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# Toll-Like Receptors-Autophagy Immuno-Inflammatory “Molecular Cross-talks” in Hypoxic Tumor Microenvironment in Complex Neurological Diseases Primarily Glioblastoma: Translational Research Impact in Genetically Susceptible Population-Pools in Covid-19/Omicron Pandemic Era

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Deciphering the underlying cellular/molecular and genetic basis of inflammatory tumor microenvironment in complex neurological diseases especially glioblastoma warrants dynamic collaborations in clinical research worldwide. The overwhelming disproportionate share of morbidity and mortality amongst genetically and ethnically heterogeneous population-pools symptomatic of early vs advanced stage/grade brain tumors is certainly intriguing; adequate public health-oriented endeavors for meaningful patient-centric evidence-based pragmatic outcomes for successful design and development of clinically validated biomarkers for glioblastoma management would prove to be a “neurophysiological genetic roadmap” for patient-friendly immunotherapeutically safe precision medicine-oriented treatment.

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

Furthermore, cross-sectional/longitudinal/prospective/retrospective innovative study-designs with logical inclusion and exclusion criteria along with adherence to core tenets of good clinical practice, scientific integrity and bioethics, enrolling adequate samples of clinically confirmed cases of glioblastoma 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); considerable statistical power with an adequate sample-size leading to minimal selection-bias warrants collaborative multicentric gene-epidemiology studies conducted by biomedical researchers to draw meaningful conclusive interpretation of the data-sets thereby yielding unambiguous reproducible end-points for evidence based clinical management of glioblastoma along with other neurological disorders/ailments of complex etiopathogenesis.

Eventually, evidence-based neuro-immunomodulation-based innovative therapeutics in pragmatic timely clinical management of glioblastoma amongst susceptible cohorts of ethnically disparate populations worldwide warrants 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 computed tomography-magnetic resonance imaging for locating the inflammatory tumor core prior to neurosurgical intervention(s) offer fascinating avenues in the complex neuro-immuno-oncology field. The biochemical/metabolic cross-talks amongst the enigmatic array of TLRs and Autophagy signalosome 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 are emerging as elegant “neuro-immune molecular rheostats” for development of predictive and/or prognostic biomarkers and pharmacological scaffolds in timeline-driven cost-effective risk-stratification and management of glioblastoma in susceptible populations worldwide in the Covid-19/Omicron pandemic era [1-3].

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