Abstracts

We developed an orthotopic CHLA-06.ffLuc xenograft model. We tested BT12.ffLuc, BT37.ffLuc) as well as a CHLA-06-derived B7-H3 knockout. Obtained from healthy donors and produced as an “off-the-shelf” product. CAR-NK cells have several advantages over CAR-T cells. NK cells can be targeted to CHLA-06 orthotopic xenograft bearing mice, B7-H3 CAR NK cells eliminate tumor cells and prolong survival, whereas unmodified NK cells did not. CAR vs. no-CAR NK-mediated target killing. When delivered intracranially into xenografts, CAR-NK cells exhibited enhanced antitumor activity. In vivo study was performed in our xenograft with intratumoral delivery of CAR-NK cell functionality using in vitro co-culture and cytotoxicity assays.

BACKGROUND: Atypical teratoid rhabdoid tumors (ATRTs) remain a dire need for new safe and effective therapies. These therapy-resistant tumors are the most common malignant CNS tumor in infants. AT/RT patients have a poor prognosis with current therapy options. We have developed a platform to engineer CAR-NK cells targeting ATRT-specific antigens and have demonstrated clinical efficacy in patients with therapy-resistant ATRT. We previously reported that ATRT is a genetically diverse group of tumors with three main molecular subgroups identified: (1) MYC-driver tumors, (2) SHH-driver tumors, and (3) TYR-driver tumors. We used AT/RT patient-derived organoids to investigate tumor cell populations and their differentiation trajectories in each subgroup. Functional validation of these findings in ATRT organoid models may provide guidance for subgroup-based therapies.

We performed an unsupervised cellular trajectory analysis of AT/RT organoids using single-cell RNA sequencing (scRNA-seq) to identify tumor cell populations and their differentiation trajectories. We observed three main differentiation trajectories: (1) forebrain-like trajectory mainly enriched in ATRT-TYR, (2) mesenchymal trajectory mainly enriched in ATRT-MYC, and (3) radial glia-like trajectory mainly enriched in ATRT-SHH. However, we identified a population of intermediate neural cell populations and ATRT-MYC mainly demonstrated a mesenchymal-like cell population. We next performed a supervised cellular trajectory analysis using SMART-seq transcriptomics to further investigate tumor cell populations. Separation of malignant cells from benign cells was successfully achieved using scRNA-seq (n = 9) and SMART-seq (n = 4) samples (ATRT-TYR = 6, ATRT-SHH = 9, ATRT-MYC = 4). Validation of these findings in ATRT organoid models may provide guidance for subgroup-based therapies.

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ATRT-12. EXPLORING FGFR INHIBITION AND COMBINATION THERAPIES FOR ATYPICAL TERATOID/RHABDOID TUMORS
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BACKGROUND: Atypical teratoid/rhabdoid tumors (AT/RTs) are aggressive pediatric brain neoplasms characterized by an inactivation of the SWI/SNF chromatin remodeling complex members SMARCB1 or SMARCA4. Based on epigenetic profiling AT/RTs can be divided into four different molecular subgroups. Despite improvements in treatment strategies, the prognosis for AT/RT patients remains dismal. The FGF/FGFR signaling pathway plays a crucial role in many physiological processes, including embryonic development, tissue repair, angiogenesis. Dysregulation of the signaling axis is driving tumorigenesis. Targeted therapeutic approaches, particularly FGFR inhibitors, have demonstrated potential in enhancing treatment outcomes for various tumors, including pediatric brain tumors. METHODS: We used bulk and single-cell RNA sequencing (scRNA-seq) data to examine the expression patterns of FGF family members in AT/RTs. Subsequently, we conducted in vitro analysis on a panel of FGFR inhibitors and combination treatments. RESULTS: Transcriptomic analysis of more than 130 AT/RT tissues samples, revealed a widespread expression of FGFR1 and FGFR2 across all AT/RT subtypes. Notably, FGFR1 displayed distinctly elevated expression in AT/RT-SHH, surpassing levels seen in other AT/RT subtypes and brain tumor types. Utilizing scRNA-seq data of murine AT/RT models, we elucidated an autocrine FGFR signaling loop. To assess the therapeutic feasibility of targeting FGFR, we evaluated a panel of FGFR inhibitors, currently in clinical development, across 10 in house established patient-derived cell models (6 AT/RT-MYC, 5 AT/RT-SHH, 1 AT/RT-TYR), revealing sensitivity in a nanomolar to a low-micromolar range. We further explored combination therapies, demonstrating that Erdbodtib, the most effective inhibitor when combined with Abemaciclib and radiation, exhibited enhanced synergistic effects in 2D as well as in 3D tissue-engineer models. Investigations towards testing these combinations in an organoid co-culture system, along with in vivo models are ongoing. CONCLUSIONS: This study emphasizes the prospect of combining FGFR inhibition with radiation and CDK4/6 inhibition as a therapeutic target for AT/RTs.