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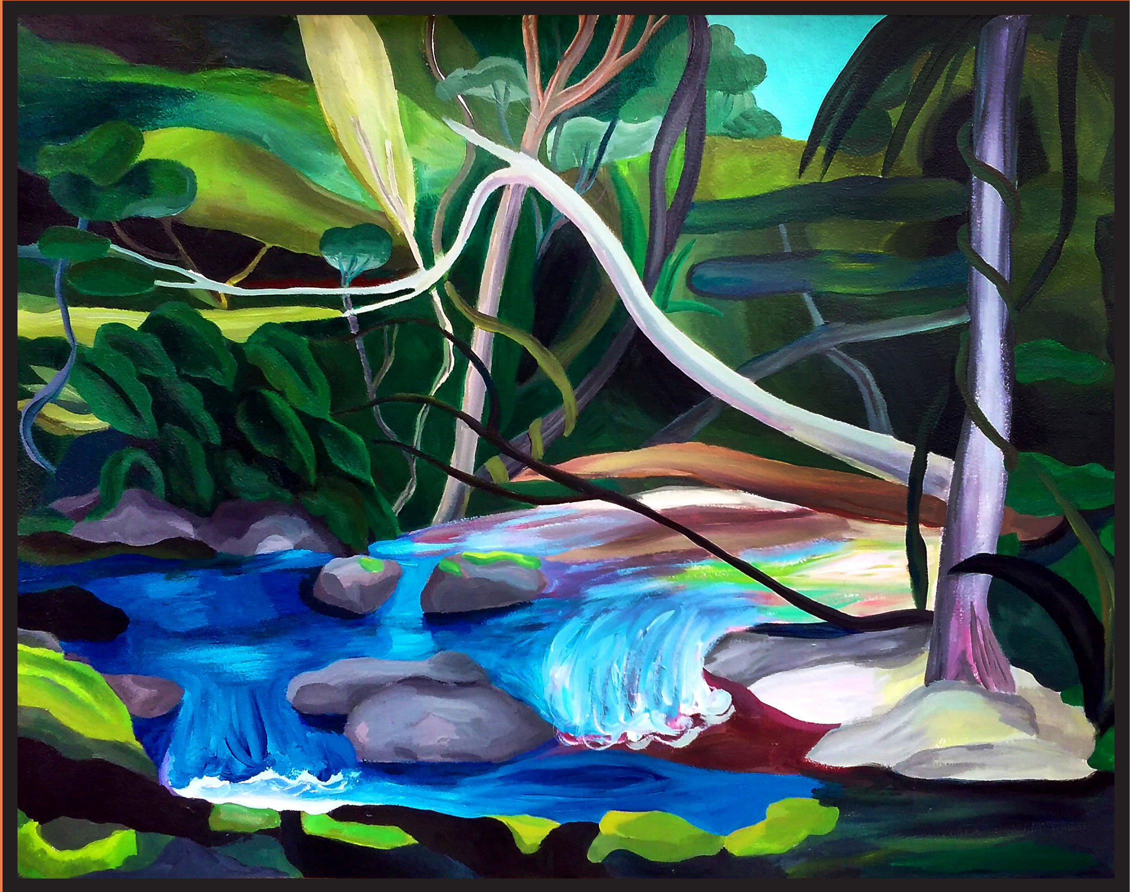

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REUNIÓN CONJUNTA SAIC SAB AAFE AACYTAL 2023

LXVIII REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INVESTIGACIÓN CLÍNICA (SAIC)

XXV JORNADAS ANUALES DE LA SOCIEDAD ARGENTINA DE BIOLOGÍA (SAB)

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15-17 de noviembre de 2023
Hotel 13 de Julio – Mar del Plata

EDITORES RESPONSABLES
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JOINT MEETING SAIC SAB AAFE AACYTAL 2023

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13 de Julio Hotel – Mar del Plata

