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CD97 and Its Role in Glioblastoma Stem Cell Self-Renewal

Authors : Niklas Ravn-Boess, Nainita Bhowmick, Takamitsu Hattori, Shohei Koide, Christopher Park, Dimitris Placantonakis

Abstract : Background: Glioblastoma (GBM) is the most common and deadly primary brain malignancy in adults. Tumor propagation, brain invasion, and resistance to therapy critically depend on GBM stem-like cells (GSCs); however, the mechanisms that regulate GSC self-renewal are incompletely understood. Given the aggressiveness and poor prognosis of GBM, it is imperative to find biomarkers that could also translate into novel drug targets. Along these lines, we have identified a cell surface antigen, CD97 (ADGRE5), an adhesion G protein-coupled receptor (GPCR), that is expressed on GBM cells but is absent from non-neoplastic brain tissue. CD97 has been shown to promote invasiveness, angiogenesis, and migration in several human cancers, but its frequency of expression and functional role in regulating GBM growth and survival, and its potential as a therapeutic target has not been investigated. Design: We assessed CD97 mRNA and protein expression in patient derived GBM samples and cell lines using publicly available RNA-sequencing datasets and flow cytometry, respectively. To assess CD97 function, we generated shRNA lentiviral constructs that target a sequence in the CD97 extracellular domain (ECD). A scrambled shRNA (scr) with no predicted targets in the genome was used as a control. We evaluated CD97 shRNA lentivirally transduced GBM cells for Ki67, Annexin V, and DAPI. We also tested CD97 KD cells for their ability to self-renew using clonogenic tumorsphere formation assays. Further, we utilized synthetic Abs (sAbs) generated against the ECD of CD97 to test for potential antitumor effects using patient-derived GBM cell lines. Results: CD97 mRNA expression was expressed at high levels in all GBM samples available in the TCGA cohort. We found high levels of surface CD97 protein expression in 6/6 patient-derived GBM cell cultures, but not human neural stem cells. Flow cytometry confirmed downregulation of CD97 in CD97 shRNA lentivirally transduced cells. CD97 KD induced a significant reduction in cell growth in 3 independent GBM cell lines representing mesenchymal and proneural subtypes, which was accompanied by reduced (~20%) Ki67 staining and increased (~30%) apoptosis. Incubation of GBM cells with sAbs (20 ug/ ml) against the ECD of CD97 for 3 days induced GSC differentiation, as determined by the expression of GFAP and Tubulin. Using three unique GBM patient derived cultures, we found that CD97 KD attenuated the ability of GBM cells to initiate sphere formation by over 300 fold, consistent with an impairment in GSC self-renewal. Conclusion: Loss of CD97 expression in patient-derived GBM cells markedly decreases proliferation, induces cell death, and reduces tumorsphere formation. sAbs against the ECD of CD97 reduce tumorsphere formation, recapitulating the phenotype of CD97 KD, suggesting that sAbs that inhibit CD97 function exhibit anti-tumor activity. Collectively, these findings indicate that CD97 is necessary for the proliferation and survival of human GBM cells and identify CD97 as a promising therapeutically targetable vulnerability in GBM.

Keywords : adhesion GPCR, CD97, GBM stem cell, glioblastoma
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