DISSECTING THE TUMOR ASSOCIATED ASTROCYTES USING THE BACTRAP ANIMAL MODEL OF SHH-MEDULLOBLASTOMA AND THEIR POTENTIAL VALUE AS THERAPEUTIC TARGETS

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Background Pediatric tumors like medulloblastoma (MB), despite being considered ‘cold’ tumors, differ greatly between their subgroups, with the infant SHH-MB subgroup showing the highest level of immune cell infiltration into the tumor microenvironment. In this regard, the immune microenvironment of tumor can play a critical role in promoting tumor progression, and the astrocyte-immune axis is a new topic that is increasingly being studied in this context. These tumor-associated astrocytes offers an intriguing opportunity for new therapeutic approaches.

Methods Using a novel immunocompetent preclinical mouse model of SHH-MB created by mating astrocyte-specific Aldh1L1-TRAP mice with Math1-Cre/PTCH1lox/lox mice, we characterized the tumor immune environment of these animals.

Results 12.5% of cerebellar granule neuron precursors (GCP)-targeted early onset triple mice developed tumors that had succumbed to MB by 56 days and were euthanized due to clinical manifestations of the disease, including head swelling, weight loss, poor grooming, inactivity, and circling. Tumor slices that underwent histological investigation revealed that the tumor had a typical MB histology. The Aldh111-TRAP:Math1-Cre:Ptch1lox/lox tumors presented mitotic indices, evident by KI67 expression. According to immunohistochemical labeling, these tumors contain higher levels of astrogliosis (GFAP+ cells). The complexity of the cell fate of these tumor-associated astrocytes was also enhanced by co-staining for Nestin, Sox9, GFAP, and S100beta. In our Aldh111-TRAP:Math1-Cre:Ptch1lox/lox immunocompetent mouse model, RNA was extracted from tumor cells, and the levels of CD24, CD276 (B7-H3), CD47, CTLA-4, PDCD1, and PD-L1 were quantified. Our findings are in accordance with previous results carried out with pediatric human SHH-MB.

Conclusions Our triple Aldh111-TRAP:Math1-Cre:Ptch1lox/lox mouse model represents a useful tool in the field of medulloblastoma immunotherapy, and it has the potential to test additional therapeutic targets that, alone or in combination with standard or newer therapies, can enhance the treatment of MB-SHH patients.

Ethics Approval The study involve genetically engineered mice with Animal Welfare Assurance Number (OLAW) 45315021.0.0000.5437

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