Impaired COVID-19 Vaccine Humoral Responses in Hematologic Malignancies

Hematologic malignancy patients are highly susceptible to severe coronavirus disease-19 (COVID-19) illness and are a high-priority group for vaccination to mitigate COVID-19-related morbidity and mortality. Chung et al. find differential COVID-19 vaccine humoral responses between hematologic malignancy subtypes and disease-specific therapies across patient cohorts. Hematologic malignancy patients undergoing active therapy have baseline humoral responses that are further suppressed. Importantly, antibody titers alone are an imperfect measure of immunity, as many patients with positive anti-SARS-CoV-2 antibody titers have insufficient neutralizing capacity. These findings together provide important metrics for optimizing the clinical care of this vulnerable population.

See article, p. 568.

Response to SARS-CoV-2 Vaccination after Cellular Therapies

Cellular therapies, including allogeneic and autologous hematopoietic cell transplant (allo-HCT, auto-HCT) and chimeric antigen receptor T-cell therapy (CAR T), render patients severely immunocompromised for extended periods after therapy. Tamari et al. define predictors of response to COVID-19 vaccine to nominate important factors for optimizing response to vaccination. Type of cellular therapy, timing of vaccination post-cellular therapy, and immune recovery post-cellular therapy predict response. Many patients with positive, yet low, anti-SARS-CoV-2 antibody titers demonstrate low neutralizing capacity, highlighting the limitations of using antibody titer as the only proxy for immunity.

See article, p. 577.

Classification of Pediatric Acute Myeloid Leukemia

Pediatric acute leukemias have historically been classified by immunophenotyping followed by genomic subclassification. Patients are categorized into T, B, myeloid, or mixed-lineage disease for the purpose of general treatment approach, and these regimens are then further tailored in intensity and/or targeted therapeutics when applicable. Fornerod et al. apply an integrated analysis of gene expression and mutation profiling to a cohort of pediatric patients with acute leukemias that have myeloid features. This reveals a subset of patients with shared mutational composition and gene expression that spanned three immunophenotypes: T, myeloid, and mixed-lineage acute leukemias. The authors further identify patients with the same mutations but with differential gene expression profiles and outcomes. These results suggest acute leukemia classification requires more comprehensive, sequencing-based diagnostic methods beyond flow cytometry.

See article, p. 586.

MyD88-Mutant Progenitors and Immune Changes Precede Waldenstrom Macroglobulinemia

Waldenstrom macroglobulinemia (WM) is characterized by outgrowth of mature IgM+ B cells with MYD88 mutations. Kaushal et al. show that WM lesions originate in the presence of several alterations in the immune microenvironment, including aberrant nonmalignant extrafollicular B-cell expansion, myeloid inflammation, and WM-specific T-cell immune responses. The characteristic MyD88 mutations originate in early lymphoid progenitors prior to expansion of the malignant clone. These findings suggest a new model for the origin of WM.

See article, p. 600.

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Clinical translation of CAR T-cell therapy for AML has been limited by the lack of optimal CAR targets and the risk of on-target, off-tumor toxicity. Richards et al. report a novel anti-AML CAR T-cell therapy targeting CD93 and demonstrate antileukemic activity without toxicity to critical hematopoietic stem and progenitor cells. To mitigate tissue-specificity concerns, next-generation, NOT-gated CD93 CAR T cells were engineered. Transcriptomic analysis of AML and endothelial cells demonstrates a promising target identification strategy for further advancement of this technology.

See article, p. 648.

Inhibitors of Bruton tyrosine kinase (BTKi) block pathogenic B-cell receptor (BCR) signaling, improving outcomes for patients with lymphoid malignancies. Nonetheless, resistance to BTK therapy is a frequent clinical problem that has previously been ascribed to genetic alterations. Shaffer et al. find a primary, early mechanism of BTKi resistance involving epigenetic reprogramming of the malignant cell. Specifically, the epigenetic upregulation of the small GTPase RAC2 increases its interaction with, and activation of, PLCγ2. This RAC2-dependent activation circumvents the requirement for BTK to phosphorylate PLCγ2 to trigger the prosurvival NF-κB pathway. Clinically available drugs are identified that can kill BTKi-resistant cells.

See article, p. 630.

Overall outcomes are dismal in relapsed/refractory AML (R/R AML), and therapeutic options are limited. In this phase II study, Zeidner et al. investigate the safety, feasibility, and clinical activity of immune checkpoint blockade with pembrolizumab after high-dose cytarabine (HiDAC) chemotherapy in R/R AML. The addition of pembrolizumab to HiDAC leads to an overall complete remission rate of 38%, with encouraging clinical outcomes and self-limiting immune-related adverse events. Multifaceted immunogenomic profiling before and after therapy reveals putative biomarkers of response to pembrolizumab, warranting further investigation.

See article, p. 616.
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