RESPONSIBLE EDITORS
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Dra. Silvina Pérez Martínez
Dr. Ventura Simonovich
Dr. Gabriel Pinto

In this contribution the physical interaction process between pre-osteoblasts and tumoral cells, both located at the front region of quasi-linear (q-linear) opposed fronts is studied. The q-linear fronts of murine pre-osteoblast MC-3T3 or tumoral T-47D cells from human breast are generated employing a device provided with two compartments for cell seeding separated by a central partition of micrometric dimensions. This device is located on a polystyrene patterned substrate with channels 3,3 μm in period, fixed to the bottom of a Petri dish. After the formation of congruent cell layers in both compartments, the device is withdrawn and the evolution of the fronts are followed by optical microscopy and a time-lapse system in a chamber that resembles the conditions of an incubator. Individual cell trajectories and the velocity field are determined. Results indicate that although, both MC-3T3 and T-47D cells are oriented by the channels, the former exhibit a significant increase in the velocity magnitude while for the latter it remains almost constant. Furthermore, during the "collision" of MC-3T3 and T-47D fronts, the average cell displacement perpendicular to the colony fronts decreases for MC-3T3 cells approaching the value of the average cell displacement perpendicular to the colony fronts, while it increases for T-47 cells. The parallel component of the average cell displacement increases for both type of cells and the overall result is the engulfment of T-47D agglomerates and the disruption of the pre-osteoblast monolayer. On the other hand, for two fronts of MC-3T3 cells, the perpendicular component of the displacements remains higher than the parallel one. These observations are not affected by soluble factors in the range of time of our experiments. The presented model could be useful for the design of new strategies for treating certain invading tumors based on controlling the alteration of bone microstructure originated by the disorganization of osteoblasts.

61. 438. **OXIDATIVE STRESS MODULATES GSK3β SIGNALING ASSOCIATED WITH LIPOLYSIS IN FAT CELLS**

Melania Funk[1], Athina Maniscalchi[1], Oriana Benzi Juncos[1,2], Natalia Alza[1,3], Melisa Conde[1,2], Gabriela Salvador[1,2], and Romina Uranga[1,2].
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Oxidative stress (OS) modulates fat metabolism and triggers chronic inflammation, promoting the onset of metabolic diseases such as type 2 diabetes and obesity. We have previously demonstrated that iron-induced OS increases lipolysis in mouse white adipose tissue as well as in *in vitro* differentiated adipocytes. We found that iron treatment triggered β-catenin upregulation and exacerbated lipolysis by ATGL activation. In addition, adipocytes where β-catenin had been deleted showed no ATGL upregulation by OS. Our aim was to study the role of GSK3β kinase in the modulation of β-catenin cascade in adipocytes exposed to OS. For this purpose, we used differentiated 3T3-L1 adipocytes (0.5 mM IBMX, 1 µM dexamethasone, 6 µg/ml insulin, and 5 *µ*M rosiglitazone) exposed to 500 *µ*M ferric ammonium citrate (FAC) for 24 h. We also analyzed adipose tissue and liver isolated from mice challenged with iron overload. As previously reported in adipose tissue, OS enhanced lipolysis in liver ($p<0.05$). To unravel the role of GSK3β pathway in OS-activated lipolysis, we performed experiments using LiCl (20 mM), a pharmacological inhibitor of the kinase. FAC and LiCl concentrations used in cell culture experiments had no effect on cell viability. A very well-known mechanism of β-catenin regulation and subcellular localization is its phosphorylation by GSK3β. We performed subcellular fractionation in 3T3-L1 adipocytes exposed to iron overload to study the localization of GSK3β/β-catenin. In nuclear fractions, GSK3β expression showed no significant difference between adipocytes treated with FAC, LiCl, and FAC plus LiCl. However, β-catenin expression was increased in LiCl-exposed adipocytes compared to controls ($p<0.001$) indicating that GSK3β inhibition favors β-catenin translocation to the nucleus. Our results show that nuclear translocation of β-catenin is promoted by its dephosphorylated form and that this mechanism is involved in the lipolytic response of the adipocyte to iron-triggered OS.

