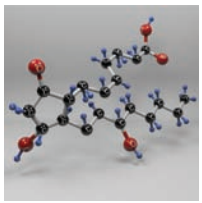
Immunology

Major Finding: IFNγ-producing NK cells induced TME remodeling and orchestrated T cell–mediated tumor control.

Concept: Prostaglandin E2 could bind EP2 and EP4 on natural killer cells, blocking this microenvironment change.

Impact: The inflammatory phenotypes in mouse tumors were seen in human tumors, with prognostic relevance.

NK CELLS MEDIATE T-CELL INFLAMMATION IN THE TUMOR MICROENVIRONMENT



Immunologically "hot" T cell–inflamed tumors that are substantially infiltrated by cytotoxic T cells often respond better to immunotherapy than their "cold" counterparts, but the steps leading to high T-cell infiltration and effector function in these tumors are not completely understood. Bonavita and colleagues extensively characterized the tumor microenvironments (TME) of highly T cell–inflamed tumors, the growth of which is restricted by the immune system in mice. This analysis revealed that immune control of cyclooxygenase (COX) enzyme–deficient tumors, which are depleted of the inflammation-associated downstream COX product prostaglandin E2 (PGE2), depended on infiltration by natural killer (NK) cells that produce IFNγ. These NK cells not only killed tumor cells effectively on their own, but also caused TME remodeling that led to accumulation of cytotoxic T cells that restricted tumor growth. The effects of PGE2 in these tumors were determined to be mediated by binding of PGE2 to the G protein–coupled receptors EP2 and EP4 on NK cells, preventing NK cell–induced TME alterations, allowing tumors to circumvent immune control. Highlighting the potential clinical relevance of these findings, an investigation of patient datasets representing a variety of cancer types, including patients receiving immune checkpoint blockade (ICB) therapies, demonstrated that the types of protumorigenic and antitumorigenic TME inflammatory profiles observed in mice were also present in human tumors and were prognostically significant and predicted response and survival with ICB. Together, these results reveal previously unknown mechanisms by which inflammation-associated tumor characteristics relate to immune control of tumors, with clear implications for ICB efficacy. ■

Bonavita E, Bromley CP, Jonsson G, Pelly VS, Sahoo S, Walwyn-Brown K, et al. Antagonistic inflammatory phenotypes dictate tumor fate and response to immune checkpoint blockade. Immunity 2020; 53:1215–29.E8.

Chemotherapy

Major Finding: In mice and nonhuman primates, a GDF-15 antibody blocked platinum-based chemotherapy side effects.

Concept: GDF-15 is a GRFAL-binding cytokine that is elevated by platinum-based drugs in patients with cancer.

Impact: This work suggests that GDF-15–GRFAL blockade may be of use for ameliorating platinum side effects.

A GDF-15 ANTIBODY PREVENTS PLATINUM-INDUCED EMESIS AND WEIGHT LOSS

Nausea, emesis, anorexia, and weight loss are notorious dose-limiting side effects of platinum-based chemotherapies, but little is known about the origins of these deleterious effects, and currently available treatments are not fully effective. Recently, growth differentiation 15 (GDF-15), a cytokine that activates the receptor GDNF family receptor α-like (GRFAL) in the hindbrain, has emerged as a potential mediator of these side effects of platinum-based chemotherapy. To investigate this, Breen and colleagues first established that serum GDF-15 levels were higher in patients with non–small cell lung cancer (NSCLC), colorectal cancer, or ovarian cancer treated with platinum-based chemotherapy compared with patients with the same tumor types treated with non–platinum-based chemotherapy and healthy controls. In wild-type mice, *Gdf15* (encoding GDF-15) knockout markedly reduced the anorexia and weight loss associated with cisplatin, oxaliplatin, or carboplatin treatment. Further, mice engineered to overexpress recombinant human GDF-15 exhibited weight loss that was reversible via treatment with a monoclonal antibody to human GDF-15, mAB1. Additionally, in nonhuman primates (cynomolgus monkeys) treated with cisplatin, circulating free GDF-15 levels increased within four hours and remained elevated over the 11-day study period, whereas monkeys pretreated with mAB1 showed no such increase in serum GDF-15. Pretreatment with mAB1 also increased food intake and decreased emesis in monkeys treated with cisplatin, consistent with the results in mice, although the study period was not long enough to evaluate body-weight changes. Notably, mAB1 was also able to reduce mouse GDF-15 levels *in vivo*, and mice bearing NSCLC xenograft tumors treated with mAB1 and cisplatin had lower weight loss and improved overall survival compared with control mice treated with cisplatin alone. Collectively, these findings indicate that GDF-15–GRFAL blockade may be a strategy of interest to reduce emesis and weight loss in patients with cancer treated with platinum-based chemotherapies. ■

Breen DM, Kim H, Bennett D, Calle RA, Collins S, Esquejo RM, et al. GDF-15 neutralization alleviates platinum-based chemotherapy-induced emesis, anorexia, and weight loss in mice and nonhuman primates. Cell Metab 2020;32:938–50.E6.

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