AN INVERSE CORRELATION OF COL1A1 WITH CAR T CELL TREATMENT RESPONSE IN RECURRENT Glioblastoma Patients

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Background Glioblastoma (GBM) is the most aggressive form of glioma with a median survival rate of less than two years. Despite aggressive standard treatments, GBM remains uniformly fatal with a poor prognosis. Achieving responsiveness of GBMs to chimeric antigen receptor (CAR) T cell therapy has been a significant challenge due to the heterogeneity and evasive mechanisms employed by solid tumors, particularly GBM, to resist therapy. Recent studies have highlighted the substantial role of cancer-associated fibroblasts (CAFs) in GBM invasion by depositing various collagen subunits, including COL1A1, COL1A2, COL5A1, COL5A2, and COL8A1, within the extracellular matrix (ECM). This collagen deposition leads to increased ECM stiffness, modulating the tumor microenvironment, inducing immune suppression, and hindering T cell trafficking, ultimately worsening clinical outcomes and patient survival. Additionally, COL1A1 has been implicated in promoting tumor aggressiveness, particularly in GBM cases with wild-type isocitrate dehydrogenase (IDH-wt) status and a poor prognosis. Based on these findings, we investigated whether the expression level of COL1A1 could influence the response to CAR T cell therapy.

Methods We performed immunofluorescent staining on tissue biopsies obtained from GBM patients to identify a subpopulation of CAFs expressing ACTA2 (alpha smooth muscle actin), PDGFRβ, and COL1A1. Confocal microscopy was used to visualize the stained CAFs. ACTA2 and PDGFRβ serve as markers for a specific subset of CAFs involved in the epithelial-to-mesenchymal transition (EMT), a process associated with immune suppression and tumor growth. The presence of these CAF subpopulations was previously confirmed in GBM patients enrolled in an IL13Ra2 targeted CAR T cell trial through single-cell RNA sequencing. Subsequently, we compared our immunostaining images with flow cytometry data obtained from cerebrospinal fluid (CSF) or tumor fragment (TF) biopsies collected from the same patients after CAR T cell therapy.

Results Our preliminary analysis revealed an increase in the number of infiltrating CD3+ cells from baseline, particularly within the effector, CD8+ subpopulation (characterized by CD27+CD28+ expression), during CAR T cell therapy in patients with low COL1A1 expression. Furthermore, FACS analysis demonstrated a significant increase in the proportion of CD8+ T cells relative to CD4+ T cells in these patients.

Conclusions Ongoing experiments are currently investigating the distribution of CAF subpopulations producing COL1A1 and their correlation with the response to CAR T cell therapy.

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