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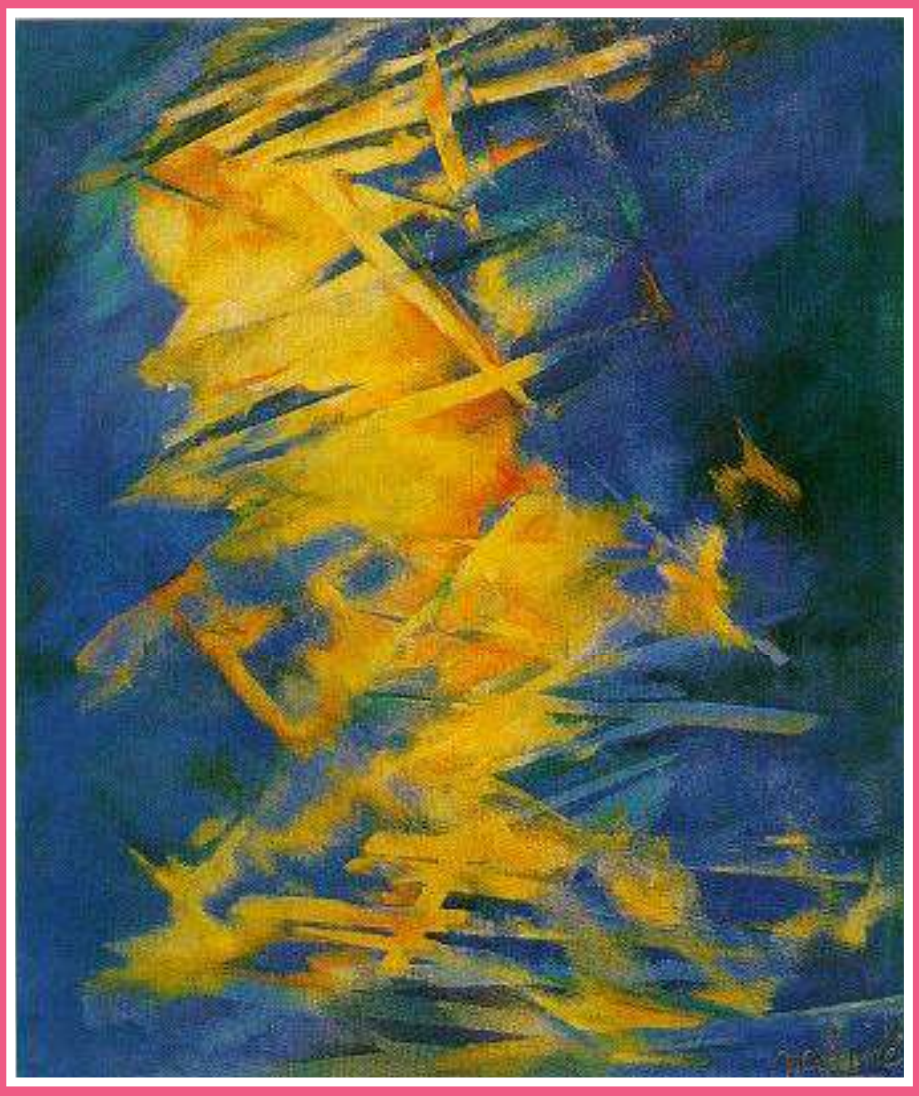

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of lymphoma-bearing mice. We also observed that Sags induce apoptosis in cells of the Jurkat-established human cell line from an acute T-carrier leukemia of the Vβ8 region in TCR. We proposed to analyze those mechanisms involved in apoptosis of Jurkat cells induced by Sag. We co-cultivated Jurkat cells with THP1 cell line (as antigen presenting cells). Then we treated them with or without different Sags (specific or not for the TCR Vβ chain) at different time points. We observed an increase in Fas-L expression analyzed by PCR and flow cytometer ($p<0.001$) suggesting that Sags activate the extrinsic pathway of apoptosis. Moreover, an increase in mitochondrial membrane potential (ΔΨm) (measured by the percentage of $DiOC_2(3)^{low}$ Jurkat cells exposed to a specific Sag) revealed the involvement of the intrinsic pathway ($p<0.001$). Also we observed an increase of truncated Bid protein (Bid-t) by western blot in Jurkat cells treated with specific Sag ($p<0.05$). This protein linked the extrinsic with intrinsic apoptosis pathway. Together, these data suggest that these two pathways are involved in Sag-induced apoptosis in Jurkat cells. The possibility of a therapeutic use of Sags in lymphoma/leukemia T cell malignancies is discussed.

Keywords: Superantigens, Apoptosis, leukemia, Jurkat

(1696) **TUMOR-EXPERIENCED NK CELLS INHIBIT T CELL PROLIFERATION AND ACTIVATION THROUGH PD-L1**

Jessica Mariel Sierra, Ximena Lucía Raffo Iraolagoitia, Sol Yanel Nuñez, Florencia Secchiari, Andrea Ziblat, Nicolás Ignacio Torres, Carolina Inés Domaica, Norberto Walter Zwirner, Mercedes Beatriz Fuertes

Laboratorio de Fisiopatología de la Inmunidad Innata (IBYME-CONICET)

