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Wnt Signaling: A Boon or Bane for Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is the most abundant form of dementia worldwide and elderly people are prone to this disease. Until now, no such therapeutic intervention has been identified to curb it. Wnt signaling being a major regulator of systemic homeostasis, plays a significant role in the disease response. Wnt signaling pathway is intrinsically associated with the regulation of synaptic plasticity, microglial activation and maintenance of blood brain barrier (BBB). In spite of these all-round executions, there is a lack of detailed study to present an opinion about the importance of this signaling cascade in AD. In this review we will uphold the major queries related to the disease which can be elucidated by Wnt signaling pathway.

Keywords: Wnt; Alzheimer's Disease; Neuron; Astrocyte; Microglia

Abbreviations: CNS: Central Nervous System; NSC: Neuronal Stem Cells; PCP: Planar Cell Polarity; ETC: Electron Transport Chain; DAM: Disease Associated Microglia

Introduction

Alzheimer's disease is one of the most prevalent neurodegenerative diseases in the world which mostly appears with aging [1,2]. Neuronal death, followed by cognitive decline and memory loss serve as an important outcome of the disease [3]. The Central Nervous System (CNS) comprises different cell types, mainly neurons and glia (Astrocytes, Microglia, Oligodendrocytes). Glial cells provide appropriate metabolic support to the neurons for their proper functioning and helps to maintain a stable bioenergetics for proper neuronal transmission [4,5]. Nonetheless, different neuronal type in different region of the brain also regulate the function of the glial cells in a spatio-temporal manner [6]. This crosstalk between neuron and glia is regulated by a multitude of signaling processes. Wnt signaling regulate the proliferation and differentiation of neuronal stem cells (NSC) and is an integral part of neurogenesis and neuronal function [7,8]. Wnt ligands also serve as important factors for the activation of the glial cells, which plays a crucial role in neuronal apoptosis during neurodegeneration [9,10]. Here, we discuss how the balance of different wnt ligands can affect the homeostasis of neuron-glia cross-talk, the anomaly of which is a major driving force of neurodegeneration.

WNT Signaling in Synaptic Transmission and Cognitive Decline

Wnt family of protein ligand comprises of 19 different secreted glycoproteins which are conserved across different mammalian species [11,12]. Although they are majorly classified in two classes canonical and non-canonical, the overlap of the signaling intermediates and outcome is quite often [13,14]. Several studies have reported the importance of this signaling in dendritic development, synaptic transmission, synaptogenesis and in different disorders [15-18]. Cognition, memory and motor movements are among several behavioral parameters which is compromised in different neurodegenerative diseases including AD [19]. Wnt7a/b is known to play a vital role in the assembly of synaptosomes and thereby contributes to the synaptic plasticity [20,21]. As reduced synaptic transmission is one of the early markers of AD [22], the variation in the level of Wnt7a/b signaling cascade in neurons and the glial cells

can be highlighted as an important area of future research. Since, Wnt signaling is known to affect the calcium uptake [23,24], an important contributor of action potential, there is scope of exploration in the role of Wnt7a/b in calcium uptake deregulation during neurodegeneration. Whether Wnt7a/b contributes in microglial activation and astrocytic metabolic disbalance is not known. Since ROR1, a well-known receptor for different ligands is also a genetic risk factor for AD, It will be intriguing to look at the interaction of different Wnt ligands (Wnt7a/b, Wnt5a, Wnt3a) with ROR1 in cell-specific context in the diseased brain.

Wnt Signaling in Disease Associated Microglia

Microglia are the immune cells residing in CNS and equipped with metabolic versatility to patrol in different regions of the brain [25,26]. During host-pathogen interaction, Wnt5a is known to regulate the uptake and autophagy mediated containment of the pathogens through alteration of cytoskeletal dynamics in macrophages [27-30]. Since impaired autophagy in neurons and microglia in diseased brain is very well characterized [31,32], further insight into the status of Wnt signaling intermediates in different brain cell types can provide deeper knowledge about the impact of this pathway in AD. Canonical Wnt3a/β-catenin signaling is known to transcriptionally regulate the expression of STUB1 [33], an E3 ubiquitin ligase intrinsically associated with the deposition of misfolded protein aggregates in AD brain [34,35]. Altogether, Wnt ligands vividly regulate the degradation machinery of misfolded proteins and cellular components in the system. Wnt ligands can also regulate the inflammatory state of the microglia [9]. Dysregulation of these above signaling parameters may activate the microglia and contribute in their M1 to M2 transition in CNS. Several lines of evidence suggest that complex Wnt signaling cascades are closely associated with deposition of cholesterol in macrophages resulting in aberrantly functioned fatty macrophages at atherosclerotic lesions [36-38]. On the other hand, cholesterol is also known to activate different modes of Wnt signaling in a concentration dependent manner [39]. In AD brains, cholesterol deposition and excessive lipid droplet formation in microglia has also been recently reported [40-42]. Taken together, dysfunctional autophagy mediated degradation machinery and deposition of cholesterol may give rise to a different class of microglia known as Disease Associated Microglia (DAM) in the AD brain with distinct transcriptional signatures [43]. It will be interesting to explore whether Wnt ligands play similar functions and steers the transformation of microglia from homeostatic state to proinflammatory DAM state in CNS. WNT/Planar Cell Polarity (PCP) pathway not only regulates the calcium balance but also contributes to cytoskeletal alteration and polarity of the cells [44]. As microglia can migrate in different regions of the brain, it will be fascinating to explore the role of WNT/PCP pathway in microglial polarization and their metabolic versatility in disease condition.

