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cells (CD45+ CD3- CD19- Ly6G- Ly6C- CD11c+) show non-significant changes. In contrast, the frequency of B cells (CD45+ CD19+, p=0,0035) and neutrophils (CD45+ CD3- CD19- Ly6G+ CD11b+, p=0.0019) increases suggesting a possible tumor promoting role for these populations. When tumor infiltrating lymphocyte where studied at day 15 post inoculation, an important reshaping of the tumor infiltrate was observed. Further studies should be done to decipher the immune mechanisms underlying the tumor promoting role of CpG-ODN in this model.

226. (377) **PHENOTYPE AND FUNCTIONAL ALTERATIONS OF HUMAN NK CELLS BY ORGANOPHOSPHATE PESTICIDES**

Adrián D Friedrich[1,2], Jésica M Sierra[1], María V Regge[1], M Cecilia Santilli[1], Aldana Trotta[1], Florencia Secchiari[1], Carolina L Domaica[1], Mercedes B Fuertes[1], Norberto W Zwirner[1,3].
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Chlorpyrifos (CPF) and Glyphosate (GLY) are organophosphate pesticides widely used in agriculture. Several evidences suggest that CPF- and GLY-based pesticides are genotoxic and their use has been linked to the increased frequency of malignancies observed in highly fumigated rural areas. However, their effect on the immune system, including cells involved in immunosurveillance of tumor cells, has been poorly explored. Here, we investigated the effects of two commercial formulations containing CPF (Clorpi48) and GLY (Roundup Plus) as well as their isolated active principles on the phenotype and function of human NK cells. First, we identified sub-apoptotic doses of these substances by flow cytometry performing a dose-response curve with human peripheral blood mononuclear cells (PMBC). Next, using such sub-apoptotic doses, we analyzed the phenotype of pesticide-treated NK cells. We observed a pesticide dose-dependent reduction in the expression of CD16 and CD62L on NK cells after a 24 h of culture with CPF, GLY, Roundup and Clorpi48. Moreover, a diminished frequency of IFN-γ-producing NK cells was observed upon exposure of cytokine-stimulated NK cells to 5 mM GLY, 0.05 mM Roundup, 0.01 mM Clorpi48 but not to 0.02 mM CPF (p<0.05). Moreover, NK cell-mediated cytotoxicity against K562 cells was also affected by pesticide treatment. After 0.05 mM Roundup and 0.01 mM Clorpi48 treatment, cytotoxicity was reduced by 27% (p<0.01) and 29% (p<0.001), respectively. In accordance with previous scientific evidence, final formulations of pesticides (which include additional compounds such as polyethoxylated alkylamines surfactants that facilitate their absorption by cells and tissues) showed a more potent effect on phenotype and function of NK cells than the isolated compounds. Therefore, we conclude that GLY- and CPF-based pesticides affect NK phenotype and function, which might impact on their ability to detect and eliminate nascent tumor cells.

227. (405) **MUC4 ENABLES IMMUNE TUMOR EVASION IN HER2+ BREAST CANCER**

Sofia Bruni1, Florencia L. Mauro1, María Florencia Mercogliano1, Agustina Roldán Deamicis1, Cecilia J. Proietti1, Rosalia Cordo-Russo1, Patricia V. Elizalde1, Roxana Schillaci1
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HER2+ is a breast cancer (BC) subtype characterized by the overexpression/amplification of HER2. Patients receive trastuzumab (Tz), but 27-42% of them do not respond. We demonstrated that the overexpression of TNFα induces Tz resistance in cells and tumors by upregulating the membrane glycoprotein MUC4, which hides Tz epitope on HER2 impairing its binding and pharmacological effects. Blocking the soluble TNFα isoform with INB03 (DN) reduces MUC4 expression, overcomes Tz resistance and unleashes an antitumor innate immune response (IIR) with a decrease in myeloid-derived suppressor cells, an increase in NK cell-activation and degranulation and a macrophage (Mφ) polarization to the M1 subtype.
We studied Mφ and NK cells contribution to the Tz-mediated antitumor IIR and MUC4 impact in human T-lymphocyte recruitment and differentiation. We genetically modified the Tz-resistant HER2+ BC cell lines JIMT-1 and KPL-4 to express a doxycycline-inducible (Dox) MUC4 shRNA (shMUC4) or a control one (shControl) and injected them into female nude mice, which were treated with IgG or Tz (5 mg/kg), DN (10 mg/kg) or the combination of Tz+DN, with (+Dox) or without (-Dox) shRNA induction.
After Mφ depletion with chlodronate or NK cell depletion with anti-asialo GM1, in -Dox tumors we found that both populations are needed to achieve Tz+DN antitumor effect (p<0.01 and p<0.05, respectively). However, upon MUC4 silencing, only Mφ are required to mediate Tz antitumor effect (p<0.01). Secretome from JIMT-1 and KPL-4 cells with MUC4 silencing promoted differentiation of activated T-cells to effector cells. Finally, in our HER2+ BC patient cohort, we found a negative correlation between tumor infiltrating lymphocytes presence and MUC4 expression (p=0,005).
We conclude that Mφ are key players in the Tz-mediated antitumor IIR and that MUC4 promotes cold HER2+ tumors with poor therapy response. Women with HER2+MUC4+ BC could benefit from the combined treatment of Tz+DN.

228. (418) **TUMORAL PD-L1 ORCHESTRATES DIFFERENT TUMOR-INDUCED IMMUNOSUPPRESSION MECHANISMS DURING BREAST CANCER PROGRESSION**

Paula Anabella Aguirre*1, Marcos Daniel Palavecino*2, Lilian Fedra Castillo*3,1, Sabrina Aldana Vallone2, Roberto Meiss4, Adriano Bertelli1, Agustina Suban1, Santiago Rodriguez-Seguí2, Omar Adrian Coso2, Eva Wertheimer5, Edith Claudia Kordon2; Marina Simian3, Andrea Emilse Errasti6, Manuel de la Mata2, Albana Gattelli2, Eugenio Antonio Carrera-Silva7, Juan Pablo Fededa1 (*These autors contributed equally)
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One of the main immunosuppressive mechanisms by which cancer avoids eradication by the immune system is the expression of PD-L1, the ligand for T-cell inhibitory receptor PD-1. PD-1 activation by PD-L1 leads to CD4+/CD8+ lymphocyte exhaustion, which is at the focal point of today's cancer immune therapies. However, little is known about which other immunosuppression mechanisms are triggered by tumor-intrinsic PD-L1 expression.
To genetically address tumor-immune system interactions in a triple negative breast cancer (TNBC) model, we developed a CRISPR/Cas9 expressing TNBC-like EO771 cell line platform. Using flow cytometry, we characterized the immune response associated with the progression of EO771 tumors, which resembled immunosuppression signatures associated with poor prognosis in TNBC patients: an increase in pro-tumoral M2 macrophage polarization, a decrease in MHCII+ Antigen Presenting Cells (APCs) and a marked increase of T-cell exhaustion.
To test the role of tumoral PD-L1 in tumor-mediated immune escape, we generated PD-L1 KO EO771 cell lines. Using CRISPR/Cas9 edited EO771 lines KO for PD-L1, we found that tumor intrinsic PD-L1 expression is required for tumor growth. Interestingly, we also found that PD-L1 expressed by the tumor cell exerts a general impact over the tumoral immune infiltrate composition: a) it is required for the differentiation of M2 macrophages and for the enrichment of myeloid derived suppressor cells and b) in the T-cell compartment, unexpectedly, tumoral PD-L1 is needed to exhaustion of effector CD4+ but not cytotoxic CD8+ cells.