Open access Journal of
Neurology & Neurosurgery
ISSN: 2476-0501

Juniper Publishers
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Review Article
Volume 12 Issue 3 - December 2019
DOI: 10.19080/OAJNN.2019.12.555840

Open Access J Neurol Neurosurg

Glia Maturation Factor in the Pathogenesis of Alzheimer's Disease

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Submission: November 13, 2019; **Published:** December 17, 2019

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Abstract

Alzheimer's Disease (AD) is a neurodegenerative and neuroinflammatory disease characterized by the presence of extracellular Amyloid Plaques (APs) and intracellular Neurofibrillary Tangles (NFTs) in the brain. There is no disease modifying therapeutic options currently available for this disease. Hippocampus, entorhinal cortex (Broadmann area 28), perirhinal cortex (Broadmann area 35) and insular cortices are areas within the brain that are first ones to be severely affected in AD. Neuroinflammation is an important factor that induces neurodegeneration in AD. Glia Maturation Factor (GMF), a proinflammatory factor plays a crucial role in AD through activation of microglia and astrocytes to release proinflammatory mediators in the brain. Through immunohistochemical studies, we have previously shown that GMF is highly expressed in the vicinity of APs and NFTs in AD brains. Glial Fibrillary Acidic Protein (GFAP), reactive astrocytes, ionized calcium binding adaptor molecule-1 (Iba-1) labelled activated microglia and GMF immunoreactive glial cells are increased in the entorhinal cortical layers especially at the sites of APs and Tau containing NFTs indicating a role for GMF. Overexpression of GMF in glial cells leads to neuroinflammation and neurodegeneration. Inhibition of GMF expression reduces neurodegeneration. Therefore, we suggest that GMF is a novel therapeutic target not only for AD but also for various other neurodegenerative diseases.

Keywords: Alzheimer's disease; Amyloid plaques; Neurofibrillary tangles; Glia maturation factor; Hippocampal formation; Neurodegenerative diseases; Glial activation; Neuroinflammation; Chemokines

Abbreviations: AD: Alzheimer's Disease; Aps: Amyloid Plaques; GMF: Glia Maturation Factor; GFAP: Glial Fibrillary Acidic Protein; NFTs: Neurofibrillary Tangles; CNS: Central Nervous System; MS: Multiple Sclerosis; EAE: Experimental Autoimmune Encephalomyelitis; MAPKs: Mitogen Activated Protein Kinases; ROS: Reactive Oxygen Species; iNOS: Nitric Oxide Synthase; LAMP1: Lysosome Associated Membrane Protein1; TNF: Tumor Necrosis Factor-alpha

Introduction

Alzheimer's Disease (AD) is a chronic progressive neurological disorder affecting 5.8 million Americans and 35 million individuals worldwide (Alzheimer's disease Association, Chicago, IL). Extracellular Amyloid Plaques (APs) and intracellular Neurofibrillary Tangles (NFTs) are the hallmarks of AD. NFTs are made up of abnormally phosphorylated Tau proteins and its number is closely associated with clinical symptoms in AD patients [1-10]. Entorhinal cortex is involved in memory formation, retrieval, and extinction. Hippocampus is important for learning and memory functions. Together with hippocampal formation, the entorhinal cortex forms the major part of medial temporal lobe that is involved in AD and has dense NFTs formation and amyloid deposits. Entorhinal cortex and hippocampus are severely affected, atrophied and inflamed in AD patients. Memory loss is one of the earliest symptoms in AD patients due to the destruction of entorhinal cortex projections and the perforant pathways to the hippocampal formation [2,3]. In this mini review, we discuss on the role of Glia Maturation Factor (GMF) in the pathogenesis of AD.

Glia maturation factor and Alzheimer's disease

Recent studies suggest that inflammation plays a critical role in the onset and progression of neuroinflammatory and neurodegenerative diseases including AD [11-15]. GMF, a brain protein was previously isolated and characterized in our laboratory is mainly found to be localized in glial cells and in some neurons in the Central Nervous System (CNS) [16-18]. GMF in excess

leads to the death of neurons by inducing neuroinflammation in neurodegenerative diseases including AD, Parkinson's Disease (PD), Multiple Sclerosis (MS) and its animal model Experimental Autoimmune Encephalomyelitis (EAE) (Figure 1) [19-28].

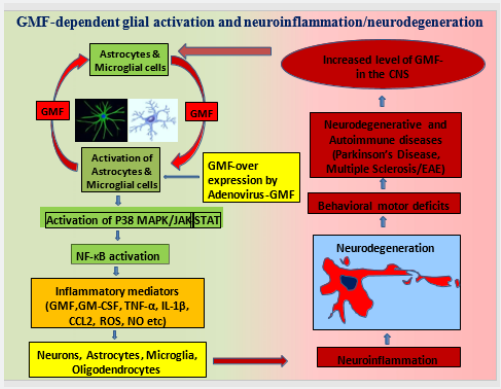

Figure 1: Schematic diagram showing GMF-β-dependent glial cells activation mediated neuroinflammation and neurodegeneration. Activated astrocytes and microglial cells release GMF-β that in turn acts on glial cells/neurons. Increased expression of GMF-β in neurodegenerative diseases or GMF-β overexpression in animas by adenoviral vector-mediated GMF gene transfection activates MAPKs/JAK-STAT and NF-kB pathways and induces the release of several neuroinflammatory mediators such as cytokines, chemokines, ROS, nitric oxide and GMF-β. These mediators induce neuroinflammation and neurodegeneration leading to dementia and motor behavioral disorders in neurodegenerative diseases/EAE.

