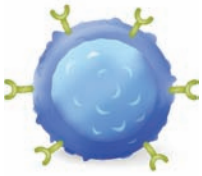
Lymphoma

Major finding: Targeting the *TRBC* gene expressed by T-cell malignancies mitigates severe immunosuppression.

Concept: T-cell lymphomas express either *TRBC1* or *TRBC2*, which can then be selectively targeted.

Impact: T-cell receptor β-chain constant region–targeting CAR T cells may be efficacious in patients with lymphoma.

THE T-CELL RECEPTOR β-CHAIN IS AN IMMUNOTHERAPY TARGET FOR LYMPHOMAS



Although there are no antigens that are selectively expressed by B-cell malignancies, CAR T cells targeting pan–B cell antigens have been effective and well tolerated in spite of the resulting B-cell aplasia. The αβ T-cell receptor (TCR) is a pan–T cell antigen that is highly expressed by peripheral T-cell lymphomas (PTCL). However, targeting the αβ TCR would result in severe immunosuppression due to T-cell aplasia, and generating a bespoke reagent for each patient's T-cell clone is impractical. Because T cells mutually exclusively express either *TRBC1* and *TRBC2*, which are the two genes associated with the TCR β-chain constant region, Maciocia and colleagues sought to determine whether targeting either TRBC1 or TRBC2 would be an effective and safe immunotherapeutic approach for patients with PTCL. Screening of Jurkat T cells expressing either TRBC1 or TRBC2 with a panel of anti-TCR antibodies revealed that the JOVI-1 mAb exhibited high specificity for TRBC1, and structural analysis identified the residues comprising the discriminating JOVI-1 epitope in TRBC1 that are targeted by JOVI-1. Flow cytometric analysis of JOVI-1–stained T cells from healthy donors or malignant T cells showed that normal αβ TCR T-cell populations are comprised of both $TRBC1^+$ and $TRBC2^+$ T cells; however, leukemia and lymphoma cell lines and malignant T cells from patients with leukemia were homogenous $TRBC1^+$ or $TRBC2^+$ populations. CAR T cells expressing the JOVI-1 ScFv exhibited selective toxicity against $TRBC1^+$ T cell malignancy–derived cell lines and T cells from patients with $TRBC1^+$ leukemias or PTCL. Further, anti-TRBC1 treatment of mice injected with $TRBC1^+$ Jurkat cells resulted in the depletion of disseminated $TRBC1^+$ malignant and normal T cells and the persistence of normal $TRBC2^+$ T cells. These results provide evidence that patients with T-cell malignancies may benefit from immunotherapies that target the TCR β-chain constant region with acceptable levels of immunosuppression. ■

Maciocia PM, Wawrzyniecka PA, Philip B, Ricciardelli I, Akarca AU, Onuoha SC, et al. Targeting the T cell receptor β-chain constant region for immunotherapy of T cell malignancies. Nature Med 2017;23:1416–23.

Immunology

Major finding: MYC promotes angiogenesis, inflammation, and immune suppression to accelerate $KRAS^{G12D}$ tumor growth.

Mechanism: MYC induces CCL9 and IL23 to stimulate angiogenesis, macrophage influx, and loss of T, B, and NK cells.

Impact: MYC remodels the stroma to create an immune-suppressive microenvironment that facilitates tumor progression.

MYC INDUCES IMMUNE SUPPRESSION TO PROMOTE LUNG TUMORIGENESIS

The *KRAS* and *MYC* oncogenes cooperate to drive tumorigenesis, and *KRAS* mutations and MYC overexpression occur frequently in patients with non–small cell lung cancer. However, the mechanisms underlying their cooperation have not been elucidated. Kortlever and colleagues used a mouse model of $KRAS^{G12D}$-driven lung cancer with inducible and reversible MYC expression to understand the contribution of MYC in KRAS-driven tumorigenesis. Induction of MYC expression in lung epithelial cells accelerated $KRAS^{G12D}$-driven lung tumorigenesis, but MYC expression did not affect the lung phenotype in the absence of $KRAS^{G12D}$. Tumors driven by MYC and $KRAS^{G12D}$ were more aggressive, exhibiting enhanced proliferation, invasion, inflammation, and angiogenesis compared with tumors driven by $KRAS^{G12D}$ alone. MYC induced rapid widespread changes to the tumor stroma, including an influx of $CD206^+$ macrophages, a loss of $CD3^+$ T cells and $B220^+$ B cells, a reduction in natural killer (NK) cells, and the onset of angiogenesis. These MYC-driven stromal changes were mediated by induction of the MYC effectors CCL9 and IL23, and blockade of CCL9 and IL23 suppressed the MYC-driven effects and induced apoptosis, resulting in a reduction in tumor burden *in vivo*. Tumors driven by MYC and $KRAS^{G12D}$ rapidly became dependent upon MYC expression, as removal of MYC expression resulted in decreased tumor cell proliferation, an efflux of macrophages, normalization of the vasculature, and an influx of T cells and NK cells. The tumor regression induced by MYC loss was NK cell–dependent and independent of $CD4^+$ and $CD8^+$ T cells, but MYC deactivation did not lead to a complete tumor regression. In addition to elucidating a mechanism by which MYC cooperates with $KRAS^{G12D}$ to promote lung tumorigenesis, these findings reveal a role for MYC in programming an immunosuppressive tumor microenvironment. ■

Kortlever RM, Sodir NM, Wilson CH, Burkhart DL, Pellegrinet L, Brown Swigart L, et al. Myc cooperates with Ras by programming inflammation and immune suppression. Cell 2017;171:1301–15.

Research Watch is written by *Cancer Discovery* editorial staff. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.