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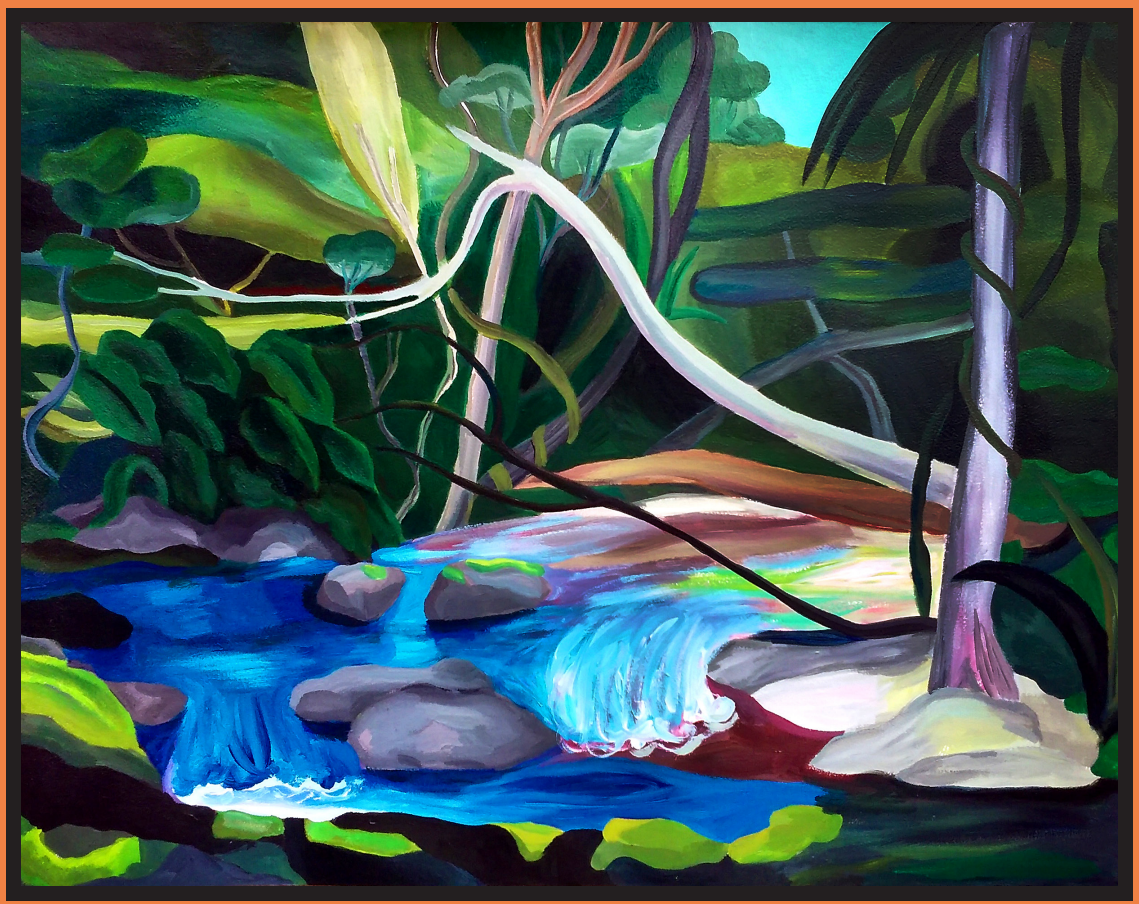

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397. 526. **TUMORAL PD-L1 MODULATES CD206+ MACROPHAGE IMMUNOSUPPRESION DURING BREAST CANCER PROGRESSION**

Paula Anabella Aguirre[1,8], Lilian Fedra Castillo[1,3,8], Marcos Daniel Palavecino[2], Paula Macarena Gonzalez[1,8], Sabrina Aldana Vallone[2], Agustina Suban[1,8], Roberto Meiss[4], Santiago Rodriguez-Seguí[2], Omar Adrián Coso[2], Eva Wertheimer[5], Edith Claudia Kordon[2], Marina Simian[3], Andrea Emilse Errasti[6], Eugenio Antonio Carrera-Silva[7], Manuel De la Mata[2], Albana Gattelli[2], Juan Pablo Fededa[1,8]

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One of the main immunosuppressive mechanisms during tumor progression is the expression of PD-L1, the ligand for T-cell inhibitory receptor PD-1. Despite PD-1 is also expressed in the myeloid lineage, it is not clear which macrophage-specific immune evasion mechanisms are modulated by tumor cell PD-L1. To interrogate this, we generated a PD-L1 KO TNBC-like tumor model in the murine EO771 cell line using CRISPR/Cas9 editing, allowing us to profile the immune infiltrates of the tumoral microenvironment (TME) *in vivo*. Profiling tumor growth in WT vs. PD-L1 KO tumors, we found that tumoral PD-L1 is partially required for EO771 tumor growth. Using flow cytometry (FC) to characterize the immune infiltrates of early vs late-stage WT tumors, we found a decrease in F480h CD206+ TAMs in late-stage tumors, suggesting that inhibition of CD206+ polarization is involved in immune evasion. Interestingly, analyzing late-stage PD-L1 KO vs WT tumors, we found that tumoral PD-L1 inhibits CD206+ macrophage polarization. Furthermore, WT tumor progression triggered PD-1+ and MHCII+ expression in CD206+ TAMs. Comparing PD-L1 KO vs WT tumors, we found that tumoral PD-L1 promotes MHCII expression in CD206+ TAMs, suggesting that PD-L1 fosters antigen presentation by MHCII *in vivo*. On the contrary, FC analysis of *in vitro* experiments showed that direct contact of tumoral PD-L1 inhibits MHCII expression in CD206+ macrophages, suggesting that indirect TME mechanisms compensate the immunosuppressive inhibition of MHCII mediated by tumoral PD-L1. Interestingly, using FC to analyze GFP+ tumor cell phagocytosis in CD11b+ F480+ TAMs, we found that tumoral PD-L1 directly suppresses phagocytosis both *in vivo* and *in vitro*. Altogether, these data suggest that tumor-intrinsic PD-L1 plays a key role in TNBC progression by triggering immune suppression mechanisms in CD206+ TAMs. By interrogating these non-canonical mechanisms, we could gain insights into novel mechanisms of resistance to PD-L1/PD-1 therapies.

