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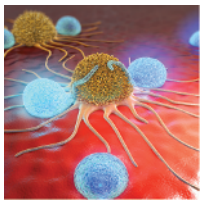
Immunotherapy

Major Finding: ICB response in mice could be predicted by pretreatment *Stat1* expression and depended on NK cells.

Concept: Pretreatment with a combination of IFNγ, anti–IL10, and poly(I:C) improved response to ICB.

Impact: Biomarkers identified in the study could be used to determine whether sensitization is needed prior to ICB.

ICB RESPONSE IS ASSOCIATED WITH PRETREATMENT STAT1 ACTIVATION



Response to immune checkpoint blockade (ICB) in cancer is highly variable, with some patients experiencing rapid recovery and others exhibiting no response. Some predictors of response to ICB have been reported, but none fully explain the differences. Using two mouse models, Zemek and colleagues found differences in the pretreatment microenvironment that correlated with response to ICB. Specifically, mice were inoculated bilaterally, allowing one tumor to be removed for analysis prior to treatment while the other's response to ICB with anti–PD-L1 and anti–CTLA4 was evaluated after treatment. Bulk and single-cell RNA sequencing along with flow cytometry revealed marked differences in gene regulation between ICB responders and nonresponders, with genes associated with type I and II interferon responses and inflammation enriched in responsive tumors in both mouse models. These gene sets were also enriched in patients with urothelial cancer who responded to the PD-L1 antibody atezolizumab. Weighted gene correlation network analysis identified signal transducer and activator of transcription 1 (*Stat1*) as a hub, and responsive tumors had greater proportions of cells with active (phosphorylated) STAT1. In both models, responding tumors had a greater proportion of natural killer (NK) cells, and depletion of NK cells prior to treatment revealed that NK cells were required for response to ICB. Pretreatment of mice with a combination of three treatments targeting regulators associated with ICB response in the pathway analysis—including IFNγ, anti–IL10, and the Toll-like receptor agonist poly(I:C)—resulted in a substantial improvement, from 0% to 10% response with ICB alone to up to 80% response in the pretreated group. Pretreatment increased the frequencies of NK cells, the presence of which was required for the improved ICB response. These results provide new biomarkers for response to ICB that could be used to help determine which patients will be immediate responders and which require pretreatment with other therapies to benefit from ICB. ■

Zemek RM, De Jong E, Chin WL, Schuster IS, Fear VS, Casey TH, et al. Sensitization to immune checkpoint blockade through activation of a STAT1/NK axis in the tumor microenvironment. Sci Transl Med 2019:11;eaav7816.

Cell Competition

Major Finding: Low-dose ionizing radiation (LDIR) induces proliferation of *Trp53*-mutant, but not wild-type, cells.

Concept: Antioxidant treatment in the context of LDIR provided a fitness advantage to *Trp53*–wild-type cells.

Impact: Interventions that provide a selective advantage to wild-type cells in aged tissue may be of interest.

OXIDATIVE STRESS CAN SHIFT THE BALANCE OF ESOPHAGEAL CELLS

With age, the human esophageal epithelium (EE) accumulates *TP53*-mutant cells, which may go on to develop into esophageal squamous cell carcinoma cells. Whether it's possible to shift the equilibrium toward healthy cells is not clear. Using mouse EE as a model tissue, Fernandez-Antoran and colleagues found, via genetic lineage tracing, that exposure to 50 mGy of low-dose ionizing radiation (LDIR)—equivalent to 3 to 4 CT scans—promoted differentiation of wild-type esophageal progenitor cells. In mouse primary EE cultures, LDIR increased mitochondrial oxidation, suggesting a mechanism for LDIR-induced cell differentiation. *In vivo*, immunostaining of a protein abundant in the nucleus after oxidative challenges (phosphoserine40 NRF) revealed that LDIR induced oxidative stress, but treatment with the antioxidant *N*-acetyl cysteine (NAC) abolished the differentiation of basal cells caused by LDIR exposure. In mice with some EE cells expressing a mutant *Trp53* allele corresponding to a human p53 variant often found in keratinocyte-derived cancers, the *Trp53*-mutant clones expanded after one or multiple doses of ionizing radiation. Suggesting a reason for the *Trp53*-mutant cells' advantage over wild-type cells after LDIR exposure, the *Trp53*-mutant cells had little mitochondrial oxidation compared to wild-type cells and were insensitive to irradiation. Importantly, NAC treatment in the absence of LDIR did not affect the *Trp53*-mutant clones' fitness; this aligns with findings that antioxidants are not effective for cancer prevention in humans and may even increase mortality. However, with NAC treatment in the setting of LDIR, the p53-mutant cells lost their competitive advantage because they were less likely to produce proliferating daughter cells, diminishing their population and enabling wild-type cells to recolonize the basal layer. These results show that external interventions can have an impact on the fitness of wild-type versus mutant cells in some contexts and suggest that therapies that increase the competitive fitness of wild-type cells above that of dangerous mutant cells may be worth investigating. ■

Fernandez-Antoran D, Piedrafita G, Murai K, Ong SH, Herms A, Frezza C, et al. Outcompeting p53-mutant cells in the normal esophagus by redox manipulation. Cell Stem Cell 2019 July 9 [Epub ahead of print].

AACR American Association for Cancer Research

CANCER DISCOVERY

ICB Response Is Associated with Pretreatment STAT1 Activation

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