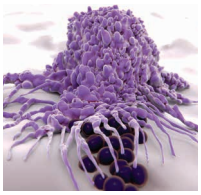
Glioblastoma

Major Finding: BACE1 inhibition reprograms macrophages to promote their phagocytosis of cancer cells reducing glioblastoma progression.

Concept: Tumor-promoting macrophages are maintained by BACE1 activation of IL6-sIL6R-STAT3 signaling.

Impact: This study supports the repurposing of BACE1 inhibitors from Alzheimer's disease to cancer therapy.

BACE1 INHIBITION STIMULATES MACROPHAGE PHAGOCYTOSIS OF GLIOBLASTOMA CELLS



Tumor-associated macrophages (TAM), when in high abundance, are associated with a poor prognosis in many tumor types including glioblastoma (GBM). Most TAMs located in the GBM microenvironment are tumor-promoting; therefore, reprogramming them into a more tumor-suppressive phenotype could improve therapy response. Zhai and colleagues, using a cell-based screen to detect small molecules able to activate TAM phagocytosis of GBM cells, identified an inhibitor targeting β-site amyloid precursor protein-cleaving enzyme 1 (BACE1; MK-8931), previously tested in clinical trials for Alzheimer disease. Treatment of GBM xenografts with MK-8931 led to an increase in TAM engulfment of glioma cells as compared with vehicle control as well as inhibited tumor growth and significantly extended survival of GBM xenograft-bearing mice. Additionally, MK-8931 induced apoptosis and reduced GBM cell proliferation *in vivo*. Further experiments revealed that treatment with the BACE1 inhibitor or genetic ablation of BACE1 induced a change in TAM phenotype, moving from a more tumor-promoting (M2) phenotype to one more tumor suppressive (M1), which aids in this BACE1-mediated suppression of tumor growth. Combination of MK-8931 with low-dose radiation, known to induce macrophage infiltration, further suppressed tumor growth and extended survival in mouse models. To elucidate how BACE1 promotes TAM polarization, the role of key transcriptional regulators of M2 polarization, STAT3 and STAT6, was investigated and showed that STAT3, but not STAT6, phosphorylation was significantly downregulated upon both genetic ablation or pharmacologic inhibition of BACE1, with ectopic expression of STAT3 rescuing the phenotype induced by BACE1 disruption or inhibition. STAT3 activation was determined to occur through BACE1 transmembrane protease activity where BACE1 cleaves IL6R into sIL6R activating the trans-IL6-sIL6R-STAT3 cascade. Moreover, investigation of clinical relevance revealed high BACE1 expression in GBM specimens was correlated with a worse prognosis. This study indicates the therapeutic promise of BACE1 in GBM through its effects on macrophage phagocytosis and polarization and suggests the repurposing of these inhibitors as an alternative to immunotherapy in cancers such as GBM. ■

Zhai K, Huang Z, Huang Q, Tao W, Fang X, Zhang A, et al. Pharmacological inhibition of BACE1 suppresses glioblastoma growth by stimulating macrophage phagocytosis of tumor cells. Nat Cancer 2021;2:1136–51.

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Drug Resistance

Major Finding: KRAS(G12C) inhibitor (G12Ci) resistance exhibits a heterogeneous pattern with no one dominant alteration.

Concept: Matched pre- and post-treatment specimens were genetically assessed for resistance-promoting alterations.

Impact: Lack of one dominant alteration suggests no all-inclusive treatment strategy for G12Ci resistance.

RESISTANT KRAS(G12C) INHIBITOR SUBCLONES EXHIBIT HETEROGENEOUS ALTERATIONS

Newly developed inhibitors targeting KRAS(G12C) have shown great promise, but potential resistance mechanisms are still under investigation. Zhao, Murciano-Goroff, Xue, Ang, and colleagues utilized paired liquid and/or tissue biopsies from 43 KRAS(G12C) inhibitor (G12Ci)-treated patients to gain genetic insight into the basis of resistance. No significant differences to baseline alterations were observed between exceptional responders and the rest of the cohort. However, in 27 of the 43 patients, treatment-induced alterations were identified and included secondary RAS alterations such as additional *KRAS* mutations or copy number gain, mutations in *NRAS*, non-V600E *BRAF* mutations, and other events including alterations to *EGFR*, *FGFR2*, *MET*, *MYC*, and *IDH1/2*. Lung and colorectal cancer patient-derived xenograft-bearing mice as well as isogenic cell lines with acquired resistance were used to gain additional insight into resistance mechanisms. Both models indicated secondary *RAS* mutations, as well as *BRAF* mutations, as critical variants in resistant models with a several-fold increase in secondary RAS mutations in the G12Ci treatment group as compared to the untreated group. To assess if these secondary mutations, either in *RAS* or *BRAF*, are enough to induce G12Ci resistance, drug-sensitive cells were engineered to express doxycycline-inducible mutants and, upon their expression, inhibition of downstream signaling was found to be attenuated as were the anti-proliferative effects, but target engagement by the drug remained unaffected. CRISPR-Cas9 screens were used to identify other vulnerabilities in these resistant cells and identified the depletion of several ERK signaling intermediates such as *SHOC2*, *ERK2*, *NRAS*, *CRAF*, and *BRAF* after G12Ci treatment. Combination treatments of G12Ci along with inhibitors of MEK, ERK, or RAF dimerization led to a more pronounced anti-proliferative effect in the presence of secondary mutations as compared to single therapy alone. This study reports heterogeneous genetic resistance alterations that emerge with KRAS(G12C) inhibitor treatment with the lack of a dominant resistance alteration suggesting the need for future biomarker-driven prospective clinical trials for patients who progress on G12Ci monotherapy. ■

Zhao Y, Murciano-Goroff YR, Xue JY, Ang A, Lucas J, Mai TT, et al. Diverse alterations associated with resistance to KRAS(G12C) inhibition. Nature 2021;599:679–83.

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