th1/Th2 response, which agrees with the cytokine profile obtained in the supernatant of stimulated spleen cells from vaccinated animals. At the cellular level, no significant differences were found between the percentage of effector or memory $CD4^+$ and $CD8^+$ T cells. Robust protection was observed after the challenge of immunized animals with virulent *T. cruzi* parasites. This work not only provides strong evidence that OMVs can be successfully decorated with *T. cruzi* antigens but also that mice immunized with engineered OMVs were partially protected against a virulent challenge. These results make recombinant OMVs a promising tool to be further investigated in Chagas disease vaccine approaches.

BT-C02-28
PHENOLIC ALDEHYDES AND FURFURAL DEGRADING FUNGI FOR THE BIOLOGICAL PRETREATMENT OF LIGNOCELLULOSIC BIOMASS

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Lignocellulosic biomasses, such as agricultural and forest residues, represent abundant, renewable, and low-cost resources to produce biofuels, chemicals, and polymers. The recalcitrant nature of lignocellulosic biomass is the major issue for its exploitation in biotechnological processes. Physicochemical pretreatments are used to improve the bioconversion of this type of biomass, but they could generate toxic by-products, as furan and phenols, that could inhibit several biological processes. In this study, 40 fungal strains were analyzed for their capability to grow with different concentrations of furfural (F) derived from dehydration of hemicellulosic carbohydrates, and the lignin derivatives vanillin (V), 4-hydroxybenzaldehyde (H), and syringaldehyde (S). Growth performance of fungal strains was analyzed at different concentrations of the inhibitors, as single molecules or mixes of them. The high-throughput screening performed with the 40 fungal strains confirmed the strong toxicity of phenolic aldehydes and furfural. Furthermore, results showed that in the presence of single-molecule solutions, the growth inhibition depends not only on the nature and concentration of the assayed compounds but also on the presence of glucose as co-substrate. *Byssochlamys nivea* MUT 6321 showed promising growth performance when the inhibitors were used as single molecules and it was the only fungus that could grow when the four molecules were simultaneously present in culture media.