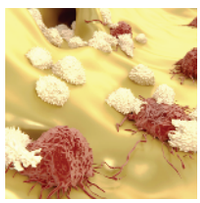
Immune Evasion

Major finding: Co-inhibition of TIGIT and PDL1 promotes CD8+ T-cell effector function and prevents tumor growth.

Mechanism: TIGIT drives CD8+ T-cell dysfunction by disrupting CD226 homodimerization *in cis*.

Impact: TIGIT may represent a useful immunotherapy target in cancer and chronic viral infections.

TIGIT PROMOTES TUMOR IMMUNE ESCAPE VIA CD8+ T-CELL EXHAUSTION



Tumor cells evade endogenous immune responses via upregulation of inhibitory receptors such as programmed cell death 1 (PD-1) and its ligand PD-L1 and exhaustion of infiltrating tumor-specific T cells. Reactivation of immune responses by blocking these inhibitory signals has achieved significant clinical success in certain types of cancer, prompting Johnston and colleagues to search for additional T-cell inhibitory receptors. Analysis of a tumor-associated T-cell–specific gene signature across a panel of various solid tumors revealed that expression of the co-inhibitory receptor T-cell immunoreceptor with Ig and ITIM domains (TIGIT) was increased in CD8+ and CD4+ tumor-infiltrating lymphocytes (TIL) and was correlated with expression of PD-1, suggesting that TIGIT contributes to the regulation of exhausted TILs and antitumor immune responses. Consistent with this idea, co-inhibition of PD-L1 and TIGIT, but not either protein alone, led to tumor shrinkage in immune-competent murine tumor models and a protective antitumor response that prevented the growth of reinoculated tumor cells. Importantly, combined PD-L1 and TIGIT blockade was unable to prevent tumor formation in mice depleted of CD8+ T cells. Co-inhibition of PD-L1 and TIGIT enhanced proinflammatory cytokine production by CD8+, but not CD4+, T cells both in a tumor context and following chronic viral infection, suggesting that PD-1/PD-L1 and TIGIT synergistically inhibit CD8+ effector T-cell activity. Mechanistically, the antitumorigenic functions of TIGIT were dependent on CD226, TIGIT's complementary costimulatory receptor. Binding of TIGIT to CD226 on the cell surface prevented CD226 homodimerization and limited its activation, and CD226 blockade prevented the ability of anti-TIGIT antibody to enhance the function of CD8+ TILs. Together, these results highlight a role for TIGIT in suppressing chronic CD8+ T-cell responses and provide a rationale for cotargeting inhibitory receptors in the treatment of cancer and viral infections. ■

Johnston RJ, Comps-Agrar L, Hackney J, Yu X, Huseni M, Yang Y, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8+ T cell effector function. Cancer Cell 2014;26:923–37.

Tumor Suppressors

Major finding: Upregulation of *IAPP* drives metabolic reprogramming and p53-deficient tumor regression.

Mechanism: IAPP (also known as amylin) inhibits glycolysis and induces ROS and apoptosis via CALCR and RAMP3.

Impact: A synthetic analogue of amylin may represent a therapeutic strategy for p53-deficient cancers.

INDUCTION OF METABOLIC REPROGRAMMING SUPPRESSES p53-NULL TUMOR GROWTH

Loss or mutation of the tumor suppressor p53 is one of the most common genetic alterations in human cancer. Restoration of wild-type p53 function has been shown to effectively suppress tumor growth in mice, but has proven difficult to achieve in patients. Venkatanarayan and colleagues found that manipulation of the p53 family members p63 and p73 in the context of p53 deficiency reactivated tumor-suppressive signaling pathways to promote tumor regression. Conditional knockout of the dominant-negative isoforms of p63 (ΔNp63) or p73 (ΔNp73) in *Trp53*-null mice significantly reduced thymic lymphoma growth via induction of apoptosis and senescence and extended tumor-free survival. This tumor-suppressive effect was associated with upregulation of the acidic transactivation domain–bearing (TA) isoforms of p63 and p73. RNA sequencing analysis of ΔNp63- and ΔNp73-deficient thymic lymphomas revealed increased expression of several genes involved in metabolic regulation, in particular islet amyloid polypeptide (*IAPP*), which encodes amylin and was transcriptionally regulated by TAp63 and TAp73. Expression of *IAPP* resulted in a reduced rate of glycolysis and increased reactive oxygen species (ROS) and apoptosis in both murine and human p53-deficient cancer cells, and induced tumor regression of p53-deficient thymic lymphomas in mice. Similarly, treatment with pramlintide, a synthetic amylin analogue, inhibited glycolysis and resulted in rapid tumor regression. Mechanistically, secreted amylin suppressed p53-deficient tumor growth via interaction with the calcitonin receptor (CALCR) and receptor activity modifying protein 3 (RAMP3), as depletion or inhibition of either receptor ablated the antitumor effects of increased IAPP *in vitro* and *in vivo*. Furthermore, coexpression of IAPP, CALCR, and RAMP3 correlated with improved survival in several cancer types. These data identify *IAPP* as a tumor suppressor gene and provide preclinical evidence that pharmacologic induction of amylin-driven metabolic reprogramming may be an effective therapeutic strategy in p53-deficient cancers. ■

Venkatanarayan A, Raulji P, Norton W, Chakravarti D, Coarfa C, Su X, et al. IAPP-driven metabolic reprogramming induces regression of p53-deficient tumors in vivo. Nature 2014 Nov 17 [Epub ahead of print].