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Can we target amino acid metabolism to affect brain tumor growth?

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Statement of the Problem: Brain tumors cause major morbidity/mortality. Glioblastoma (GBM) in adults and medulloblastoma in children are major types of clinically aggressive high-grade CNS malignancies. These have increased uptake of radio-labeled amino-acids (AA) used for PET scans. Central amino-acid Glutamine (Gln) is crucial for growth of brain tumors. Nevertheless, there aren't clinically effective pharmaceutical interventions against AA metabolism of brain tumors. In contrary, anti-metabolites like bacterial enzyme asparaginase (ASNase, which effectively depletes asparagine and Gln in blood and CSF) are successfully used to treat acute leukemias. Thus, we aimed to study if manipulation of AA metabolism may have a role in developing therapeutics against brain tumors.

Methodology & Theoretical Orientation: We conducted series of analyses on large brain tumor databases containing molecular signatures and clinical outcomes. In addition, using ASNase as a research tool, we carried out series of pre-clinical investigations on glioma cell-lines and on mice that harbor medulloblastomas.

Findings: We have shown that lower co-expressions of BCAT1, ASNS and GLS are associated with better outcome in 66 newly diagnosed GBM patients (UCLA-probesetanalyzer database). Three additional GBM datasets (r2.amc.nl) showed that at least 4 additional AA-related enzymes-which have higher expression in GBM, also predict poor outcome in 504 GBM patients (TCGA database). Several of these enzymes have differential expression in pediatric brain tumors, including subtypes of medulloblastomas. Mouse models of medulloblastomas demonstrated anti-tumor efficacy of E. coli-ASNase+TMZ against DAOY-SQ model and of Erwinia Chrysanthemi-ASNase, which shows preliminary efficacy in SMO/SMO spontaneous medulloblastoma model. All ASNase formulations showed *in vitro* activity against glioma cells with variable IC50s.

Conclusion & Significance: Our studies support the concept that AA metabolism plausibly harbors targetable nodes, which can be studied for new anti-metabolite therapeutics development for brain tumors. They provide opportunities for combined therapies due to less myelosuppressive toxicity profile.

Biography

Eduard H Panosyan is a Pediatric Hematologist-Oncologist, who as a Physician-Scientist developed his initial research expertise in studying amino acid metabolism in childhood acute lymphoblastic leukemias. His further research skills are related to studies of pediatric brain tumors. Consequentially, as an Independent Investigator, he has developed research interests on metabolic pathways and related cellular mechanisms by which brain tumor cells sustain malignant proliferation *in vitro* and *in vivo*. Main focus of his investigations is on augmented metabolism of amino acids promoting progression of malignant brain tumors. Identification of druggable targets for heterogeneous metabolic patterns in glioblastomas and medulloblastomas may allow effective therapeutics development. His lab is on the verge of conducting exciting pre-clinical experiments to test some of the anti-metabolites with chemotherapy against intracranial brain tumors.

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