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vance of the Gal1/glycan axis in controlling normal mammary gland branching and emphasize its critical role in metastatic spreading of breast cancer. We propose that the Gal1/ST6Gal1 pair might serve as a possible biomarker capable of predicting the outcome of breast cancer patients and as a therapeutic target of novel anti-metastatic therapies ($p<0.05$*;$p<0.01$**;$p<0.001$***).

487. (373) **EXTRACELLULAR VESICLES IN BREAST CANCER MICROENVIRONMENT: THE MECHANISMS UNDERLYING ENDOCRINE RESISTANCE**

Rodriguez-Baili MC, Gil GA
CIQUIBIC-CONICET. Quimica Biologica Ranwel Caputto, FCQ.UNC. CP:5000

Antiestrogen adjuvant treatments are first-line therapies in patients with estrogen receptor-positive (ER +) breast cancer. The treatment strategies need to be improved because most patients eventually become endocrine resistant and many others are initially refractory to anti-estrogen treatments. The tumor microenvironment, and mainly macrophages, play an essential role in the development and progress of cancer; however, the molecular mechanisms underlying these effects remain poorly understood. Extracellular vesicles (EVs) secreted by tumor cells or by cells from the microenvironment have been proposed as one of the main forms of cell-cell communication. Many reports involve them in processes that are essential for cancer progression such as proliferation, migration, endocrine resistance, invasion, administration of drugs, among others. We proposed that EV are one of the most important actors in cell communication and could be one of the responsible for the endocrine resistance that we had observed in our previous work. The first steps for the study of these vesicles are the isolation and characterization of EVs from our cells of interest, then we evaluate the effect of EVs from macrophages and activated macrophages on mammary cells (tumor and non-tumor). These results suggest that EVs are involved in increased proliferation of mammary cells, and this increase depends on the amount and type of EVs, as well as the recipient cells. This and other analyzes will allow us to determine whether EVs are involved in communication between tumor-associated macrophages (TAMs) and tumor cells, and whether they are responsible for endocrine resistance in estrogen receptor-positive breast cancers.

488. (375) **A NOVEL IMPLICATION OF NEURONAL PROTEINS IN CANCER: CHARACTERIZING THE ROLE OF SYNUCLEIN PROTEINS IN MELANOMA**

Lucía Zanotti[1,2*], Florencia Malizia[1,2*], Mauricio Menacho Márquez[1,2,3]
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** Contributed equally to this work*

Synucleins are small proteins expressed primarily in neural tissue and certain tumors. While alpha-synuclein (aS) was recently connected to melanoma development, gamma-synuclein (gS) was associated with a range of tumor types. Our goal was to explore the role aS and gS in melanoma. For that, we worked with mouse (B16F0, B16F10) and human (SKMEL28, A375) melanoma cells. By Western Blot (WB) and immunocytochemistry (ICC), we observed that both proteins were expressed in these cells. Then, we modulated (by shRNA and expression vectors) aS and gS levels ($P<0.01$ for both proteins by qPCR and WB). Growth studies (cells count and MTT) indicated that reduced expression of aS and gS leads to proliferative defects ($P<0.05$; $P<0.01$, respectively), while increased expression was associated with cytoskeletal changes, migration and focal adhesions ($P<0.01$ and $P<0.05$, respectively), observed by ICC. Interestingly, melanoma cells were able to uptake different exogenous aggregation species of aS. These species, although toxic for neuronal cells (SH-SY5Y, $P<0.01$), failed to trigger toxic effects on melanoma cells, promoting instead proliferation ($P<0.05$), clonogenic capacity ($P<0.05$), cytoskeletal rearrangement and migration ($P<0.01$). We confirmed these observations *in vivo* by two approaches injecting subcutaneously B16-F10 cells (control and incubated with aS fibers) in the right flank in 8-week-old female C57BL/6 mice ($7x10^4$ cells; n=5/group and $2x10^5$ cells; n=6/group). By the first method, we observed that animals injected with treated cells developed tumors within 4 weeks post-inoculation (no tumor was observed in control group at this time). By the second, we analysed melanoma growth measuring tumor volume periodically. Growth kinetics indicated that αS treatment significantly promoted tumor growth ($P<0.05$).
Altogether, our results indicate that aS and gS have a role in melanoma growth and development. Further studies should be addressed to confirm and complement our observations.

