EGFR PHOSPHORYLATION OF DCBLD2 RECRUITS TRAF6 AND STIMULATES AKT-PROMOTED TUMORIGENESIS


BACKGROUND: Oncogenic EGFR-Akt signaling is aberrantly activated in human glioblastomas. Discoid, CUC, and LCCL domain containing protein 2 (DCBLD2, also known as CLCP1 and ESDN) is a neuropilin-like membrane protein that is up-regulated in vascular injury and metastatic lung cancers. However, the role of DCBLD2 in cancer is unclear. METHODS: We examined the expression of DCBLD2 in TCGA and other data bases of clinical glioma specimens. We assessed the effects of knockdown of endogenous DCBLD2 and re-express mutated DCBLD2 in glioma cells expressing EGFRvIII in vitro and in vivo. We performed IP-WB analyses to examine EGFR-induced tyrosine phosphorylation and DCBLD2 association with TRAF6. We also examined the impact of TRAF6 in EGFRvIII driven tumorigenesis and association of p-Y EGFR and p-Y750 of DCBLD2 with tumor prognosis. We used patient-derived glioma stem cells, primary short-term culture GBM cells and established glioma cell lines in vitro, orthotopic brain glioma xenografts, various biochemical methods and IHC analysis of de-identified clinical tumor specimens of glioma samples and HNC samples in our study. RESULTS: We found that DCBLD2 is up-regulated gene in glioblastomas and head and neck cancers (HNCs) and is required for EGFR-stimulated tumorigenesis. EGFR induces tyrosine phosphorylation (p-Y) of DCBLD2 including in Y750 residue within a binding motif for TNF receptor-associated factor 6 (TRAF6). Consequently, the induced p-DCBLD2Y750 recruits TRAF6 to DCBLD2. This association causes increased TRAF6 E3 ligase activity and subsequent activation of Akt, thereby enhancing EGFR-driven tumorigenesis. CONCLUSIONS: Our findings uncover a novel pathway by which DCBLD2 functions as a signal relay for oncogenic EGFR signaling in promoting tumorigenesis, a conclusion that is supported by the association of EGFR activation and DCBLD2 phosphorylation with poor prognoses for gliomas and HNCs. These data also nominate DCBLD2 and TRAF6 as attractive therapeutic targets for human cancers that are associated with EGFR activation. SECONDARY CATEGORY: n/a.