Tumorigenesis

Major Finding: Mutant clones in normal epithelium can limit the early formation of esophageal tumors in mice.

Concept: Highly fit clones outcompete growth of emerging tumors and reduce the number of persisting lesions.

Impact: This study uncovers the novel tumor-suppressive role of mutant clones in normal epithelial tissue.

MUTANT CLONES IN ADJACENT NORMAL EPITHELIUM LIMIT EARLY TUMORIGENESIS

Epithelial tissues often acquire oncogenic mutations over time, but subsequent tumor formation remains relatively rare. These mutations in normal epithelial cells seem to undergo selection, leading Colom and colleagues to investigate whether the dynamics of competitive clones with enhanced fitness may affect the early stages of tumor formation. To examine the trajectory of premalignant tumors in a murine model of esophageal carcinogenesis, mice were administered the mutagen diethylnitrosamine (DEN) for 2 months, and esophagi were harvested at various time points up to 18 months following DEN withdrawal. After 10 days postwithdrawal, hundreds of small tumors were detected in each esophagus. Although individual tumors grew larger over time, the overall number of tumors rapidly decreased after several months. Targeted sequencing of genes implicated in epithelial carcinogenesis revealed that, although the overall spectrum of mutation types was similar between tumors harvested after 10 days and tumors harvested after 1 year, persisting tumors displayed genetic differences, with tumors after 10 days positively selecting for mutations in *Notch1* and *Trp53*, whereas tumors after 1 year were enriched for mutations in *Atp2a2*, *Notch1*, *Notch2*, *Chuk*, and *Adam10*. Mechanistically, early tumor loss did not occur through apoptosis, decreased proliferation, or immune-mediated clearance, as immunostaining revealed no detectable activated caspase-3$^+$ cells, no changes in EdU incorporation, or infiltration of immune cells. Notably, analysis of DEN-treated normal epithelium uncovered substantial numbers of mutant clones, displaying positive selection of *Notch1*, *Trp53*, and *Fat1*. To assess whether mutant clones could outcompete early tumors in the esophagus causing tumors to be extruded from the suprabasal surface of the epithelium, highly fit mutant clones were induced by expression of a dominant-negative allele of *Maml-1*, inhibiting Notch signaling. This resulted in a decrease in tumors observed 30 days post-DEN, with elimination of competitive advantage across the tissue via inhibition of Notch signaling reversing this decrease. In summary, this study demonstrates that the dynamics of mutant clonal selection in normal epithelium can play a tumor-suppressive role in early tumorigenesis. ■

Colom B, Herms A, Hall MWJ, Dentro SC, King C, Sood RK, et al. Mutant clones in normal epithelium outcompete and eliminate emerging tumors. Nature 2021;598:510–4.

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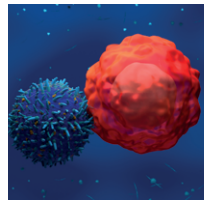
Clinical Trial

Major Finding: Dual-targeting CAR T cells show safety and efficacy in pediatric/young adult relapsed or refractory B-ALL.

Concept: In this phase I trial, mild cytokine release syndrome was observed with no dose-limiting toxicities.

Impact: These dual-targeting CAR T cells showed clinical benefit, but improved persistence is still needed.

DUAL CD19/CD22 CAR T CELLS SHOW FEASIBILITY IN PEDIATRIC/YOUNG ADULT B-ALL



The use of chimeric antigen receptor (CAR) T cells specific to CD19 or CD22 in the treatment of B-cell acute lymphoblastic leukemia (B-ALL) has shown remarkable promise, but relapse can occur due to antigen loss or downregulation. To address this issue, CAR T cells targeting both of these antigens have been developed, but the safety and efficacy of dual-targeting CAR T cells remain unclear. Cordoba, Onuoha, Thomas, and colleagues conducted a phase I clinical trial testing AUTO3, a dual-targeted CAR T cell–based therapy generated by transducing T cells with a bicistronic vector encoding CD19 and CD22 CARs, in 15 pediatric and young adult patients (1–24 years old) with relapsed or refractory B-ALL. The incidence of grade 3–5 toxicity and the frequency of dose-limiting toxicity were the primary endpoints for this study, with the secondary endpoints including the rate of morphologic remission, frequency of adverse events, expansion and persistence of AUTO3, duration of B-cell aplasia, and overall/event-free survival. The endpoints of this study were met with a favorable safety profile being observed, with 60% exhibiting grade 3–4 toxicities (fever, neutropenia, anemia, and thrombocytopenia were most common), but no dose-limiting toxicities were reported and only mild cases of cytokine release syndrome were observed. Expansion of these CAR T cells was noted in 66% of individuals, but persistence was reduced as compared to tisagenlecleucel, a CD19-directed CAR T-cell therapy. Remission rate at 1 month posttreatment—defined as complete response or complete response with incomplete bone marrow recovery—was 86%, and overall and event-free survival at 1 year were 60% and 32%, respectively, with relapses postulated to occur due to limited long-term CAR T-cell persistence. In summary, the results of this phase I trial show that AUTO3 use in pediatric or young adult relapsed or refractory B-ALL is both safe and feasible, but future studies on improving long-term persistence of these CAR T cells are still needed. ■

Cordoba S, Onuoha S, Thomas S, Pignataro DS, Hough R, Ghorashian S, et al. CAR T cells with dual targeting of CD19 and CD22 in pediatric and young adult patients with relapsed or refractory B cell acute lymphoblastic leukemia: a phase I trial. Nat Med 2021;27:1797–805.

doi: 10.1158/2159-8290.CD-RW2021-150