489. (380) **Rac1-DEPENDENT Vav2 INVOLVEMENT IN MELANOMA**

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Melanoma is the most dangerous form of skin cancer, associated with an increasing incidence in the population.
Vav proteins are guanosine nucleotide exchange factors (GEFs) for the Rho GTPase family (mainly composed by Rac1, RhoA and Cdc42). In previous works we explored the role of Vav2 in events associated to melanoma development. We modulated Vav2 expression in the mouse-derived melanoma cell line B16-F0 observing that Vav2 is involved in cellular processes linked to proliferation, migration and cytoskeletal rearrangement, promoting melanoma development.
In this work, we studied the dependency of these phenotypes on Rac1 introducing by lipotransfection a fast cycling form of Rac1 (Rac1F28L) in Vav2-deficient cells. By MTT based methods we observed that defective proliferation and migration associated to reduced levels of Vav2 ($P<0.01$) were rescued by Rac1 expression. When cells were subcutaneously injected on C57BL/6 animals (n=4), we observed that Rac1 restored the defective tumor growth associated to a decreased in Vav2 ($P<0.05$). Indeed, defective expression of the epithelial markers beta-catenin observed by Western Blot, was increased by Rac1 ($P<0.05$) to similar levels observed in catalytically active Vav2 expressing cells.
As enhanced nuclear plasticity can promote cell migration during invasive processes, we evaluated the impact of Vav2 modulation on nuclear shape by DAPI staining, noting that decreased levels of Vav2 in melanoma cells was associated to an increased percentage of rounded nuclei and a lower amount of elongated ones ($P<0.01$).
Finally, to analyze the impact of Vav2 on melanoma cytokines production, we quantify by RT-PCR IL-6 expression, noting that Vav2-deficient cells expressed reduced levels of IL6 ($P<0.05$). Dependency of these two last phenotypes on Vav2 GEF activity needs to be addressed.
Altogether, our data indicate that Vav2 could participate in different cellular processes in melanoma cells through Rac1 activity, promoting tumor development.

490. (388) **CHARACTERIZATION OF A LUMINAL B AND A HER2 BREAST CANCER PATIENT-DERIVED XENOGRAFT**

Gabriela Pataccini[1], Marcela Coianis[1], Ramiro Perrotta[1], Silvia I. Vanzulli[2], Claudia Lanari[1], Caroline Lamb[1].
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Molecular classification of breast cancer (BC) includes four main subtypes defined as luminal A and B, both of which express estrogen receptor alpha (ERα); HER2+-enriched, which overexpress HER2 and are $ERα^-$, and triple negative (TN) tumors, which are $ERα^-$/$HER2^-$. Patient-derived tumor xenografts (PDX) are generated by implanting tumor fragments directly from patients into immune-deficient mice. This model reflects more accurately the human tumor

biology as compared with cell line xenografts and have potential applications in precision medical treatments. We have recently established and genetically characterized 9 PDX (2 luminal, 1 HER2+, and 6 TN) derived from BC patients from *Hospital Magdalena V. de Martínez*. The aim of this study was to characterize one of the luminal PDX (707) and the HER2+ PDX (474) in terms of biomarker expression and treatment response to be used as models of these BC subtypes. PDX707 and the parental tumor are both $ER^+/PR^-/HER2^-$, while PDX474 and its parental tumor are $ER^-/PR^-/HER2^+$. Androgen receptor (AR) expression was also evaluated being both PDXs AR+. PDX707 was treated with tamoxifen (TAM; 5 mg/kg/5 days a week, sc) or testosterone (TESTO; 20 mg *pellet*, sc) and PDX474 with trastuzumab (TZ) and TZ emtansine (TDM1; 15 mg/kg/3 days a week, sc). Treatments started when tumors were 25 mm^2. TAM and TESTO inhibited PDX707 tumor growth ($p<0.001$) and, TZ and TDM1, inhibited PDX 474 tumor growth ($p<0.001$), being the effect of the latter more effective than the former. In conclusion, we have developed and characterized one luminal PDX suitable to explore the effect of combined endocrine therapies, and one HER2+ breast cancer model sensitive to HER2 inhibitors that may be used to test novel HER2 ligands or combined therapies for personalized medicine. Our results also highlight the role of AR ligands in ER+PR- tumors which have earlier recurrence than ER+PR+ tumors.

491. (403) **BIOLOGICAL RELEVANCE OF GALECTINS IN PATIENT-DERIVED GLIOMA STEM CELLS AND THEIR POTENTIAL APPLICATION IN THE DEVELOPMENT OF PERSONALIZED ANTINEOPLASTIC STRATEGIES**

Guillermo Agustín Videla-Richardson*[1], Mariana Belén Vera*[1], Nicolás Ignacio Torres[2], Luisina Belén Ripari[1], Olivia Morris-Hanon[1], Myrian Inés Esquivel[1], Gustavo Emilio Sevlever[1], Gabriel Adrián Rabinovich[2],