WNT Signaling in Astrocytes

Astrocytes are known to be the most important metabolic lifeline for neurons [45,46]. Astrocytic Wnt signaling is crucial for maintenance of BBB and protect the neurons [47]. Neurons generate tons of free fatty acids and different metabolic byproducts during synaptic transmission but they are not equipped with efficient cellular machinery to reduce that metabolic stress. Interestingly, mitochondria in astrocytes are fortified to reduce the Fatty Acid and lipid stress for neurons due to their efficient ETC (Electron Transport Chain) complex I assembly and function [48]. Astrocytic activation and dysfunction are one of the very early manifests of the disease [49], failing of which leads to neuronal apoptosis. Wnt signaling has not yet been studied extensively in astrocytic activation. Astrocyte-neuron lactate shuttle is one of the well-established metabolic pipelines between neurons and astrocytes. Wnt ligands, being a regulator of vesicle transport inside the cells presumably play a major role in maintenance of the shuttle.

Discussion

Alzheimer's Disease comprises the most abundant form of dementia. Tau aggregates and Aβ- plaques are the early manifests of the disease which results in neuronal death and successive neurodegeneration [50]. In CNS different cell types are intrinsically wired to maintain proper synaptic plasticity resulting in cognition and memory function. In AD brain, activated microglia are the major bearer of tau spreading and neuroinflammation [51]. The inflammatory cytokines released by activated microglia are serious threat for the neurons [52]. On the other hand, aberrantly activated astrocytes in the diseased condition are uncooperative to take the metabolic burden from neurons and this in turn can activate the microglia to come close together and phagocytose the dying neurons. Wnt signaling, being a central regulator of development and neurogenesis [53] supposedly play a significant role in this crosstalk which has not been investigated till now. GSK3β, one of the intermediates of canonical Wnt signaling has been showed to regulate Tau hyperphosphorylation and aggregation [54]. However, GSK3β can also be regulated by Insulin signaling cascade through AKT [55]. So, only pin-pointing GSK3β makes the role of Wnt signaling inconclusive in the disease. Although, few reports mentioned about the variation of specific Wnts in different cell types at mRNA level, the mechanistic details are still missing [56]. Few reports suggest Wnt signaling as beneficial but there are studies showing the detrimental role of this signaling [57,58]. To address this question, Wnt signaling cascade needs to be dissected in a cell-specific manner. With identification of Wnt receptor ROR1 as a genetic risk factor [59], there is an urgency to study the importance of this signaling in the disease. LRP1, a co-receptor for many Wnt ligands also known to interact with Tau and promotes Tau seeding in neurons [60]. Apoβ4, the strongest genetic

risk factor of AD is known to regulate Wnt signaling pathway in neuroendocrine cells [61]. All these discrete studies are bringing Wnt signaling into limelight for AD and demands more comprehensive insight for the role of Wnt signaling and its intermediates in the disease. Different modes of activation or inactivation of this signaling may unlock some novel therapeutic interventions for the disease.

Conclusion

Right now there are more than 55 million Alzheimer's Disease patients worldwide and the number is expected to reach around 139 million by 2050 [62]. These increasing numbers expose the failure of a successful therapeutic intervention for the disease. Wnt signaling pathway has already been targeted in cancer and in some cases the inhibitors are successful in restraining the disease [63-65]. In AD, there is a lack of mechanistic insight about the role of Wnt signaling in disease progression. Considering the significance of Wnt signaling in neurogenesis, synaptic development and neuroinflammation, a comprehensive study of this signaling pathway in AD may guide the discovery of a successful treatment alternative.

Conflict of Interest

The authors declare no conflict of interest.

Author Contribution

S.J conceived the idea and wrote the manuscript. S.K did the literature search and helped in writing.

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