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treated with ICB revealed that macrophages of non-responding biopsies upregulate a specific glycosylation-related signature and show an immunosuppressive expression profile associated with resistance. We observed that these macrophages have an M2-like phenotype regulated by the activation of specific transcription factors and signaling pathways such as TGFb, hypoxia, and VEGF. To study the molecular mechanisms and test therapeutic strategies to overcome cross-resistance, we developed an immunocompetent mouse model of resistance to BRAFi/MEKi in BRAFmut melanoma which mimicry the immune profile related to M2 macrophages seen in melanoma patients.
We hypothesize that there are Gal-1/glycan interactions that could promote an immunosuppressive microenvironment in BRAFi-resistant tumors, preventing subsequent response to immunotherapies.

442. (8) **SOLUBLE TNFα BLOCKADE OVERCOMES LAPATINIB RESISTANCE AND UNLEASHES AN INNATE IMMUNE RESPONSE IN HER2+ BREAST CANCER**

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Lapatinib (L) is a dual EGFR/HER2 tyrosine kinase inhibitor used in HER2+ metastatic breast cancer (BC), but its clinical benefit is less than 30%. We showed that soluble TNFα (sTNFα) induces trastuzumab (T) resistance by upregulating mucin 4 (MUC4), a transmembrane glycoprotein that shields the T epitope on the HER2 molecule, and that women with HER2+/MUC4+ BC have worse survival. Here we studied the role of sTNFα blockade in cell migration, tumor growth, and in the innate immune response in JIMT-1, a T and L-resistant HER2+ BC model. To block sTNFα we used INB03, a TNFα dominant-negative protein (DN). JIMT-1 cell migration was not prevented by L or DN treatment alone, but the combination of L+DN inhibited migration by 50% ($p<0.001$ vs control). When MUC4 was knocked down, L alone reduced cell migration and sTNFα blockade did not further enhance this effect. In the in vivo setting, L+DN treatment inhibited JIMT-1 tumor growth by 54% vs IgG, L or DN ($p<0.001$) in nude mice. Tumor immune cell infiltration analysis by immunofluorescence and flow cytometry showed a higher activation and degranulation of NK cells and a decrease in myeloid-derived suppressor cells in the L+DN group, regarding the control groups. Taken as a whole, we proved that sTNFα blockade is able to overcome L resistance, inhibiting cell migration and tumor growth. Moreover, sTNFα neutralization along with L treatment triggers an anti-tumor innate immune response. These findings highlight the potential use of L+DN in HER2+/MUC4+ BC, especially in patients with brain metastasis since L and DN both cross the blood brain barrier.

443. (56) **DECIDUAL FACTORS AND VASOACTIVE INTESTINAL PEPTIDE GUIDE MONOCYTES AND DECICUAL MACROPHAGES TO HIGHER MIGRATION, EFFEROCYTOSIS AND WOUND HEALING IN TERM HUMAN PREGNANCY**

Daniel E. Paparini[1,*]; Esteban N. Grasso[1,2,*]; Laura Fernandez[1]; Fátima Merech[1]; Rodrigo B. Weingrill[2]; Simone Correa-Silva[2]; Gustavo Izbizky[3]; José I. Abasolo[3]; Vanesa Hauk[1]; Rosanna Ramhorst[1]; Estela Bevilaqcua[2], Claudia Pérez Leirós[1]
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The recruitment and differentiation of monocytes (Mo) at the decidua are critical events that determine the outcome of pregnancy. Their functional plasticity limits the extent of injury after implantation and promotes tissue homeostasis maintenance. The vasoactive intestinal peptide (VIP) is an immunoregulatory peptide synthesized by trophoblast and decidual cells that promotes trophoblast (Tb) invasion, vascular remodelling and functional shaping of decidual macrophages (dMA) in first trimester placenta. Here we studied the role of VIP in human term placenta as a regulator of Mo and dMA function.
Peripheral blood monocytes were isolated from non-pregnant (NON-P) and pregnant (P) volunteers and normal placental samples were obtained at term. Mo were treated *in vitro* with VIP, or conditioned media from decidual explants (D) or decidual explants cultured with VIP [D (VIP)]. Mo or dMA isolated by positive selection with magnetic beads were used to study efferocytosis with CFSE-labelled autologous apoptotic neutrophils by flow cytometry and their wound healing capacity on human endometrial stromal cell line (HESC) monolayers.
NON-P Mo presented higher percentage of efferocytosis than P (34.5±4.5 *vs.* 21.8±3.3; $p<0.05$) which was accompanied by higher expression of CD36. On the contrary, NON-P Mo were less effective in HESC wound healing than P Mo (24.7±1.7 *vs.* 38.7±3.1; $p<0.05$). Remarkably, conditioned media from D or D (VIP) restored the effects. VIP increased TGF-β secretion without altering TNF-α or IL-1β in dMA, as well as their efferocytic capacity. When Mo and dMA from the same patient were analyzed, D (VIP) increased efferocytosis in Mo and dMA to a similar extent.
The results suggest that VIP might regulate Mo and dMA phenotypes directly or by regulating the secretion of decidual factors favoring efferocytosis and wound healing with an increment in TGF-β without changing pro-inflammatory cytokines at term.

444. (65) **B. ABORTUS DOWN MODULATES INFLAMMATION IN MONOCYTES/MACROPHAGES THROUGH MTOR ACTIVATION**

Agustina Pilar Melnyczajko, Ayelén Pesce Viglietti, Constanza Arriola Benítez, María Virginia Gentilini, Álvaro López Malizia, María Victoria Delpino, Guillermo Giambartolomei and Ana María Rodríguez
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Brucellosis, caused by *Brucella* spp, is a disease with a large inflammatory component. *B. abortus* has been shown to activate cells of innate immunity, inducing the secretion of pro-inflammatory factors. However, *B. abortus* has different mechanisms whereby it modulates the immune response, in order to evade it and survive intracellularly. mTOR (mammalian target of rapamycin) is a protein kinase that regulates essential signaling pathways, regulating several cellular functions, such as innate immunity, among others. The aim of this work was to elucidate whether *B. abortus* can modulate the functionality of monocytes and macrophages through the activation of mTOR. *B. abortus* was capable to activate mTOR (evaluated by flow cytometry) during the infection of human monocytes and murine macrophages (RAW 264.7). As heat-killed *B. abortus* recapitulates the effect, we concluded that bacterial viability is not necessary to induce mTOR activation. A significant increase in the expression of TNF-α ($p<0.0005$), IL-6 ($p<0.05$), IL-1β ($p<0.005$) and IL-10 ($p<0.05$), as well as metalloproteinase (MMP)-9 ($p<0.0005$) was observed when infected-cells were pre-treated with rapamycin, a pharmacological inhibitor of mTOR. Together, our results demonstrate that *B. abortus* activates mTOR, which negatively regulates the inflammatory response, potentially contributing to the escape of the immune response, allowing *B. abortus* to survive within monocytes/macrophages for prolonged periods, generating an infection.

445. (69) **MACROPHAGE´S ROLE IN THE MICROENVIRONMENT AGAINST EPASTEIN BARR VIRUS (EBV) IN TONSILS FROM PEDIACTRIC PATIENTS**

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Our aim was to study the macrophage´s role in pediatric EBV infection to help clarify viral contribution to lymphomagenesis.