TARGETING CD73 MAY IMPROVE IMMUNOTHERAPY EFFICACY IN GliOBLASTOMA

Immune-checkpoint blockade’s (ICB) efficacy in some cancer types vastly exceeds its efficacy in other cancer types. Although the reasons for these disparities are not fully understood, some recent studies have pointed to differences in the tumor-infiltrating lymphocyte (TIL) populations associated with different cancer types. Goswami, Walle, Cornish, Basu, and colleagues compared immune infiltrates in tumors from patients with non–small cell lung cancer, renal cell carcinoma, colorectal cancer without microsatellite instability, prostate cancer, and glioblastoma multiforme. This analysis revealed differences in the phenotypes of TILs across these cancer types; of note, CD73hi macrophages were overrepresented in glioblastomas, which are notoriously resistant to ICB. CD73hi cells exhibited high expression of MARCO, TGFB, and multiple SIGLEC genes. In data from The Cancer Genome Atlas, this CD73hi gene signature was associated with poorer overall survival in patients with glioblastoma. Additionally, analysis of glioblastoma samples from patients treated with anti–PD-1 therapy showed that the treatment did not cause a marked shift in the tumor microenvironment, which remained enriched with CD73hi cells that may have inhibited the infiltration of T cells and contributed to the lack of clinical response to ICB. In a mouse model of glioblastoma, Nt5e (encoding CD73) knock-out increased the efficacy of combination therapy with anti–PD-1 and anti-CTLA4. Mechanistically, this enhanced efficacy may have been related to an observed increase in T-cell infiltration and macrophage polarization in Nt5e-knockout mice. In summary, this study provides multiple lines of evidence that CD73 expression may be a key mediator of response to immune-checkpoint blockade. Preclinical and early clinical studies have demonstrated promising results for treatment with anti-CD73, and this study suggests that the addition of anti-CD73 may be a useful strategy to improve outcomes in patients with glioblastoma treated with other immunotherapies.


Metabolism

Major Finding: A mutant RAS-induced redistribution of V-ATPase to membranes mediated macropinocytosis in cells.

Concept: In a KRAS-mutant pancreatic cancer mouse model, knockdown of SLC4A7 reduced tumor growth.

Impact: This work sheds light on mutant RAS-induced macropinocytosis, which fuels tumor growth.

V-ATPASE LOCALIZATION MEDIATES MUTANT RAS–INDUCED MACROPINOCYTOSIS

Oncogenic mutations in RAS proteins can enhance macropinocytosis, a cellular process implicated in both tumorigenesis and metastasis—by which certain nutrients are endocytosed from the environment. Ramirez, Hauser, and colleagues found that vacuolar ATPase (V-ATPase), a transmembrane protein complex responsible for transducing protons across cellular and organellar membranes, is vital for RAS-mediated macropinocytosis. Expression of oncogenic RAS mutant proteins (HRASG12V or KRAS G12V) caused redistribution of V-ATPase from the cytoplasm to the plasma membrane, a critical step in macropinocytosis. Cells in which plasma membrane V-ATPase was depleted exhibited abnormal cholesterol trafficking, reducing the membrane association of RAC1, the proper localization of which is required for the membrane-ruffling step of macropinocytosis. Further experiments revealed that macropinocytosis caused by expression of oncogenic RAS mutants was dependent on the soluble adenylate cyclase (sAC)-protein kinase A pathway. The fact that sAC activation is highly dependent on bicarbonate availability prompted an investigation of the source of bicarbonate in cells exhibiting mutant RAS-mediated macropinocytosis. Experiments aimed at addressing this question showed that the process depended on mutant RAS-induced upregulation of the expression of SLC4A7, a sodium bicarbonate cotransporter. In a mouse xenograft model of KRAS-mutant pancreatic cancer, shRNA-mediated SLC4A7 knockdown reduced tumor growth and, in some cases, was even associated with tumor regression. Notably, this effect was not seen in mice xenografted with human pancreatic cancer cells expressing wild-type KRAS, providing further evidence for the specific role of SLC4A7 in pancreatic cancer harboring mutations affecting RAS proteins. Collectively, this work provides a foundational understanding of a key pathway underlying macropinocytosis in cancer cells and demonstrates its relevance in a mouse model of pancreatic cancer.

V-ATPase Localization Mediates Mutant RAS–Induced Macropinocytosis