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 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 coculture 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.


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**The Tumor Microenvironment Mediates GBM Resistance to CSF1R Blockade**

The 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 naive hosts. Recurrent tumors developed adjacent to gliotic scar tissue 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.

Structural Variations Disrupting the PD-L1 3’-UTR Enable Immune Evasion


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