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Immunomodulation of Ceramide-Toll Like Receptors Biochemical Signalling Cascades in Neuro-inflammation: Translational Research Perspective .

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Introduction:

Immunotherapeutic targeting of Ceramide, a sphingosine-based lipid molecule, and Toll-like Receptors (TLR 1-10) is emerging as a promising pharmacological strategy for myriad inflammatory diseases, including neurodegeneration, Alzheimer's Disease, bipolar disorder, schizophrenia, dementia, and glioblastoma; metabolic tilting of the host cell in normal asymptomatic versus symptomatic disease condition with physiologically perturbed altered mileu primarily due to stress, glucose depletion, starvation, hypoxia and vascular insufficiency leads to aberrant cellular differentiation, proliferation, apoptosis, senescence and autophagy. In my expert opinion with substantial scientific contributions in the complex ever-expanding field of inflammatory diseases with experience of advanced biomedical public health impact oriented innovative research with emphasis on compassionate meaningful respectful patient-care amongst ethnically disparate cohorts of United States of America (Nebraska-Midwest, Texas and New York) as well as Asia-Pacific India, there is an urgency for dynamic ethical collaborations for reducing the disproportionate share of morbidity and mortality associated with neuro-inflammatory diseases and designing a "biochemical-genetic roadmap" for successful patient-care in both high and low-resource settings with relative paucity of financial support for effective medical critical care emergency treatment.

Sphingomyelinase-dependent hydrolysis of sphingomyelin and de novo synthesis with metabolic coordinated reaction sequelae of serine-palmitoyl transferase and ceramide synthase are the two major signalling pathways involved in ceramide synthesis (1); furthermore, clustering of plasma membrane rafts into ceramide-enriched platforms serves as an important transmembrane signalling mechanism for cell surface receptors, including the enigmatic array of Toll-like Receptors (2) with significant implications in inflammation and neuro-immunomodulation in neurons and neurosynaptic intersections in intriguing maze of the "neuronal web" in symptomatic patients of neuro-inflammatory

diseases. The adaptor proteins, myeloid differentiation factor 88 and Toll IL-1 receptor (TIR) domain containing adaptor inducing IFN-b (TRIF) are the pivotal players in the TLR signalling cascade triggering activation of nuclear factor (NF)-kB and interferon regulatory factor-3, respectively (3).

Biomedical research clinically impactful innovative convincing studies have demonstrated that cultured hippocampal neurons pre-treated with ceramide results in death-associated protein kinase (DAP) activation and subsequent neuronal cell death (4). Galactocerebroside mediated transmembrane signalling has been experimentally demonstrated in modulation of voltage-sensitive Ca2+ channels in U-87 MG human glioma cell line (5); evidence-based translational research further corroborated the critical role of nuclear sphingomyelinase/sphingomyelin synthase balance/tilt in serum deprivation-induced apoptosis in HN9.10e embryonal hippocampal cell line adversely affecting the neurodevelopment with aberrant endocytosis coupled with disruption of neuronal lysosomal proton gradient with accumulation of neurotoxic amyloid peptide (6). Minoretti et al. (7) have substantiated that TLR-4 Asp299Gly variant may confer protective effect in host towards susceptibility to Late onset Alzheimer's disease, thereby warranting future replicative causal genetic epidemiology large sample size based prospective cross-sectional multicentric studies for development of patient-friendly immunotherapeutic regimens alongwith pharmacological scaffolds and novel heterocyclic drugs, Ceramide analogues and TLR antagonists as potent neuro-immunomodulators for cost-effective treatment of neuronal diseases.

Dissecting the intricacies associated with complex neuro-inflammatory diseases involves considerable expertise, knowledge and dedication by adherence to good practice clinical-biomedical research with scientific integrity following the core tenets of bioethics for cost-effective evidence-based disease management amongst susceptible population-subsets of varying genetic landscapes and lifestyles for eventual design of predictive and prognostic biomarkers globally.

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