62. 521. **FUNCTIONAL ANALYSIS OF GLUCOCORTICOID AND PROGESTERONE RECEPTOR CROSSTALK**

Maximiliano Gutierrez [1], Norma Roxana Carina Alves [2], Adali Pecci [1,2], María Florencia Ogara [1]
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The glucocorticoid and progesterone receptors (GR and PR, respectively) are closely related members of the steroid receptor family of transcription factors. Despite they share similar structural and functional properties, as their DNA sequence recognition motif, the cognate hormones display very distinct physiological responses and even in tissues expressing both receptors they exert opposite biological actions in proliferation, differentiation and cell death. Results from our group demonstrated an antagonistic effect of activated GR on PR-dependent features in mammary epithelial cells. To evaluate whether GR activation could affect PR function, we analyzed the expression of several progestin target genes in MCF-7L cells which express both PR and GR. RT-qPCRs of selected genes show that GR activation by Dexamethasone (DEX) [10 nM] inhibited the R5020 [10 nM]-dependent induction of STAT5A, SNAI1A and EGFR, wherein potentiated R5020-mediated GREB1 and ELF5 expression induction. These results were confirmed by siRNA-mediated GR knockdown, where the progestin-dependent expression of those genes was restored. Moreover, cell cycle analyses performed in cells treated for 18 h with R5020 show that the percentage of cells accumulated in S phase was significantly higher compared to untreated cells (13.7±0.7% vs 10.2±0.3%). DEX alone did not affect S phase accumulation (10.3±0.6%) but inhibited R5020-mediated action (10.9±0.9%). To assess whether the presence of GR affects proliferation, survival and cell migration induced by progestin, clonogenic and wound healing assays were performed in MCF-7L cells. Clonogenic assay shows that treatment with R5020+DEX decreases the proportion of colonies by half compared to R5020 alone. In the same way, wound closure decreased by 20% when treated with both ligands compared to R5020 alone. These results seem to indicate that activated GR modulates PR-dependent cell proliferation and migration in mammary tumor epithelial cells.

63. 558. **PULMONARY NEUTROPHILIC INFLAMMATION CAUSES MUTATIONS IN GENOMIC DNA**

Lopez CM[1], Ramírez DC[2], Gomez-Mejiba SE[1]
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Pulmonary neutrophilic inflammation (PNI) is caused by the homing and activation of neutrophils in the lung microvasculature exposed to environmental irritants. Upon activation, neutrophils release myeloperoxidase (MPO), the only enzyme that can, under physiological pH, use H_2O_2 to oxidize chloride ions to hypochlorous acid (HOCl). Released MPO can be taken up by surrounding lung epithelial cells, where it can produce HOCl. Genomic DNA oxidation by intracellularly produced HOCl can lead to mutagenesis and further cell transformation. The hypoxanthine phosphoribosyl transferase (*hprt*) gene is one of the most sensitive genes to oxidative mutagenesis. The *hrpt* mutated cells survive in the presence of 6-thioguanine (6-TG). Herein we used an *in vitro* experimental model to test whether intracellularly produced HOCl can damage the genome, and whether the nitrone spin trap 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) can protect the genome. To accomplish our aim we used human lung epithelial cells (A549 cell line) and incubate them to human MPO or human neutrophils activated with a phorbol ester (PMA) a well-characterized model of PNI. After these incubations, MPO was traced inside A549 epithelial cells very close to the cell nuclei (Confocal). Upon exposure of MPO-loaded A549 cells to H_2O_2, HOCl was intracellularly generated (luminol assay), 8-oxo-deoxyguanosine (8-oxodG) was formed (ELISA in isolated DNA), and 6-TG-resistant cells