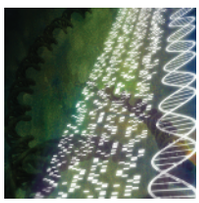
Immunotherapy

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.

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. ■

Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124–8.

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 ($p53^{3KR}$) 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 $p53^{3KR}$ 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, nonapoptotic form of cell death, in both p53–wild-type and $p53^{3KR}$ 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 $p53^{3KR}$-induced ferroptosis and significantly diminished the tumor-suppressive function of $p53^{3KR}$ 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. ■

Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, et al. Ferroptosis as a p53-mediated activity during tumor suppression. Nature 2015;520:57–62.

Note: *Research Watch* is written by *Cancer Discovery* Science Writers. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.