There is specific upregulation of GMF expression in glial cells associated with APs and NFTs in the entorhinal cortical layers and hippocampus of AD brains [2,3]. We believe that GMF is a novel therapeutic target and therefore inhibition of GMF expression can inhibit the onset and progression of neurodegenerative diseases including AD [29-33]. GMF and Glial Fibrillary Acidic Protein (GFAP) are increasingly expressed in the hippocampus and entorhinal cortex of AD brain especially at the sites of APs and NFTs [2-6]. During normal aging process hippocampus and entorhinal cortex are subjected to widespread oxidative stress, decreased antioxidant function and enhanced expression of GFAP. GMF accelerates and potentiates these processes and makes the neuronal cells more susceptible to degeneration in neuroinflammatory conditions [3-7,17,34,35]. Neuronal death in AD is mediated by APs and NFTs. Other factors such as local inflammatory infiltrates including glial cells (microglia/astrocytes) and release of inflammatory molecules contribute to neuroinflammation and disease severity [4,16,36-38]. AD pathogenesis involves sustained neuroinflammation by glial activation that produces proinflammatory cytokines, chemokines, free radicals such as reactive oxygen species/ reactive nitrogen species, and activation of transcription factor nuclear factor-kappa B (NF-κB) and Mitogen Activated Protein Kinases (MAPKs) [4,7,16,36-38]. Mitochondrial dysfunction plays a crucial role in the development and progression of AD. Mitochondria are the main sites for Reactive Oxygen Species (ROS) production. Increased expression of Inducible Nitric Oxide Synthase (iNOS) around the plaques has been shown to contribute to the oxidative stress in AD brains. Uncoupling Proteins (UCPs) are inner mitochondrial proteins that protect neurons by reducing the production of free radicals [7]. UCP2 and UCP4 are down regulated in AD brains with upregulation of GMF expression in the glial cells along with increased iNOS and NF-κB activities thereby indicating that GMF plays a proinflammatory role in the pathogenesis of AD probably by promoting mitochondrial dysfunction through down regulation of the UCPs. Mitochondrial dynamics in AD may be regulated on one hand by UCPs through their action on FASN/fatty acid synthase and on other hand by GMF through its action on the NLRP3 inflammasome [7].

Recently, we have shown that in human AD brains, GMF co-localizes with the NLRP3 inflammasome and the autophagosome markers Lysosome Associated Membrane Protein1 (LAMP1) and autophagic protein sequestosome1 (SQSTM1)/p62, clearly pointing to the role of GMF in increased Aβ level in AD aggregates. Analysis of human AD brain tissue sections from the temporal cortex showed besides GMF increased expression of the inflammasome components NACHT, LRR and PYD domains-containing protein 3 (NLRP3) and caspase-1 along with the products interleukin-1beta (IL-1β and IL-18 [39]. The co-localization of inflammasome components and pro-inflammatory cytokines with GMF was found in the vicinity and periphery of APs and NFTs. GMF and apolipoprotein E4 (ApoE4) are strongly expressed and co-associated in the APs and reactive astrocytes surrounding APs in AD brains [40]. These results show that GMF and ApoE4 should together be contributing to the neuropathological changes associated with AD. GMF enhances astrocyte activation through secretion of Granulocyte-Macrophage-Colony Stimulating Factor (GM-CSF) [19]. High level expression of GMF in activated glial cells further augments chemoattraction, proliferation, activation and release of inflammatory mediators IL1, IL-33, Tumor Necrosis Factor-alpha (TNF-a), Macrophage Inflammatory Proteins-1 beta (MIP-1β), complement protein C1q, class II Major Histocompatibility Complex (MHC) proteins, 12-lipoxygenase

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and chemokine CX3C and exacerbating the pathogenesis of AD. This reflects the paracrine and/or autocrine signaling by GMF [1-4,16,41,42]. Increased expression of GMF in association with β-amyloid (Aβ) has been shown to amplify the deleterious inflammation propagated by the NLRP3 inflammasome causing mitochondrial dysfunction, and further that GMF and A β synergize in bringing upon this dysfunction by changing mitochondrial dynamics through alterations in fission and fusion proteins [43].

Conclusion

Increased expression of GMF by glial cells in the temporal cortex of AD brain suggests GMF's proinflammatory role of neurodegeneration in the pathogenesis of AD. Furthermore, we suggest that GMF is a novel therapeutic target not only for AD but also for various other neurodegenerative diseases.

Acknowledgement

This work was supported by the National Institutes of Health (NIH) Grant AG048205 and Veterans Affairs Research Career Scientist Award to Asgar Zaheer.

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DOI: 10.19080/OAJNN.2019.12.5558340

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