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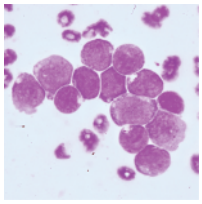
Leukemia

Major Finding: Differentiated AML-derived cells are able to revert into leukemogenic states.

Concept: The progression of AML cells into differentiated states, as triggered by ATRA, is reversible.

Impact: Eradicating tumor cells at all developmental stages may be important in AML.

AML DIFFERENTIATION PLASTICITY MAY CONTRIBUTE TO RELAPSE



Tumorigenic cancer stem cells (CSC) are important in acute myeloid leukemia (AML) and other malignancies, and therapies intended to eliminate them or promote their differentiation, such as FLT3 inhibitors and mutant IDH1/2 inhibitors, have recently entered the clinic. The pioneer transcription factor PU.1 (SPI1) is required for normal myelopoiesis and for AML differentiation caused by treatment with all-*trans* retinoic acid (ATRA) or LSD1 inhibitors, and a reduction in PU.1 activity is common in AML. McKenzie, Ghisi, Oxley, and colleagues found that PU.1 knockdown drove AML development in a mouse model of p53-deficient AML and that restoration of PU.1 led to leukemia differentiation and remission. Suppression of PU.1 in differentiated AML-derived cells caused them to dedifferentiate back to a clonogenic, leukemogenic state, indicating that their maturation was reversible. Chromatin accessibility and the expression of myeloid maturation genes was regulated by PU.1, and PU.1's continuous presence at regulatory elements was essential to maintain a differentiated state in mature AML-derived cells. In a mouse model of acute promyelocytic leukemia (APL), discontinuation of ATRA reverted mature APL cells to leukemogenic states, and differentiation of human APL cells triggered by ATRA was also reversible after cessation of therapy. These results suggest that eliminating tumor cells at all stages of maturation may be important to achieve full AML cures. ■

McKenzie MD, Ghisi M, Oxley EP, Ngo S, Cimmino L, Esnault C, et al. Interconversion between tumorigenic and differentiated states in acute myeloid leukemia. Cell Stem Cell 2019;25:258–72. E9.

Immunotherapy

Major Finding: TRAF2 inactivation sensitizes tumor cells to T-cell elimination and increases anti–PD-1 efficacy.

Mechanism: Inactivation of TRAF2 in melanomas caused RIPK1 cleavage by T cells, leading to cell death.

Impact: Investigation of the TNF pathway may yield new immunotherapy targets.

TNF-PATHWAY PROTEINS MODULATE TUMOR SUSCEPTIBILITY TO T-CELL ATTACK

Cytokines such as IFNγ contribute to cytotoxic T cells' antitumor activity, but systematic, unbiased analyses of IFNγ-independent tumor signaling pathways are lacking. Through a genome-wide CRISPR–Cas9 knockout screen of IFNγ receptor–deficient melanoma, Vredevoogd and colleagues uncovered genes that sensitized tumor cells to elimination by T cells independently of IFNγ; of these, the top hits were tumor necrosis factor (TNF) receptor–associated factor 2 (*TRAF2*) followed by *BIRC2* (which encodes cellular Inhibitor of apoptosis 1 [cIAP1]). TRAF2 and cIAP2 are involved in the same pathway: TRAF2 recruits cIAP2 to inhibit death receptor–mediated apoptosis. Comparing patient cohorts before and after immune-checkpoint blockade therapy revealed that neither TNF expression nor mutations in TNF-pathway genes affected prognosis at baseline. This was further substantiated by *in vitro* dose-titration experiments, which showed that even high TNF concentrations were not cytotoxic. However, in patients who respond to immunotherapy, expression of TNF and TNF response signatures were increased. *TRAF2* inactivation in melanomas was associated with receptor interacting protein kinase 1 (RIPK1) cleavage by T cells, which causes RIPK1-dependent cell death, and inactivation of *TRAF2* greatly increased sensitivity of tumor cells to TNF toxicity at physiologically relevant concentrations *in vitro* and *in vivo*. Although no small-molecule inhibitor of TRAF2 is available, it is known that Fn14 stimulation by its ligand TWEAK can cause lysosomal degradation of TRAF2, and treatment with the Fn14 antibody enavatuzumab led to TRAF2 degradation and a TRAF2-dependent increase in susceptibility to T-cell cytotoxicity in two melanoma cell lines. Demonstrating the broader applicability of these findings, *TRAF2* inactivation in 9 of 11 tested melanoma and lung cancer cell lines led to increased susceptibility to T-cell killing. TRAF2–cIAP complex inhibition sensitized all 11 tested cancer cell lines to T-cell killing *in vitro* while also increasing the efficacy of anti–PD-1 therapy in a xenograft mouse model of melanoma. These results indicate that further examination of the TNF signaling pathway in tumor cells for targets relevant to immuno-oncology may be fruitful. ■

Vredevoogd DW, Kuilman T, Ligtenberg MA, Boshuizen J, Stecker KE, de Bruijn B, et al. Augmenting immunotherapy impact by lowering tumor TNF cytotoxicity threshold. Cell 2019;178:585–99.E15.

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CANCER DISCOVERY

TNF-Pathway Proteins Modulate Tumor Susceptibility to T-cell Attack

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