PI3Kγ

Precision medicine in oncology leverages clinical observations of exceptional response. Toward an understanding of the molecular features that define this response, Li et al. applied an integrated, multiplatform analysis of RNA profiles derived from clinically annotated glioblastoma samples. This analysis suggested that specimens from exceptional responders are characterized by decreased accumulation of microglia/macrophages in the glioblastoma microenvironment. Glioblastoma-associated microglia/macrophages secreted interleukin 11 (IL11) to activate STAT3-MYC signaling in glioblastoma cells. This signaling induced stem cell states that confer enhanced tumorigenicity and resistance to the standard-of-care chemotherapy, temozolomide (TMZ). Targeting a myeloid cell restricted an isoform of phosphoinositide-3-kinase, phosphoinositide-3-kinase gamma isoform (PI3Kγ), by pharmacologic inhibition or genetic inactivation disrupted this signaling axis by reducing microglia/macrophage-associated IL11 secretion in the tumor microenvironment. Mirroring the clinical outcomes of exceptional responders, PI3Kγ inhibition synergistically enhanced the anti-neoplastic effects of TMZ in orthotopic murine glioblastoma models. Moreover, inhibition or genetic inactivation of PI3Kγ in murine glioblastoma models recapitulated expression profiles observed in clinical specimens isolated from exceptional responders. Our results suggest key contributions from tumor-associated microglia/macrophages in exceptional responses and highlight the translational potential for PI3Kγ inhibition as a glioblastoma therapy [1)]

1)
Li J, Kaneda MM, Ma J, Li M, Shepard RM, Patel K, Koga T, Sarver A, Furnari F, Xu B, Dhawan S, Ning J, Zhu H, Wu A, You G, Jiang T, Venteicher AS, Rich JN, Glass CK, Varner JA, Chen CC. PI3Kγ inhibition suppresses microglia/TAM accumulation in glioblastoma microenvironment to promote exceptional temozolomide response. Proc Natl Acad Sci U S A. 2021 Apr 20;118(16):e2009290118. doi: 10.1073/pnas.2009290118. PMID: 33846242.