Background Recent advances in T cell-based immunotherapies have shown promise in controlling tumor growth, but their effectiveness is limited in immune-excluded tumors. Understanding the role of cancer-associated fibroblasts (CAFs) in the tumor microenvironment is crucial for improving these therapies. Single-cell RNA-sequencing has revealed distinct subtypes of CAFs; however, it remains unclear which subtype hinders T cell infiltration into the tumor parenchyma, affecting therapy efficacy. Targeted interventions that selectively block T cell-excluding CAFs or therapies aimed at reprogramming CAFs into an anti-tumorigenic phenotype may hold promise for improving the effectiveness of T cell-based immunotherapies. In the context of soft-tissue sarcomas (STS), where T cell-based immunotherapies have low response rates, investigating CAFs is particularly important.

Methods Two novel immunocompetent models of STS, which recapitulate immune-infiltrated and immune-excluded tumor microenvironments, were utilized to investigate the role of CAF subsets in T-cell exclusion. To explore differences in CAF heterogeneity in the two models, we utilized a combination of scRNA-seq, flow cytometry, and spatial assays. Mice were treated with a GLUT1 inhibitor (BAY-876, 6mg/kg) alone or in combination with Doxorubicin (DOX, 5mg/kg) and changes in T-cell infiltration, cytotoxicity, and CAF composition were assessed by flow cytometry and immunofluorescence.

Results Glycolytic cancer associated fibroblasts (glyCAF) are enriched at the periphery of immune-excluded tumors near CD8+ T cells compared to inflamed tumors which have significantly lower levels of glyCAF accumulation at the tumor margin. Inhibiting glycolysis of glyCAFs using a GLUT1 inhibitor (GLUT1i, BAY-876, 5mg/kg) led to a reduction of glyCAF and enhanced CD8+ T-cell infiltration in vivo. In vitro CD8+ T cell migration was significantly impaired by glyCAF but was rescued by knockdown or pharmacological inhibition of GLUT1. Combination treatment of GLUT1i with doxorubicin resulted in significant reduction of tumor growth in a CD8+ T cell dependent manner.

Conclusions These data suggest that reprogramming glyCAF by neutralizing their glucose metabolism is a promising therapeutic approach to reshape the tumor microenvironment to enhance T cell infiltration and overcome chemo-resistance. These findings offer new avenues for combinatorial therapeutic interventions in sarcomas including immune checkpoint blockade, and adoptive T cell therapies, such as CAR-T cells, which have been challenging to address in clinical settings due to defects in T-cell trafficking into solid tumors. Further studies and clinical trials are warranted to validate these potential strategies.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1432