398. 605. **EFFECT OF GLYCODRUGS IN THE CHEMOTHERAPEUTIC RESPONSE IN PANCREATIC CANCER**

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Drug glycosylation has emerged an alternative approach to improve pharmacokinetic properties, bioavailability and reduce the toxicity. Using as model pancreatic ductal adenocarcinoma (PDAC), the most common histological subtype of pancreatic cancer, we aimed at evaluating the anti-tumoral properties of glycosylated version of two polyphenolic chemotherapeutic agents (4-methylumbelliferone (4MU) and resorcinol (R) alone or in combination with standard cytotoxic therapy for PDAC. The enzymatic addition of the disaccharide rutinose using a diglycosidase was performed to obtain the respective glycodrugs named 4-methylumbelliferilrutinose (4MUR) and resorcinol-rutinoside (RR). Our experiments showed that the monotreatment with the glycodrugs did not affect significantly cell viability, however, the combination with gemcitabine, a commonly used chemotherapeutic agent, show a synergistic effect in PDAC cell models. In Panc-1 cells, 4MUR showed an antineoplastic effect decreasing the cell viability 44% (100 nM of Gemcitabine/ 50nM of 4-MUR, 48 h, $p<0.05$) and in MiaPaCa-2 cells, the cell viability was 70% after the co-treatment with RR (100 nM of Gemcitabine/100 nM of RR, 48 h, $p<0.05$). Next, in search of the mechanism underlying this combination, we evaluate the expression of genes related to hyaluronic acid metabolism (CD44, HYAL2, HAS2 and HAS3) and the ECM degraded compounds gene MMP-2 in PDAC cells by qPCR after 4MUR and RR treatment. Genes related to hyaluronic receptors and synthesis were downregulated and, simultaneously, Hyal2 gene was upregulated. Remarkably, MMP-2 expression was downregulated after glycodrugs treatments. In summary, our findings demonstrate that glycodrugs improve gemcitabine therapeutic effectiveness in PDAC, suggesting glycosylation as a novel and effective approach for PDAC treatment.

399. 612. **THE IRON EFFECT ON THE CELL SURVIVAL OF BREAST CANCER DEPENDS ON ITS OVERLOAD LEVEL**

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Cancer cells develop metabolic alterations to sustain an increased proliferation. The iron is an essential element required for many biological processes and its metabolism is disrupted in breast cancer (BC) cells. It has been reported that high cellular iron concentration accelerates the proliferation of BC cells. However, recent works described that the iron overload induce cell death by ferroptosis, a form of cell death caused by iron-catalyzed excessive peroxidation of polyunsaturated fatty acids; being a promising therapeutic target for therapy-resistant cancers. In this study we aimed to analyze the behavior of BC cells exposed to an increasing iron overload. To that end, the murine BC cell line, LM3, was treated with increasing ferric ammonium citrate (FAC) concentrations (0- 400 μM) for 48 h and cell viability (by crystal violet), intracellular iron (by Prussian Blue), reactive oxygen species (ROS) (by DFCA), lipid peroxidation (TBARS) (by MDA accumulation) and the expression of divalent metal transporter 1 (DMT1) by immunocytochemistry, were analyzed. LM3 cell viability increased after FAC treatment with 25 μM and 50 μM ($p< 0.05$) but decreased with 200 μM and 400 μM FAC ($p< 0.05$ and $p< 0.01$, respectively), respect to vehicle. The ROS levels increased after FAC treatment with 50 μM ($p< 0.05$), 200 μM ($p< 0.001$) and 400 μM ($p< 0.001$) compared to vehicle. In addition, we detected an increase in lipid peroxidation in LM3 cells treated with 200 μM and 400 μM of FAC compared to vehicle ($p< 0.01$, in both). Also, we found iron accumulation as hemosiderin form and high DMT1 importer expression in LM3 cells treated with 200 μM and 400 μM of FAC, compared to vehicle. Altogether these results suggest that the effect of iron on cell viability depends on its overload level and that a high iron overload promotes the iron entry through DMT1 and its accumulation as hemosiderin inducing lower cell viability through lipid peroxidation-dependent mechanisms.

400. 633. **DIFFERENTIAL REGULATION OF MULTIDRUG RESISTANCE ASSOCIATED PROTEIN 4 (MRP4/ABCC4) EXPRESSION IN RESPONSE TO EPIDERMAL GROWTH FACTOR (EGF) IN HUMAN PANCREATIC DUCTAL ADENOCARCINOMA AND HEPATOCELLULAR CELL LINES**

Zaher Bazzi[1], Julieta Allegro[1], Rodrigo Lagos[1], Natalia