Summary

Intercellular crosstalk between patient-derived parotid gland cancer cells and CAFs via the BDNF/TRKB pathway

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The molecular features of parotid gland cancer (PGC) are not fully understood enough to develop an effective drug therapy because of the rarity. Given the poor prognosis of many human cancers in which TRKB is highly expressed, we investigated the involvement of the BDNF/TRKB pathway in PGC tissue using clinical specimens and observed high expressions of TRKB and BDNF in both tumor cells and stromal cells such as cancer-associated fibroblasts (CAFs). Therefore, to obtain more detail information of BDNF/TRKB signaling in PGC, we established primary co-culture system of patient-derived PGC cells and CAFs. In the culture system, PGC cells co-cultured with CAFs exhibited significant upregulation of BDNF and epithelial-mesenchymal transition (EMT). Similar results were observed in PGC cells treated with conditioned medium (CM) from co-culture of PGC cells and CAFs. TRK inhibitors suppressed BDNF- or CM-induced Snail upregulation and cell migration in PGC cells. Importantly, immunohistochemical and clinicopathological analyses of tumors from the patients with PGC revealed that TRKB expression levels in PGC cells were significantly correlated with aggressive features, including vascular invasion, nodal metastasis, and poor prognosis. Collectively, these data suggest that the BDNF/TRKB pathway regulates PGC cell aggressiveness via cross-talk with CAFs and is a potential therapeutic target for PGC harboring invasive and metastatic features.