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New in vivo avatars of diffuse intrinsic pontine gliomas (DIPG) from stereotactic biopsies performed at diagnosis.

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Abstract

Diffuse Instrinsic Pontine Glioma is the most aggressive form of High Grade Gliomas in children. The lack of biological material and the absence of relevant models have hampered the development of new therapeutics. Their extensive infiltration of the brainstem renders any surgical resection impossible and until recently biopsies were considered not informative enough and therefore not recommended. Thus, most models were derived from autopsy material. We aimed to develop relevant in vivo DIPG models that mimic this specific disease and its molecular diversity from tumor material obtained at diagnosis. Eight patient-derived orthotopic xenograft models were obtained after direct stereotactic injection of a mixed cell suspension containing tumor cells and stromal cells in the brainstem or thalamus of nude mice and serially passaged thereafter. In parallel, we developed 6 cell-derived xenograft models after orthotopic injection of tumor-initiating cells cultured from stereotactic biopsies. Cells were modified to express luciferase to enable longitudinal tumor growth monitoring, and fluorescent reporter proteins to trace the tumor cells in the brain.These models do not form a tumor mass, they are invasive, show the H3K27 trimethylation loss in vivo and the tumor type diversity observed in patients in terms of histone H3 mutations and lineage markers. Histological and MRI features at 11.7 Tesla show similarities with treatment naïve human DIPG, and in this respect, both direct and indirect orthotopic xenograft looked alike. These DIPG models will therefore constitute valuable tools for evaluating new therapeutic approaches in this devastating disease.

KEYWORDS: bioluminescence; brain tumor model; child; infiltrative midline glioma with histone H3-K27M mutation; tumor-initiating cell

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