Classical functions of Natural Killer (NK) cells include the elimination of tumor and virus-infected cells, however, novel reports show a regulatory role for NK cells in different models of autoimmunity and viral infections. Our previous results demonstrated that NK cells from tumor bearing mice express the inhibitory molecule PD-L1 and control the magnitude of $CD8^+$ T cell priming to tumor antigens *in vivo*. Moreover, we also observed that PD-L1 expression is up-regulated on human NK cells upon tumor recognition, but little is known about the function of human $PD\text{-}L1^{hi}$ NK cells. Thus, the objective of this work was to further study the phenotype and activity of tumor-experienced human $PD\text{-}L1^{hi}$ NK cells and their possible immunoregulatory role. To this end, we cultured peripheral blood mononuclear cells (PBMC) from healthy human donors with K562 tumor cells for 48 h and we evaluated the expression of the activation markers CD25 and CD69, and the effector molecules TRAIL, FasL, CD107a and IFN-γ on $PD\text{-}L1^{hi}$ and $PD\text{-}L1^{-/low}$ NK cells ($CD56^+CD3^-$) by flow cytometry. We observed that all markers were preferentially expressed in $PD\text{-}L1^{hi}$ NK cells ($p<0.05$ for all markers). To evaluate the immunosuppressive potential of these NK cells, CFSE-labeled autologous T cells were stimulated with anti-CD3/anti-CD28 antibodies (Ab) and cultured in the absence or in the presence of sorted tumor-experienced NK cells or control NK cells, and in the absence or in the presence of anti-PD-L1 blocking Ab. After 5 days, T cell proliferation and activation (evaluated as CFSE dilution and CD25 expression by flow cytometry) were diminished in the presence of tumor-experienced NK cells compared to control NK cells, and this inhibition was reverted by PD-L1 blockade. These results show that tumor-induced $PD\text{-}L1^{hi}$ NK cells exhibit an activated phenotype and increased effector functions in response to tumor cells, however these NK cells can inhibit autologous T cell proliferation and activation trough PD-L1.

Keywords: PD-L1, NK cells, T cells, tumor

(845) **THE THYROID STATUS MODULATES THE COMPOSITION OF TUMOR MICROENVIRONMENT AND THE ANTITUMOR IMMUNE RESPONSE IN A 4T1 MURINE BREAST CANCER MODEL**

Ximena Hildebrandt (1), María Alejandra Paulazo (1), Mariana Gabriela García (2), Marcela Fabiana Bolontrade (3), Graciela Alicia Cremaschi (1, 4), Helena Andrea Sterle (1)

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Several findings suggest that the patient's hormonal context plays a crucial role in determining the outcome of cancer. However, very little is known about the nature of thyroid hormone action on tumor growth. Our aim was to evaluate the effect of thyroid status on the immunity and microenvironment of breast cancer. For this, Balb/c mice were orthotopically inoculated with 4T1 breast carcinoma cells after the treatment with thyroxine (12mg/l) for 30 days or propylthiouracil (500mg/l) for 15 days in the drinking water to obtain hyperthyroid (hyper) or hypothyroid (hypo) mice, respectively. An increased tumor growth rate was seen in hyper mice compared to controls ($p<0.05$), while hypo mice bared tumors with reduced volume ($p<0.05$), but developed a greater number of lung metastases ($p<0.05$). The analysis of immune subsets indicated that hyper tumors presented a decreased immune cell infiltration ($p<0.05$), with a reduced percentage of activated $CD4^+$ and $CD8^+$ T cells ($p<0.05$). Tumor draining lymph nodes (TDLN) of hyper mice also showed a reduced number of activated $CD8^+$ T cells ($p<0.01$) and NK cells ($p<0.01$), but increased percentage of activated $CD4^+$ T cells ($p<0.001$). Additionally, a decreased number ($p<0.01$) and activity ($p<0.05$) of NK cells was detected in hyper spleens, accompanied by increased percentages of MDSC ($p<0.05$). On the other hand, hypo mice showed a higher percentage of activated $CD8^+$ tumor infiltrating T cells ($p<0.05$), but a decreased number of these cells in TDLN ($p<0.05$). To evaluate the effect of thyroid status on the migration of mesenchymal stromal cells (MSCs) to 4T1 tumors, MSC were inoculated in the tail vein of tumor-bearing mice and analyzed by *in vivo* imaging. Hyper tumors and lungs showed a decreased presence of MSC compared to control and hypo mice ($p<0.05$). Our results suggest that the thyroid status modulates the antitumor immune responses and the migration of MSC to the 4T1 tumors, thus modifying tumor growth and metastasis formation.

Keywords: hyperthyroidism, hypothyroidism, breast cancer, mesenchymal stromal cells, antitumor immunity.

(1362) **THERAPEUTIC BLOCKADE OF FOXP3 USING GENE THERAPY VECTORS**

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Our previous results indicate that systemic administration of a cell penetrating peptide (P60) that inhibits Foxp3, a transcription factor required for Treg function, improves the efficacy of antitumor vaccines in experimental breast cancer. Although there is controversy over the role of Foxp3 in tumor cells, we found that P60 inhibits survival and release of IL-10 in $Foxp3^+$ breast tumor cells. Here we aimed to evaluate the regulatory pathways that control Foxp3 expression in LM3 breast tumor cells and to develop gene therapy vectors encoding P60. We assessed the effect of recombinant TGF-β, mTOR inhibitor rapamycin and COX-2 inhibitor indomethacin, all of which modulate Foxp3 expression in Tregs. Stimulation of LM3 cells with TGF-β and rapamicyn upregulated Foxp3 expression ($p<0.05$) as assessed by flow cytometry, whereas indomethacin inhibited Foxp3 expression ($p<0.05$), suggesting that the regulatory mechanisms of Foxp3 expression are similar in tumor cells and Tregs. We next developed a plasmid that encodes P60 linked to dTomato as a reporter gene (pCMV.P60.dTomato) and a control plasmid. Transduction efficiency of these plasmids was evaluated in 4T1 cells, which exhibit low expression of Foxp3 and thus are not affected by P60. Expression of d.Tomato was readily detected by fluorescence microscopy. Conditioned media from pCMV.P60.dTomato-transfected 4T1 cells