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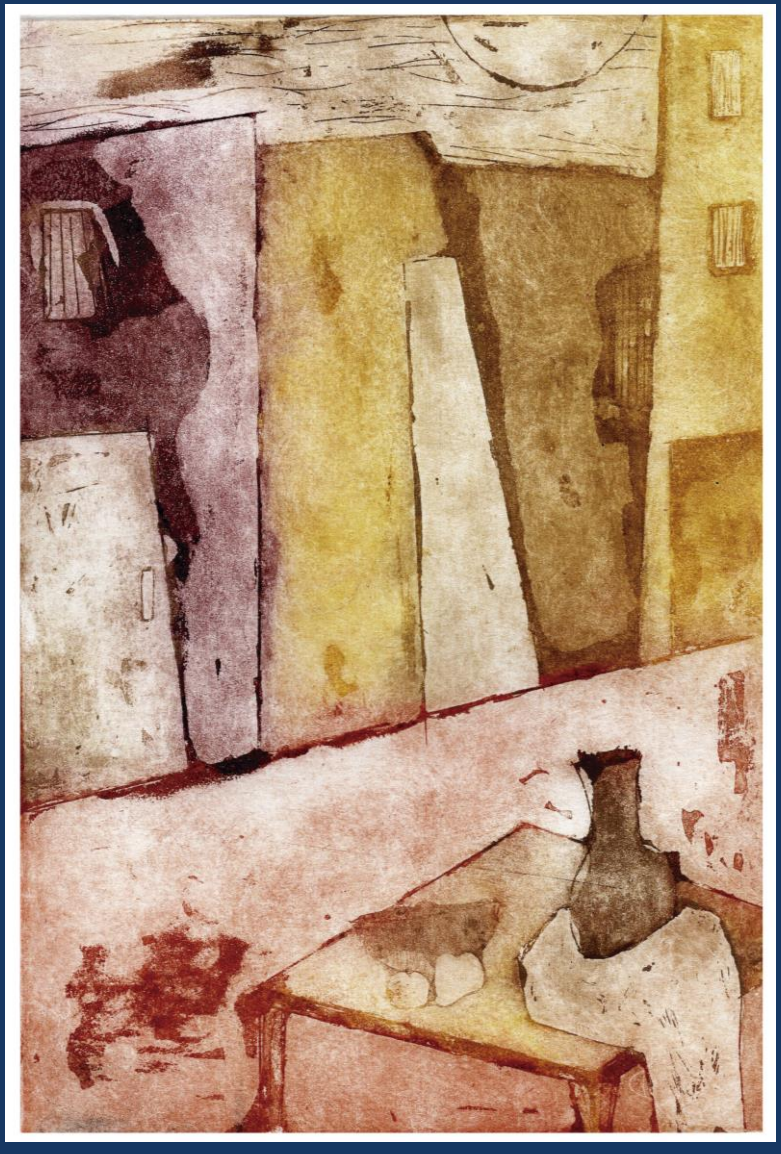

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La Tapa (Ver pág. 4)
Atardecer en la tarde
Antonella Ricagni

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Tel. 5287-3827 Int. 73919 y 4523-6619
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CUTANEOUS MELANOMA PATIENT A TCRB REPERTOIRE FOUND AT VACCINATION SITE AND TUMOR INFILTRATING LYMPHOCYTES THAT PERSISTED IN BLOOD

Mariana ARIS (1) | Alicia Inés BRAVO(2) | Heli Magalí GARCIA ALVAREZ(3) | Ibel CARRI(3) | Enrique PODAZA(1) | Paula Alejandra BLANCO(1) | Cecilia ROTONDARO(4) | Sofía BENTIVEGNA(4) | Morten NIELSEN(3) | María Marcela BARRIO(1) | José MORDOH(1)

CENTRO DE INVESTIGACIONES ONCOLÓGICAS-FUCA (1); HOSPITAL INTERZONAL GENERAL DE AGUDOS EVA PERÓN (2); INSTITUTO DE INVESTIGACIONES BIOTECNOLÓGICAS (IIB-UNSAM-CONICET) (3); LELOIR INSTITUTE FOUNDATION - IIBBA CONICET (4)

Abstract/Resumen: The CSF-470 cellular vaccine plus BCG and rhGM-CSF increased distant metastases-free survival in Cutaneous Melanoma (CM) patients stages IIB-IIC-III relative to medium dose IFN-a2b (CASVAC-0401 study). Patient-045 developed a mature vaccination site (VAC-SITE) and a regional cutaneous metastasis (C-MTS) which were excised during the protocol, remaining disease-free 36 months following vaccination. CDR3-TCRB repertoire sequencing in PBMC and tissue samples, along with skin-DTH score and IFN-G ELISPOT assay were performed to analyze the T-cell immune response dynamics throughout the immunization protocol. Histopathological analysis of the VAC-SITE revealed a highly-inflamed granulomatous structure encircled by CD11c+nested-clusters, brisk CD8+ and scarce FOXP3+ lymphocytes; with numerous Langhans multinucleated-giant-cells and macrophages. A large tumor-regression area fulfilled the C-MTS with brisk lymphocyte infiltration, mainly composed of CD8+PD1+ T-cells, CD20+ B-cells, and scarce FOXP3+ cells. Increasing DTH score and IFN-G ELISPOT assay against CSF-470 vaccine-lysate was evidenced. TCRB repertoire analysis revealed for the first time the presence of common clonotypes between a VAC-SITE and a C-MTS; most of them persisted in blood by the end of the immunization protocol. In-vitro boost with vaccine-lysate revealed expansion of persistent clones infiltrating the VAC-SITE and/or the C-MTS. Expansion of such persistent clonotypes might derive from two different although complementary mechanisms: proliferation of specific clones as well as expansion of redundant clones, which increased the number of nucleotide rearrangements per clonotype, suggesting a functional antigenic selection. In this patient, immunization with the CSF-470 vaccine plus BCG and rhGM-CSF induced a T-cell repertoire at the VAC-SITE that was able to infiltrate an emerging C-MTS, resulting in the expansion of a T-cell repertoire which persisted in blood by the end of the 2-year treatment.

