Naïve T-cell Deficits at Diagnosis and after Chemotherapy Impair Cell Therapy Potential in Pediatric Cancers

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Précis: A prospective, longitudinal analysis of T-cell expansion ability across 10 different pediatric cancers reveals intrinsic and chemotherapy-induced immune deficits that may affect the development of T cell–based therapies.

See commentary, p. 466

Detection and Surveillance of Bladder Cancer Using Urine Tumor DNA


Précis: Cell-free DNA profiling of urine samples from patients with bladder cancer identified the presence of early-stage and recurrent disease with greater sensitivity than standard assays.

Transcriptomic Profiling of the Tumor Microenvironment Reveals Distinct Subgroups of Clear Cell Renal Cell Cancer: Data from a Randomized Phase III Trial


Précis: Angiogenesis and macrophage infiltration are predictors of response to TKIs in patients with metastatic RCC enrolled in the COMPARZ phase III trial.
MAPK Pathway Suppression Unmasks Latent DNA Repair Defects and Confers a Chemical Synthetic Vulnerability in BRAF-, NRAS-, and NF1-Mutant Melanomas


Précis: Combined BRAF/MEK and HDAC inhibition cooperates to suppress DNA repair and augments DNA repair defects in a subset of RAS pathway-mutated melanomas.

See commentary, p. 469

Molecular and Genetic Characterization of MHC Deficiency Identifies EZH2 as Therapeutic Target for Enhancing Immune Recognition


Précis: Pharmacologic inhibition of mutant EZH2 restores MHC expression in germinal center B cell-like diffuse large B-cell lymphoma.

See commentary, p. 472

ON THE COVER

Using a multiomics approach to analyze 347 cases of diffuse large B-cell lymphoma (DLBCL), Ennishi, Takata, and colleagues observed that loss of MHC expression defines a molecular subgroup of germinal center B cell-like DLBCL with reduced T-cell infiltration, an immune-suppressed microenvironment, and poor survival. EZH2 was the most frequently mutated gene in MHC-deficient DLBCL, and Ezh2 mutation in mouse models reduced MHC levels and amounts of T-cell infiltrates and resulted in shorter survival. EZH2 inhibition restored MHC expression in DLBCL cells by reducing repressive histone methylation at the promoters of MHC trans-activator genes. These findings identify an EZH2-mediated epigenetic mechanism of immune escape in DLBCL and suggest that EZH2 inhibition could be used to improve responses to immunotherapy. For details, please see the article by Ennishi, Takata, and colleagues on page 546.