Immunotherapy

Major finding: Anti–PD-1 and anti–PD-L1 antibodies elicit durable objective responses in phase I trials.

Clinical relevance: Tumors resistant to other types of immunotherapy respond to blockade of PD-1/PD-L1.

Impact: PD-1/PD-L1 immunotherapy is safe and effective in a wide spectrum of pretreated solid tumors.

PD-1/PD-L1 IMMUNOTHERAPY IS EFFECTIVE IN ADVANCED SOLID TUMORS

Many solid tumors selectively express programmed death 1-ligand 1 (PD-L1), which suppresses T-cell functions by binding programmed death 1 (PD-1), an inhibitory receptor expressed on activated lymphocytes. Blocking the PD-1/PD-L1 interaction may therefore be a broadly effective way to stimulate antitumor immune responses while minimizing immune-related toxicity. Topalian and colleagues evaluated an anti–PD-1 antibody, and Brahmer and colleagues evaluated an anti–PD-L1 antibody in phase I dose-escalation studies in patients with advanced solid tumors. Complete or partial responses to the anti–PD-1 and anti–PD-L1 blocking antibodies were observed in non–small cell lung cancer (18% and 10% of patients, respectively), melanoma (28% and 17% of patients, respectively), and renal cell cancer (27% and 12% of patients, respectively), with stable disease lasting 24 weeks or longer in additional patients. These findings were particularly striking given that lung cancers have been resistant to other forms of immunotherapy and that many of the study patients had been heavily pretreated with cytotoxic and targeted therapies. Importantly, among responding patients with at least 1 year of follow-up, durable responses of 1 year or longer were observed in two thirds of patients treated with anti–PD-1 and half of patients treated with anti–PD-L1, indicative of a persistent antitumor immune response. Additionally, immunohistochemical analysis of a subset of pretreatment tumor biopsies indicated that objective responses to anti-PD-1 only occurred in patients whose tumors expressed PD-L1, suggesting that PD-L1 expression may be a useful marker to identify potential responders. Significant drug-related adverse events were observed in only 14% and 9% of patients treated with anti-PD-1 and anti-PD-L1 antibodies, respectively, although 3 of 296 patients died of anti–PD-1-related pulmonary toxicity. Targeting the PD-1/PD-L1 pathway may thus be a safe, effective way to induce immune responses to advanced solid tumors. Phase II trials are currently under way. ■

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012 Jun 2 [Epub ahead of print].

Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012 Jun 2 [Epub ahead of print].

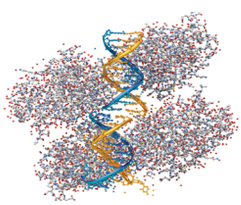
Drug Discovery

Major finding: An *in silico* screen identifies compounds that specifically inhibit p53-mutant cells.

Mechanism: Zinc chelation and redox changes promote restoration of $p53^{R175}$ to the wild-type conformation.

Impact: Thiosemicarbazones may represent lead compounds for targeting mutant p53 alleles.

MUTANT p53 ALLELES CAN BE RESTORED TO THE WILD-TYPE CONFORMATION



The majority of *TP53* mutations are missense mutations that affect the structural properties of the p53 protein and result in a gain-of-function phenotype. As *TP53* is the most commonly mutated gene in human tumors, pharmacologic inhibition of mutant p53 activity would likely have clinical benefit. Yu and colleagues ranked the 48,129 chemical compounds used in the National Cancer Institute anticancer drug screen of 60 cancer cell lines for their ability to preferentially inhibit the growth of p53-mutant cells. Among the highest scoring compounds were thiosemicarbazones, metal ion chelators that inhibit DNA synthesis at high concentrations. One compound, NSC319726, was nontoxic to wild-type cells but potently inhibited the growth of cells with an arginine-175 mutation ($p53^{R175}$). Interestingly, NSC319726 treatment rendered $p53^{R175}$ unrecognizable by a mutant conformation-specific p53 antibody, suggesting that this compound could restore the wild-type protein structure in $p53^{R175}$-mutant cells. Indeed, binding by the wild-type–specific p53 antibody increased after NSC319726 treatment and was accompanied by the restoration of p53 promoter binding and transactivation of target genes *p21*, *PUMA*, and *MDM2*. NSC319726 treatment led to widespread apoptosis in $p53^{R175}$-knockin mice and significant growth inhibition of $p53^{R175}$ tumor xenografts, further indicating that this compound can reactivate normal p53 function. The activity of NSC319726 was dependent on its metal ion chelating and oxidative properties, suggesting that NSC319726 may promote refolding of the $p53^{R175}$ mutant by acting as a metallochaperone and regulating cellular redox levels. The identification of thiosemicarbazone compounds as selective inhibitors of p53-mutant cells that restore wild-type p53 structure and function suggests that targeting specific p53 mutant alleles may be a viable therapeutic option. ■

Yu X, Vazquez A, Levine AJ, Carpizo DR. Allele-specific p53 mutant reactivation. Cancer Cell 2012;21:614–25.

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