**Lymphoblastic Leukemia**

**Major Finding:** CD8+ tumor-infiltrating lymphocytes mount a response to neoantigens in acute lymphoblastic leukemia.

**Concept:** Low mutational burden is not always correlated with insufficient T-cell response.

**Impact:** Pediatric cancers with low mutation burdens may respond to immunotherapies targeting neoantigens.

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**Pediatric Cancers with Low Mutation Burden Can Be Immunogenic**

Therapies targeting cancers via T-cell–mediated mechanisms have primarily been studied in adult solid tumors, which generally have a high mutational burden compared with pediatric cancers, but it’s not clear whether pediatric cancers with relatively low tumor mutation burden have inherently poor T-cell responses. Zamora and colleagues set out to investigate the endogenous CD8+ T-cell response in pediatric acute lymphoblastic leukemia (ALL). In a cohort of 11 patients with pediatric ALL, predicted neoepitopes and bone marrow–infiltrating CD8+ T cells were observed in all patients, and in a directly ex vivo analysis of cytokine production by CD8+ T cells co-cultured with artificial antigen-presenting cells and neoantigen peptides in the three patients with the greatest number of CD8+ T cells, all tested peptides led to at least some response—sometimes a strong response—in each patient sample. Further investigation using direct stimulation of bone marrow from six patients revealed that all samples responded to one or more neoantigenic peptides tested. An analysis of global neoantigen-specific CD8+ T-cell response in six patients revealed that each had at least one neoepitope-specific CD8+ tumor-infiltrating lymphocyte (TIL) population. Demonstrating that the neoepitopes caused CD8+ T cells to mount an antitumor response, 68% of 25 tested patient-specific tetramers bound TILs above the level of nonspecific HLA-matched tetramers. Collectively, these findings show that there is a CD8+ T-cell response with a substantial number of neoepitopes being targeted by the immune system in pediatric ALL. Within a patient, these responses formed hierarchies of immunodominance. CD8+ T cells could also target common gene fusions observed in ALL, such as the ETV6–RUNX1 fusion seen in 20%–25% of pediatric ALL. Transcriptional profiling of neoepitope-specific CD8+ TILs revealed heterogeneity across patients and was consistent with functional effector differentiation. Although studies with larger patient cohorts are needed to confirm the broad applicability of these findings, these results suggest that some pediatric cancers may be candidates for immunotherapies targeting tumor-specific neoantigens.


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**Pancreatic Cancer**

**Major Finding:** The tumor-associated glycan CA19-9 causes pancreatitis and accelerates pancreatic cancer in mice.

**Mechanism:** CA19-9 increases EGFR pathway flux in mice via binding of putative EGFR ligand fibulin-3.

**Impact:** CA19-9 may be a relevant therapeutic target in patients with pancreatitis and pancreatic cancer.

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**CA19 Contributes to Pancreatic Pathogenesis**

Pancreatitis is a painful, sometimes recurrent condition that increases the risk of developing pancreatic cancer. The glycan carbohydrate antigen 19-9 (CA19-9) is elevated in the blood in 10%–30% of patients with pancreatitis and 75% of patients with pancreatic cancer, making it an important biomarker for both conditions, but its role is unclear. Using two mouse models with inducible CA19-9, Engle and colleagues investigated the role of the glycan in pancreatic disease. The mice exhibited pancreatitis upon CA19-9 induction, with amylase and lipase levels increasing within 24 hours of induction. Analysis of expression patterns of CA19-9 in the mouse models as well as human pancreata revealed that the expression pattern of CA19-9 is similar in the mouse models and human patients with pancreatitis and pancreatic cancer, with particularly high expression in the reactive and metastatic ducts. Gene set enrichment analysis revealed that CA19-9 altered the expression of several genes, including some involved in extracellular matrix–receptor interactions and the ERBB, PI3K, and AKT signaling pathways. Deeper investigation of some of the enriched pathways showed that EGFR phosphorylation was increased and total EGFR was decreased—both indications of increased flux through the pathway—when CA19-9 was expressed. The increase in EGFR signaling was mediated by the matricellular protein and EGFR ligand fibulin-3 (FBLN3): CA19-9 expression led to a rise in FBLN3 glycosylation, increasing FBLN3’s association with EGFR. Further evidence that CA19-9 plays a causal role in pancreatitis development in mice is that when CA19-9 expression was ceased after three days of induction, pancreatitis resolved, and treatment with CA19-9 antibodies decreased phosphorylation of EGFR in the ductal and acinar compartments and quelled macrophage recruitment. As a consequence of CA19-9-precipitated pancreatitis and CA19-9 induction, invasive and metastatic cancer progression was markedly accelerated, shortening the time to death by more than 50% in Kras mutant mice. Therefore, CA19-9 may be a therapeutic target worth investigating in both pancreatitis and pancreatic cancer.

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