Immune Evasion

Major finding: Structural variations in the *PD-L1 3′*-UTR promote elevated PD-L1 expression and immune escape.

Concept: *PD-L1* transcripts are stabilized by truncation of the 3′-UTR in multiple cancer types.

Impact: Detecting *PD-L1 3′*-UTR–disrupting alterations may identify tumors that can evade antitumor immunity.

STRUCTURAL VARIATIONS DISRUPTING THE *PD-L1 3′*-UTR ENABLE IMMUNE EVASION

Immunotherapy targeting programmed cell death 1 (PD-1) or its ligand (PD-L1) has been successful in preventing immune escape in many patients with advanced cancer. *PD-L1* amplifications or translocations promote immune escape in some tumor types; however, in tumors lacking these alterations, the genetic mechanisms underlying PD-1/PD-L1–mediated immune escape remain unclear. Using whole-genome and RNA sequencing of structural variations (SV) in adult T-cell leukemia/lymphoma, Kataoka, Shiraishi, Takeda, and colleagues identified a prominent recurrent breakpoint cluster within the 3′ region of the *PD-L1* locus. Alterations at this locus resulted in elevated expression of abnormal *PD-L1* transcripts lacking an intact 3′ untranslated region (UTR), and increased expression of aberrant but functional PD-L1 proteins. Evaluation of tumor samples from The Cancer Genome Atlas revealed clonal selection of cells carrying aberrant 3′-UTR–truncated *PD-L1* transcripts in multiple tumor types, including diffuse large B-cell lymphoma and stomach adenocarcinoma. To determine if 3′-UTR loss was responsible for the SV-associated increase in *PD-L1* expression, CRISPR/Cas9 was used to introduce large deletions/inversions in the *PD-L1* 3′-UTR; disruption of the 3′-UTR resulted in elevated PD-L1 expression. Moreover, a tumor cell line expressing both wild-type and 3′-UTR–disrupted *PD-L1* exhibited delayed clearance of truncated *PD-L1* mRNA compared to wild-type *PD-L1*, suggesting that the 3′-UTR regulates *PD-L1* mRNA stability. Furthermore, loss of the *PD-L1* 3′-UTR in cancer cells enhanced T-cell apoptosis in co-culture experiments and attenuated antitumor immune responses *in vivo*. PD-L1 blockade restored cytotoxic T-cell infiltration and tumor regression in mice harboring *PD-L1* 3′-UTR–disrupted tumors, indicating that PD-L1 overexpression as a result of disruption of the 3′-UTR allowed cells to escape antitumor immunity. Taken together, these findings identify a mechanism by which PD-L1 expression can be enhanced to promote immune escape, and suggest that *PD-L1* 3′-UTR disruption may be a genetic marker for immune-evading tumors that may respond to PD-1/PD-L1 blockade. ■

Kataoka K, Shiraishi Y, Takeda Y, Sakata S, Matsumoto M, Nagano S, et al. Aberrant PD-L1 *expression through 3′-UTR disruption in multiple cancers. Nature 2016 May 23 [Epub ahead of print].*

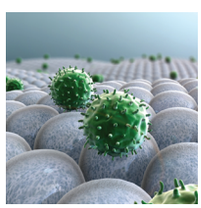
Tumor Microenvironment

Major finding: Macrophage-derived IGF1 drives acquired resistance to CSF1R blockade in mouse models of GBM.

Mechanism: IL4 induces secretion of IGF1 from TAMs, activating IGF1R and PI3K signaling in tumor cells.

Impact: Combined inhibition of CSF1R and IGF1R or PI3K may improve overall survival in patients with GBM.

THE TUMOR MICROENVIRONMENT MEDIATES GBM RESISTANCE TO CSF1R BLOCKADE



Therapeutic targeting of the tumor microenvironment is a promising strategy for treating glioblastoma multiforme (GBM), which is characterized by abundant tumor-associated macrophages (TAM). Colony-stimulating factor-1 receptor (CSF1R) inhibitors targeting these TAMs have shown activity in mouse models of high-grade GBM and are under evaluation in clinical trials. However, the long-term effects of CSF1R blockade in GBM are unknown, prompting Quail and colleagues to investigate whether CSF1R inhibition leads to acquired resistance. In a mouse model of GBM, treatment with a small-molecule inhibitor of CSF1R, BLZ945, resulted in substantial tumor regression in all animals, followed by a dormancy phase and the acquisition of drug resistance in 56% of mice. Recurrent tumors exhibited increased PI3K signaling, and combined treatment with the PI3K inhibitor BKM120 extended median survival, indicating that PI3K signaling underlies CSF1R inhibitor resistance. This resistance was mediated by the tumor microenvironment, as intracranially transplanted GBM cells isolated from recurrent tumors responded to CSF1R inhibition with BLZ945 in naïve hosts. Recurrent tumors developed adjacent to glial scarring and harbored protumorigenic TAMs that exhibited upregulation of a wound-associated gene program driven by IL4. In particular, expression of the IL4 target gene *Igf1* in rebound TAMs was mediated by the NFAT and STAT6 transcription factors and stimulated the proliferation of recurrent tumor cells via activation of tumor cell IGF1R and downstream PI3K signaling. Consequently, treatment with an IGF1R inhibitor, OSI906, in combination with CSF1R blockade extended survival in genetic models of GBM and patient-derived orthotopic xenografts. Together, these results provide a mechanism by which the tumor microenvironment can promote resistance to CSF1R blockade, and suggest that combined inhibition of IGF1R, PI3K, or NFAT may improve survival in patients with GBM. ■

Quail DF, Bowman RL, Akkari L, Quick ML, Schuhmacher AJ, Huse JT, et al. The tumor microenvironment underlies acquired resistance to CSF-1R inhibition in gliomas. Science 2016;352:aad3018.