Genomics

Major finding: The IPRES signature is related to anti–PD-1 response, and high mutational load predicts survival.

Approach: Mutational and transcriptomic landscapes were generated from melanomas treated with anti–PD-1.

Impact: Targeting IPRES-related biological processes may enhance response to anti–PD-1 therapy.

A SET OF TRANSCRIPTOMIC CHANGES IS ASSOCIATED WITH ANTI–PD-1 RESISTANCE

Immune checkpoint blockade therapy targeting programmed cell death 1 (PD-1) has been efficacious against a number of cancer types, most prominently melanoma. However, patients with metastatic melanoma frequently exhibit innate resistance to anti–PD-1 therapy due to unknown molecular mechanisms. To identify the genomic determinants of anti–PD-1 response in patients with melanoma, Hugo, Zaretsky, and colleagues performed whole-exome sequencing (WES) and transcriptomic profiling of melanomas from patients treated with anti–PD-1 antibodies, a subset of whom had received prior MAPK inhibitor (MAPKi) treatment. WES of melanomas from responding and nonresponding patients showed that while high mutational load correlated with improved patient survival, there was no statistically significant association between high mutational load and response to anti–PD-1 therapy. Examination of individual mutations revealed that *BRCA2* was more frequently mutated in anti–PD-1 responsive melanomas than in nonresponsive melanomas. Bioinformatic analysis of differentially enriched gene sets identified the innate anti–PD-1 resistance (IPRES) signature, which consisted of a set of co-enriched gene sets in nonresponders. A subset of these gene sets were found to be induced by MAPKi. The IPRES signature represented a group of 26 transcriptomic signatures associated with increased mesenchymal transition, inflammation, wound healing, and angiogenesis. Similarly, gene ontology analysis of differentially expressed genes showed that nonresponding tumors exhibited upregulation of genes associated with biological processes such as cell adhesion, extracellular matrix organization, response to wounding, and vasculature development. Examination of additional patient cohorts revealed that the IPRES signature was enriched more frequently in metastatic cutaneous melanoma compared to primary cutaneous melanoma and was enriched in subsets of other malignancies, such as lung adenocarcinoma and colon adenocarcinoma. Together, these results describe potential genomic determinants of response to anti–PD-1 therapy and suggest that treatment with anti–PD-1 or the combination of anti–PD-1 and MAPKi may be enhanced by targeting IPRES-related biological processes. ■

Hugo W, Zaretsky JM, Sun L, Song C, Moreno BH, Hu-Lieskovan S, et al. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. Cell 2016;165:35–44.

Immune Evasion

Major finding: MYC promotes tumorigenic immune evasion by inducing expression of CD47 and PD-L1.

Concept: CD47 and PD-L1 are required for the antitumor effects of MYC inactivation.

Impact: Immune checkpoint inhibitors may have a clinical benefit in MYC-overexpressing cancers.

MYC PROMOTES TUMORIGENESIS VIA ACTIVATION OF CD47 AND PD-L1

Activation of the oncogenic MYC transcription factor has been observed in a variety of cancers and is known to drive tumor initiation and maintenance in murine cancer models. Complete tumor clearance in mice following MYC suppression requires a host-dependent immune response, but the mechanism by which MYC triggers this response is unknown. To determine how MYC modulates antitumor immune responses, Casey and colleagues used a Tet-off murine model of MYC-dependent T-cell acute lymphoblastic leukemia (T-ALL). While MYC was expressed, Cluster of Differentiation 47 (CD47), an innate and adaptive immune regulator, and programmed death-ligand 1 (PD-L1), an immune checkpoint protein, were both expressed. However, suppression of MYC through the addition of tetracycline led to the rapid downregulation of CD47 and PD-L1 both *in vitro* and *in vivo*. In line with these findings, MYC knockdown or inhibition with the bromodomain inhibitor JQ1 in human T-ALL cells led to a similar reduction in CD47 and PD-L1 expression. MYC was also shown to regulate PD-L1 and CD47 in human melanoma, kidney, and liver tumor–derived cell lines. Chromatin immunoprecipitation sequencing analysis indicated that MYC directly regulates CD47 and PD-L1 at the transcriptional level by binding to their promoters. Further, suppression of CD47 and PD-L1 was required for immune-mediated tumor clearance following MYC inactivation, as forced expression of CD47 or PD-L1 in T-ALL cells following MYC inactivation prevented tumor regression by reducing the recruitment of T cells and macrophages to the tumor, maintaining angiogenesis, and blocking the induction of senescence. Together, these results suggest that MYC-mediated inhibition of innate and adaptive antitumor responses via activation of CD47 and PD-L1 contributes to tumor maintenance, and indicates that reactivation of antitumor immune responses, by either suppression of MYC or immune checkpoint blockade, may have a clinical benefit in cancer cells that overexpress MYC. ■

Casey SC, Tong L, Li Y, Do R, Walz S, Fitzgerald KN, et al. MYC regulates the antitumor immune response through CD47 and PD-L1. Science 2016;352:227–31.