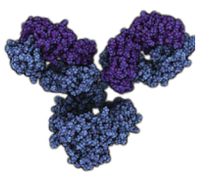
Neuroblastoma

Major finding: KIR3DL1 and HLA-B allele combinations predict response to anti-GD2 mAb in neuroblastoma.

Mechanism: Strong interactions between KIR3DL1 and HLA-B are associated with poor response to anti-GD2 mAb.

Impact: KIR3DL1 and HLA-B subtyping may guide treatment of patients with high-risk neuroblastoma.

KIR3DL1/HLA-B INTERACTIONS MODULATE RESPONSE TO ANTI-GD2 ANTIBODIES



In patients with neuroblastoma, immunotherapy with 3F8, a mAb against the disialoganglioside GD2, promotes natural killer (NK) cell–mediated toxicity. NK cells possess inhibitory killer immunoglobulin-like receptors (KIR; encoded by *KIR3DL1*) that bind to HLA class I molecules, licensing NK cells to target cells lacking self-HLA, but also attenuating their tumor cytotoxicity. Allelic diversity exists for *KIR3DL1* and *HLA-Bw4*, and the outcome of 3F8 treatment is improved in patients lacking the HLA class I ligands. These observations prompted Forlenza and colleagues to hypothesize that polymorphisms could alter the strength of the interaction between KIR3DL1 and HLA-Bw4, and modulate the NK response to 3F8. To test this hypothesis a retrospective analysis was performed to determine the *KIRDL1* and *HLA-B* subtype of 245 patients with high-risk neuroblastoma treated with 3F8. *HLA* typing indicated that 58% of patients harbored at least one *HLA-Bw4* allele, whereas the other 42% were homozygous for Bw6 alleles. *Bw4* alleles were associated with a worse overall and progression-free survival than *Bw6*. KIR3DL1 subtyping classified patients as KIR3DL1-high (48.4%), KIR3DL1-low (15.9%), KIR3DL1-null (16.3%), and activating KIR3DS1 (19.4%). The KIR3DL1 subtype had no impact on survival independent of HLA-B. Patients were further classified by the predicted strength of the interaction between KIR3DL1 and HLA-B subtypes. The noninteracting combinations had the best overall and progression-free survival outcomes after 3F8 therapy, and the strong interacting subtypes had the poorest survival outcomes. Moreover, treating neuroblastoma cells with IFNγ to induce HLA class I expression resulted in inhibition of KIR3DL1-high NK cells in the presence of 3F8, but had little effect on KIR3DL1-null and KIR3DS1 NK cells. Altogether, these results indicate that noninteracting KIR3DL1 and HLA-B alleles promote neuroblastoma survival and subtyping KIR3DL1 and HLA-B may predict the response to neuroblastoma 3F8 immunotherapy. These findings suggest the possibility for improving therapy by disrupting KIR/HLA interactions. ■

Forlenza CJ, Boudreau JE, Zheng J, Le Ludec J-B, Chamberlain E, Heller G, et al. KIR3DL1 allelic polymorphism and HLA-B epitopes modulate response to anti-GD2 monoclonal antibody in patients with neuroblastoma. J Clin Oncol 2016 Apr 11 [Epub ahead of print].

Colorectal Cancer

Major finding: CCL5 produced by T cells at invasive margins of colorectal cancer metastases promotes tumor growth.

Clinical relevance: CCR5 blockade in metastatic colorectal cancer leads to antitumoral macrophage repolarization.

Impact: Targeting CCR5 alters inflammation and leads to objective responses in cancer patients.

ANTI-CCR5 THERAPY CIRCUMVENTS IMMUNE CELL EXPLOITATION BY TUMORS

Cross-talk between immune cells and cancer cells influences the progression of colorectal cancer. The presence of immune cells can be beneficial, but cancer cells can modulate the immune microenvironment and immune cell function, resulting in immunosuppression and immune evasion. To understand how the immune microenvironment contributes to tumor progression, Halama and colleagues investigated the invasive margin of colorectal cancer metastases, which contain specific immune cells including large groups of T cells and monocytes. Analysis of cytokine and chemokine concentrations in 60 liver metastases revealed that the invasive margins had an immunologically distinct microenvironment with increased levels of chemokines such as CCL5, which was exclusively produced by T cells at the invasive margin. The CCL5 receptor, CCR5, is not typically expressed on primary colorectal tumor cells, but was expressed by metastatic tumor cells. The production of CCL5 by T cells in the microenvironment promoted tumor cell proliferation and invasion, and increased production of matrix metalloproteinases by tumor-associated macrophages (TAM). In a tumor explant model, CCR5 blockade with the HIV drug maraviroc resulted in tumor cell death and a reduction in inflammatory cytokines. These effects were TAM dependent, as CCR5 inhibition resulted in STAT3-mediated macrophage repolarization, and depletion of TAMs reversed the effects of CCR5 blockade. Based on these results, the authors initiated a phase I clinical trial investigating the safety and feasibility of maraviroc in 14 patients with advanced refractory metastatic colorectal cancer. Maraviroc was well tolerated, and after 8–10 days of treatment, tumor biopsies exhibited reduced tumor proliferation and increased tumor cell death. Five patients were re-exposed to chemotherapy after maraviroc treatment; partial responses were observed in three patients, and one patient had stable disease. Together, these data reveal a tumor-promoting role for T cells in metastatic colorectal cancer that can be mitigated by CCR5 blockade, and support further investigation of CCR5 blockade in larger clinical trials. ■

Halama N, Zoernig I, Berthel A, Kahlert C, Klupp F, Suarez-Carmona M, et al. Tumoral immune cell exploitation in colorectal cancer metastases can be targeted effectively by anti-CCR5 therapy in cancer patients. Cancer Cell 2016;29:587–601.