HGF Blockade Is Safe with Preliminary Efficacy in Refractory AML

Ficlatuzumab is a first-in-class monoclonal antibody that blocks oncogenic MET signaling by blocking its ligand HGF. Here Wang et al. report on the safety and efficacy of ficlatuzumab combination with cytarabine in 17 patients with relapsed/refractory acute myeloid leukemia. Nine of the patients (53%) achieved a complete remission. Progression-free survival was 31.2 months, and median overall survival has not been reached. These outcomes compare favorably to historical data but remain to be validated in larger, randomized trials. Phosphoproteomic analysis identified S6 and MET phosphorylation as molecular correlates of response. Ras and GTPase gene expression signature was higher in prospective responders, whereas prospective nonresponders had elevated interferon and Myc signature. ■ See article, p. 434.

Systemic Immune Landscape Shifts Driven by Viral Adult T-cell Leukemogenesis

Human T-cell leukemia virus type-1 (HTLV-1) infection can progress to adult T-cell leukemia/lymphoma (ATL). To elucidate determinants of HTLV-1–driven oncogenesis, Koya et al. characterize circulating blood cells of healthy donors, HTLV-1 carriers, and patients with ATL by genome sequencing and CITE-seq combined with TCR-seq and BCR-seq. This high-dimensional single-cell analysis identifies Treg phenotype as a hallmark of premalignant clonal outgrowth. As the neoplastic clones progress to ATL, their expansion is accompanied by a proportional expansion of the myeloid compartment and immunosuppressive phenotypes including PD-L1 upregulation. The study delineates a new mechanism of PD-L1 acquisition by protein transfer from ATL to nonmalignant cells. ■ See article, p. 450.

Bortezomib Activates Anti-Myeloma Immune Response via STING

Immunologic consequences of cell death contribute to clinical efficacy of certain chemotherapeutics, and identification of immunogenic drugs is essential for their optimal clinical use alone and in combination with immunotherapy. In this work, Gulla et al. have shown that a specific anti–multiple myeloma (MM) immunity occurs upon cell death induced by the proteasome inhibitor bortezomib, leading to immunologic memory and long-term clinical response. Intrinsic activation of STING followed by a viral mimicry state further contributes to the immunogenic effect, and combination of bortezomib with a STING agonist potentiates tumor cell–immune microenvironment interplay. These findings invite a deeper characterization of the immunologic effects of anti-MM agents and inform novel chemo-immunotherapy combinations. ■ See article, p. 468.

Somatic Mutations in Pediatric AML Patient-Matched Blasts and HSPCs

To obtain insight into the etiology of childhood leukemia, Brandsma et al. determined mutation burden of leukemic blasts and normal hematopoietic stem and progenitor cells (HSPC) from pediatric acute myeloid leukemia (pAML) patients and healthy age-matched controls. Integrating these data with available adult cohorts, they established a baseline of HSPC mutation accrual over the entire human lifespan. A subset of pediatric leukemia cases falling above the baseline harbored more genetic driver events and associated with better survival. The mutation pattern, characteristic of cells with high proliferation and oxidative stress, suggests a more committed progenitor as a cell of origin in this pAML subset. ■ See article, p. 484.
**ZBTB33 Mutations in Clonal Hematopoiesis and MDS**

While the most frequent drivers of clonal hematopoiesis have been characterized previously, mutations in these genes are not present in about half of clonal hematopoiesis cases. By identifying recurrent mutations in the blood of large numbers of healthy people, Beauchamp et al. discover additional genes likely to drive clonal hematopoiesis and thus regulating hematopoietic stem cell (HSC) expansion. Modeling ZBTB33 mutations in mouse HSCs, the authors observe that the edited cells expand and have a competitive advantage compared with control cells. Cells with Zbtb33 mutations also have altered intron retention, potentially connecting ZBTB33 to RNA splicing, a commonly mutated pathway in clonal hematopoiesis and myelodysplastic syndromes.

See article, p. 500.

**BET Inhibitor Response Is Tethered to AML Monocytic Differentiation**

Romine et al. characterize acute myeloid leukemia (AML) sensitivity to BET inhibitors (BETi) by two orthogonal approaches: ex vivo drug screening of genetically defined primary AML samples, and genome-wide CRISPR screens of BETi-sensitive and BETi-resistant cells. Both identify loss of monocytic differentiation regulators as drivers of BETi resistance. BETi-resistant AML cells express low levels of myeloid markers; conversely, forced myeloid differentiation sensitizes AML cells to BETi. CRISPR dropout screens in BETi-resistant cells reveal BCL2 and CDK4/6 as targetable vulnerabilities to overcome BETi resistance. Moreover, monocytic AML refractory to BCL2 inhibition, an unmet clinical challenge, shows preclinical responses to combined Bcl2 and BETi.

See article, p. 518.

**Overcoming Plasma Protein Inhibition of Tyrosine Kinase Inhibitors**

Binding of tyrosine kinase inhibitors (TKI) by plasma proteins, most notably alpha-1-acid glycoprotein (AGP), can dramatically reduce TKI bioavailability and thus clinical potency. In this work, Young et al. characterize AGP impact on staurosporine-derived TKI (STS-TKI) activity against FLT3-mutated acute myeloid leukemia (AML). Under physiologic conditions and drug concentrations, AGP quenches STS-TKI activity to subtherapeutic levels due to high-affinity drug–protein interactions. To overcome this, the authors screen for drugs restoring TKI activity in the presence of AGP, identifying mifepristone. In an in vivo model, mifepristone coadministration restores midostaurin clearance of AML cells. These results suggest a combinatorial approach for unlocking TKI activity to potentiate therapeutic responses in FLT3-mutated AML.

See article, p. 532.
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