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Editorial

Toll-Like Receptors-Autophagy Immuno-Inflammatory Networks as "Molecular Rheostats" in Hypoxic Tumor Microenvironment in Complex Neurological Diseases Primarily Glioblastoma and Spinal Meningioma: Translational Research Perspective with Public Health Impact in Genetically Susceptible Population-Pools in Covid-19/Omicron Pandemic Era

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Demystifying the underlying cellular/molecular and genetic basis of inflammatory tumor microenvironment in human diseases primarily neurological diseases especially glioblastoma and spinal meningioma is emerging as a primary clinical research objective of both emerging and established translational health investigators worldwide. The disproportionate share of morbidity and mortality amongst genetically heterogeneous population-pools symptomatic of early vs advanced stage/grade brain tumors is indeed intriguing and certainly warrants adequate public health-oriented endeavors for meaningful patient-centric evidence-based pragmatic outcomes for successful design and development of clinically validated biomarkers for glioblastoma and meningioma management.

In my expert opinion, enthusiastic clinical researchers worldwide should dynamically collaborate and actively investigate the complex neuro-immune signalling networks/intersections in glioblastoma and spinal meningioma by selective immunotherapeutic targeting of biochemical/metabolic signaling networks (viz. Toll-like Receptors-Autophagy-Apoptosis-Ceramide/Sphingolipids, etc.) in aberrant physiologic mileu in the inflammatory brain tumor microenvironment with vascular insufficiency and hypoxia, coupled with precision-based transcriptomics, proteomics and metabolomics for eventual design of cost-effective predictive and/or prognostic biomarkers along with novel drugs and pharmacological scaffolds for personalized tailor-made gene therapy in genetically susceptible population-subsets of asymptomatic vs symptomatic cohorts of varying ethnicities and life-styles in the current overwhelming Covid-19/Omicron pandemic era.

Moreover, prospective and retrospective study-designs with precise inclusion and exclusion criteria along with adherence to core tenets of good practice clinical research and bioethics, enrolling adequate samples of clinically confirmed cases of glioblastoma and spinal meningioma and age-/ethnicity-matched healthy disease-free controls from random population(s) with a case-control genetic association approach would prove immensely beneficial in risk-stratification of early vs advanced grade/stage of inflammatory brain tumors of heterogeneous tumor core(s); however, retrospective case-control genetic-association studies usually lack considerable statistical power with an inadequate sample-size leading to selection-bias with a relatively low study-power. In this context, collaborative multicentric gene-epidemiology biomedical researchers should stringently re-evaluate their patient-centric data-sets and clinical variables/parameters in a large sample size of clinically confirmed glioblastoma and benign/metastatic spinal meningioma symptomatic cohorts of ethnically disparate cohorts of genetically heterogeneous population-admixture(s) so as to draw meaningful conclusive interpretation of the findings thereby yielding accurate error-free/ unambiguous reproducible end points for drawing definitive conclusions in evidence-

based clinical management of glioblastoma and spinal meningioma along with other neurological disorders/ailments of complex pathophysiology. Designing an ethically acceptable structured clinical questionnaire for demographic profile, family history of neurological diseases, life-style: dietary-patterns, alcohol/tobacco-consumption (smokers vs chewers), pre-operative vs post-operative adverse events in glioblastoma and meningioma cases following radio-surgery/chemotherapy, fertility potential post-treatment and eventual patient-satisfaction trends, should be analysed for long-term evidence-based neuro-immunomodulation-based innovative therapeutics in pragmatic timely clinical management of glioblastoma and benign/metastatic spinal meningioma amongst susceptible cohorts of ethnically disparate populations worldwide.

Precision-based high-throughput, non-invasive neuro-radiosurgery especially Gamma-Knife based procedure(s) with precise targeting of the inflammatory tumor core in glioblastoma, and diagnostic spinal magnetic resonance imaging for locating the inflammatory tumor core prior to treatment/intervention(s) are certainly a boon in the complex neuro-immuno-oncology field. The biochemical/metabolic cross-talks amongst the enigmatic array of TLRs and Autophagy signaling components primarily Beclin-1, Microtubule-associated-Light-Chain-Protein (LC-3) isoforms I and II, Atg 2/5/7 and apoptosis/necrosis markers Bcl-2 and High-Mobility-Group Box-1 (HMGB1), and Ceramide/Sphingolipid-Wnt signaling cascade offer fascinating neuro-immuno-oncology-based therapeutic avenues for elegant development of predictive and/or prognostic biomarkers in timeline-driven cost-effective risk-stratification and management of glioblastoma and meningioma in susceptible populations: North American, Asian-Indian (North/South Indian), Chinese, European (British, Danish, Nordic, etc.), African, Australian, etc. worldwide in the Covid-19/Omicron pandemic era [1,2].

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