THE NSCLC MUTATIONAL LANDSCAPE INFLUENCES RESPONSE TO PD-1 BLOCKADE

Inhibition of the immune checkpoint receptor programmed cell death 1 (PD-1) has shown clinical activity in a subset of patients with non–small cell lung cancer (NSCLC), but the mechanisms underlying sensitivity to PD-1 blockade are not well understood. To gain insight into the genetic determinants of response to anti–PD-1 therapy, Rizvi, Hellmann, Snyder, and colleagues performed whole-exome sequencing of NSCLCs and matched normal tissues from patients enrolled in a phase I study of the anti–PD-1 antibody pembrolizumab. A significantly greater number of patients with a high nonsynonymous mutation burden experienced a durable partial or stable response than patients with a low mutation burden, and the objective response rate and progression-free survival were significantly higher in patients with a high nonsynonymous mutation burden than those with a lower burden. Of note, pembrolizumab efficacy was greatest in patients with a smoking-associated mutational signature, which correlated with nonsynonymous mutation burden. A high nonsynonymous mutational burden was correlated with a higher quantity of putative neoantigens with high binding affinity to patient-specific HLA alleles, and patients who had a durable clinical response had a higher neoantigen burden than those who did not, suggesting that T-cell responses to neoantigens created by somatic mutations may underlie pembrolizumab activity in NSCLC. Indeed, a T-cell response against a mutation-associated neoantigen was detected in peripheral blood lymphocytes from one responder after the initiation of pembrolizumab treatment and correlated with tumor regression, also raising the possibility that a blood-based assay may be used to assess response to PD-1 blockade. Collectively, these observations suggest that recognition of neoantigens created by nonsynonymous mutations may underlie the activity of PD-1 inhibition in NSCLC, that nonsynonymous mutation burden may be a predictive biomarker of response to anti–PD-1 therapy, and that immunotherapy may be especially beneficial for smoking-associated lung cancers.


Immunotherapy

**Major finding:** The nonsynonymous mutation burden is associated with pembrolizumab efficacy in NSCLC.

**Clinical relevance:** PD-1 blockade was most effective against tumors with a smoking-associated mutation signature.

**Impact:** Nonsynonymous mutation burden may be a predictive biomarker of response to anti–PD-1 therapy in NSCLC.

Tumor Suppressors

**Major finding:** p53 sensitizes cells to ferroptosis through repression of SLC7A11 to suppress tumor growth.

**Mechanism:** SLC7A11 repression by p53 reduces cystine uptake and induces ferroptosis upon ROS stress.

**Impact:** p53 regulation of ferroptosis is independent of cell-cycle arrest, apoptosis, and senescence.

**p53 PROMOTES FERROPTOSIS DURING ROS STRESS TO SUPPRESS TUMORIGENESIS**

Many human cancers exhibit inactivation of p53, which is important for stress-induced cell-cycle arrest, apoptosis, and senescence. These functions of p53 are thought to underlie its tumor-suppressive activity and are regulated by acetylation of p53. However, an acetylation-defective mutant p53 (p53KR) retains tumor-suppressive functions, suggesting a role for the modulation of metabolic p53 targets in tumor suppression. Jiang, Kon, and colleagues found that p53 bound the promoter region of solute carrier family 7 member 11 (SLC7A11), which encodes a component of the cystine/glutamate antiporter, resulting in reduced expression of SLC7A11 and decreased cystine uptake. Acetylation-defective mutant p53KR retained the ability to transcriptionally inhibit SLC7A11 expression and suppress cystine uptake, similar to wild-type p53, indicating that this function is independent of the role of p53 in cell-cycle arrest, apoptosis, and senescence. p53-mediated repression of SLC7A11 resulted in the induction of ferroptosis, an iron-dependent, non-apoptotic form of cell death, in both p53-wild-type and p53KR cells in response to reactive oxygen species (ROS)–induced stress, but not DNA damage. Importantly, SLC7A11 was upregulated in multiple types of human cancers, and overexpression of SLC7A11 rescued human cancer cells from p53KR-induced ferroptosis and significantly diminished the tumor-suppressive function of p53KR in xenograft models, indicating that repression of SLC7A11 is necessary for the tumor-suppressive function of p53. Furthermore, p53-mediated suppression of Slc7a11 and induction of ferroptosis contributed to the developmental abnormalities observed in Mdm2-null embryos, supporting a role for p53-driven metabolic regulation in embryonic development. Together, these data identify a critical role of this noncanonical metabolic function of p53 in tumor suppression via the regulation of SLC7A11-dependent ferroptotic cell death.

p53 Promotes Ferroptosis during ROS Stress to Suppress Tumorigenesis

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