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High-grade gliomas exhibit a hierarchical organization that relies on a minor subpopulation of gliomas stem cells (GSC). When injected into immunodeficient mice, these highly tumorigenic cells can develop and propagate brain tumors. GSCs are characterized by their self-renewal potential and their differentiation capacity. The use of multiple patient-derived GSCs constitutes a valuable tool to understand the biology of gliomas in greater detail and to develop translational projects that might contribute to personalized therapies. In the past years, many studies have demonstrated that galectins, a family of highly conserved glycan-binding proteins, play key roles in different aspects of cancer biology, including cellular transformation, proliferation, and apoptosis. In addition, these lectins contribute to tumor progression by favoring angiogenesis, tumor invasion and immune escape. In this study, we found that patient-derived GSC lines exhibit high expression of galectins-1 and -3 and an intermediate expression of galectins-2, -8, and -9. Importantly, by siRNA-mediated gene silencing, we found that galectins-1 and -3 participate in the control of different processes associated with GSCs. By Ki-67 immunostaining, we determined that decreased levels of these galectins lead to a reduction in GSC proliferation from 38,8% to 51,6% ($p<0.05$, n=3). Also, propidium iodide staining revealed that downregulation of galectin-1 exacerbates cell death in a cell line-specific manner from 76,7% to 126,6% ($p<0.05$, n=3), and this effect occurs only when galectin-3 expression is unaltered. Finally, as shown by cell spreading migration assays, silencing of these galectins also impairs GSC migration from 17% to 48% ($p<0.05$, n=3). Thus, involvement of these lectins in multiple processes associated with GSCs suggests their role as potential targets of therapeutic strategies in high-grade gliomas.

492. (412) **CHARACTERIZING A TUMOR SUPPRESSOR ROLE FOR Vav3 IN MELANOMA**

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Melanoma is the most deadly form of skin cancer, with globally increasing prevalence and mortality. A better understanding of this pathology at molecular level is a key challenge to improve diagnostic and therapy.

Vav proteins are Rho GTPases guanosine nucleotide exchange factors (GEFs). They modulate processes associated to tumor development and metastasis. As GEFS, these proteins were classically considered as protumoral.

We previously characterized the role of Vav2 in melanoma. Now we describe that Vav3 and Vav2 display antagonistic roles in this tumor type, contrary to what is described in other cancer types (including non-melanoma skin cancers). Through bioinformatic approaches we found that Vav3 expression varies significantly between healthy skin and melanoma ($P\leq0.01$) while this GEF acts like a double agent in other tumor types.

We modulated Vav3 expression in B16-F0 cells. By MTT assays we observed that Vav3 expression affects proliferation ($P\leq0.001$). We also found Vav3 levels affect both cell morphology and migration capacity; decreased Vav3 promotes a star shape associated to greater migratory capacity by wound healing assays ($P\leq0.001$), while increased expression induces elongated shape and poor migration ($P\leq0.001$). Indeed, increased expression of Vav3 promotes apoptosis by starvation.

By *in vivo* assays with 8-weeks old C57BL/6 female mice (n=6/group) subcutaneously injected, we demonstrated that Vav3 downmodulation increases tumor growth while high Vav3 levels drastically impairs tumor kinetics.

Altogether our data suggest a new tumor suppressor role for Vav3 in melanoma.

493. (416) **EFFECT OF TRANSDIFFERENTIATION ON PANCREATIC DUCTAL ADENOCARCINOMA CELLS**

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Pancreatic ductal adenocarcinomas (PDAC) represent the fourth leading cause of cancer-related deaths in the world. The 5-year survival rate of patients is 9%, and this is largely due to the great metastatic potential of this type of tumor.

Different studies have shown that ectopic expression of specific transcription factors can successfully transdifferentiate pancreatic tumor cells from the exocrine to the endocrine lineage. Our aim was to analyze the effect of the exocrine-endocrine transdifferentiation of PDAC in relation to their migratory phenotype, and to develop an *in vivo* model for pancreatic cancer studies.

We compared the gene expression profiles of ductal and endocrine pancreatic cells through the analysis of single cell RNA-seq. We identified 371 genes that are expressed at least twice as much in ductal as in endocrine pancreatic cells and performed a functional analysis of ontologies and signaling pathways (GO and KEGG). 54 genes were identified by both strategies as potentially related to tumor aggressiveness through characteristics such as cell migration and cell adhesion.

Additionally, PANC-1 and SW1990 cells were implanted on the chorioallantoic membrane (CAM) of chick embryos, and tumor growth was analyzed at different stages. We found significant tumor growth 10 days after implantation.

In order to induce transdifferentiation, PANC-1 cells were treated with BRD7552 for either 4 or 9 days, and migration rates were analyzed by wound healing assays. Significant decreases in migration