646 TRANSCRIPTOME ANALYSIS OF TUMOR AND MATCHED INFILTRATING LYMPHOCYTES IDENTIFIES POTENTIAL NEW TARGETS FOR AUGMENTING INTRA-TUMORAL NK FUNCTION IN SOFT TISSUE SARCOMAS

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Background The success of current immunotherapies in soft tissue sarcomas (STS) has been limited, although pre-clinical studies have shown evidence of natural killer (NK) cell activity. We set out to evaluate the gene expression profile of tumor-infiltrating NK cells, tumor-infiltrating T cells, and tumor-intrinsic genes with the goal of identifying potential novel therapeutic targets and potential drivers of immune infiltration.

Methods Matched peripheral blood and freshly excised STS tissue were collected and processed for FACS isolation of purified peripheral and tumor-infiltrating NK and T cells and tumor cells from STS patients undergoing surgery. Sorted CD45+CD3-CD56+ and CD45+CD3+CD56- immune populations and viable CD45- tumor cells were then evaluated by RNA sequencing analysis. To allow for analysis of survival differences and differential gene expression based on gene expression, we also queried the publicly available TCGA database to compare outcomes in high and low gene expression.

Results Comparing differential gene expression (DGE) of intratumoral NK cells to circulating NK cells revealed upregulation of genes involved in mitogen signaling inhibition (DUSP4) and metabolic function (SMPD3, SLC7A5) ($P < 0.05$), but not of genes associated with cytotoxic function (e.g. IFNG, GZMB). In contrast, intra-tumoral T cells showed significant upregulation of established activating (CD137) and inhibitory genes (TIM-3) compared to circulating T cells. Tumors with higher immune infiltration exhibited significantly increased expression of the pro-inflammatory receptor TLR4. TCGA analysis demonstrated that patients with high TLR4 expression had significantly improved survival compared to low expression ($P = 0.03$).

Conclusions Unlike T cells, which demonstrated significant DGE in activating and inhibiting receptors between circulating and tumor-infiltrating subsets, NK cells appear to have a more similar gene expression pattern between blood and tumor, with alterations in metabolic pathways. Tumor expression of TLR4 is associated with increased immune infiltration and warrants evaluation as a potential prognostic and predictive factor in STS.

Ethics Approval The collection of matched whole blood and tumor specimens was approved by the IRB at the University of California, Davis (Protocol # 218204-9).

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