0240 - INVOLVEMENT OF MICROENVIRONMENT FACTORS IN THE PTHRP EFFECT ON THE AGGRESSIVE BEHAVIOR OF COLORECTAL CANCER CELLS

María Belen NOVOA DIAZ | Pedro CARRIERE | Natalia Graciela CALVO | Claudia Rosana GENTILI

INBIOSUR, DEPARTAMENTO DE BIOLOGÍA, BIOQUÍMICA Y FARMACIA, UNS-CONICET

Abstract/Resumen: PTHrP is a factor from the tumor and its microenvironment that has been associated with the aggressiveness of different types of cancer. Colorectal cancer (CRC) is a heterogeneous disease where microenvironment and tumor factors act together leading to the progression of the tumor towards advanced stages. Previously, we observed that in the cell line HCT116 derived from human CRC, the treatment with exogenous PTHrP stimulates its transcription and also modulates the expression of markers associated with aggressive behavior such as E-Cadherin, FAK, Met and CD44. In addition PTHrP activates mitogenic pathways in HMEC-1 endothelial cells. To understand the PTHrP role in tumor progression through its influence on microenvironment cells, in this work we first evaluated in HMEC cells the effects of PTHrP in the regulation of cytokines expression and we observed by Western blot analysis that the treatment with the hormone for 1 and 16 h increases protein levels of TGF-ß, which is a protumoral factor known to be closely linked to PTHrP. Then we evaluate the effect of the conditioned medium (CM) from the HMEC-1 cells treated with PTHrP on the intestinal tumor cells HCT116. According with our previous results regarding to PTHrP direct action on HCT116 cells, the CM also induces an increase in the protein expression of FAK and CD44 in a time-dependent manner, and decreases the protein level of E-cadherin but at shorter times respect to the direct action of PTHrP. Previously we found that PTHrP increases the protein levels of Met in HCT116 cells and herein we observed by CM treatment the same effect but at longer times of exposure. The results of this work allow us to postulate a mechanism based in the action of PTHrP on tumor niche cells leading to the subsequent release of factors to the environment that could contribute to its protumoral effect.

0246 - BROWNING OF WHITE ADIPOSE CELLS BY INTERMEDIATE METABOLITES: AN ADAPTIVE MECHANISM TO TUMOR ENVIRONMENT

Mariana GANTOV (1) | Priscila Ayelén PAGNOTTA(1) | Gustavo RINDONE(2) | Maria Fernanda RIERA(2) | Silvina Beatriz MERONI(2) | Juan Carlos CALVO(1) | Judith TONEATTO(1)

IBYME-CONICET (1); HOSPITAL DE NIÑOS RICARDO GUTIÉRREZ, CEDIE - CONICET (2)

Abstract/Resumen: Interaction between epithelial cells and the adipose environment is a fundamental step in the regulation of tumor behavior in mammary cancer. It has been shown that adipocyte differentiation, browning and thermogenesis, contribute to lactate metabolism, leading to a Warburg effect. We, previously, demonstrated morphologic changes in adipocytes indirectly cocultured with breast cancer cells, suggesting a first step towards browning. We, now, suggest that soluble factors released by breast cancer cells impact adipose lactate metabolism by regulation of MCTs expression. We evaluated the effect of 72 h conditioned media (CMs) from a normal mouse mammary epithelial cells (NMuMG) and three mouse mammary cancer cell lines (LM3, 4T1 and MC4L1), as well as indirect coculture (IC, transwells) on UCP1 uncoupling protein, MCT4 lactate transporter expression (Western blot) and lactate release into the medium by 3T3-L1 adipocytes, compared to control adipocytes. Results obtained (times over control) showed that the cancer cell lines increased UCP1 (CMs: Control= 1, NMuMG= 2.10, LM3= 2.14, 4T1= 5.05, MC4L1= 2.92; IC: Control= 1, NMuMG= 3.82, LM3= 2.12, 4T1= 4.19, MC4L1= 1.28), as well as MCT4 expression (CMs: Control= 1, NMuMG= 1.26, LM3= 1.33, 4T1= 2.95, MC4L1= 2.56; IC: Control= 1, NMuMG= 2.25, LM3= 0.86, 4T1= 2.30, MC4L1= 1.29). When lactate released into the culture medium, an increase was also observed with the cancer cell lines (CMs: Control= 1, LM3= 1.06, 4T1= 1.32; IC: Control= 1, LM3= 2.43, 4T1= 4.08). In conclusion, taken together, these results clearly show the metabolic and phenotypic switch (browning) on 3T3-L1 adipocytes when presented to soluble factors secreted by mammary epithelial cancer cells. This could represent an adaptive mechanism to changes in the microenvironment.

0249 - TRANSCRIPTOMIC ANALYSIS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA AT DIAGNOSIS AND ITS ASSOCIATION WITH CLINICAL EVOLUTION

Maria Mercedes ABBATE (1) | Maria Cecilia RICCHERI(2) | Laura ORELLANO(3) | Marta ALONSO(2) | Karina GUIÑAZU(4) | Marcela GUTIERREZ(4) | Luis AVERSA(4) | Virginia SCHUTTENBERG(3) | Elba VAZQUEZ(1) | Javier COTIGNOLA(1)