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Perspective

New Emerging Trends in Alzheimer's Disease Drug Research

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Alzheimer's disease (AD) is a progressive slow growing neurodegenerative disorder of the brain. It is associated with memory impairment, progressive cognitive decline and changes in personality and behavior [1]. It has been estimated that the global prevalence of the disease would be near to 106 million by 2050. The characteristic neuropathology of AD involves cholinergic loss, extracellular deposition of amyloid-β plaques, and formation of intracellular neurofibrillary tangles, chronic brain inflammation, oxidative damage and mitochondrial dysfunction [2]. Currently approved US-FDA drugs provide only symptomatic relief in ameliorating cognitive impairment of AD. With growing research and advent of new technologies in the field of AD, the understanding of the complex pathophysiology on how AD develops proceeds significantly. This advancement promotes drug discovery to identify new potential emerging therapeutic targets which may emerge new pathway towards the diagnosis and treatment of AD [3]. Till date, due to the complexity of this disease, there are no effective treatments available that can slow or halt the progression of this deadly disease. Therefore, there is emergent need to explore and develop effective drug strategies for AD and its management.

Different hypotheses have been put forward such as amyloid-β (Aβ) protein aggregation, excessive metal ions, oxidative stress and mitochondrial dysfunction hypotheses to understand the complex pathophysiology of AD. Out of these, amyloid hypothesis has been widely accepted as the key pathological feature of AD in which plaques are formed from cleavage products of the amyloid precursor protein (APP). According to the amyloid hypothesis of Alzheimer pathogenesis, it is evidenced that amyloid β-protein (Aβ) initiates a cascade leading to neurotoxicity and neurodegeneration [1].

As reported earlier that, tau protein is also required for the microtubule assembly and stabilization. In AD, tau abnormally hyperphosphorylated known as tauopathies form paired helical filaments (PHFs) which then form a compact filamentous network called neurofibrillary tangles (NFTs) [1]. These NFTs have been reported in different neurodegenerative diseases such as AD, supranuclear palsy, Parkinson's disease and amyotrophic lateral sclerosis. It has been reported that this abnormal tau protein hyperphosphorylation is regulated by protein kinases and phosphatases such as glycogen synthase kinase 3β (GSK-3β) and the cyclin-dependent kinase 5 (CDK5). Other kinases involved in the phosphorylation process were casein kinase 1delta (CK-1δ), mitogen-activated protein kinases (MAPKs), cAMP-dependent protein kinase (PKA), and calcium/calmodulin-dependent protein kinase II (CaMKII) [4]. The inhibition of abnormal hyperphosphorylation of tau, is one of the most promising therapeutic approaches for the development of disease modifying drugs in AD. The inhibition of neurofibrillary degeneration is of great advantage by evaluating the levels of total tau and tau phosphorylation at various known abnormally hyperphosphorylated sites in the cerebrospinal fluid of AD patients. In AD, glycogen synthase kinase-3 (GSK-3) interacts with multiple components of the plaque-producing amyloid beta (Aβ), phosphorylating the microtubule-associated protein tau leading to the formation of NFTs and presenilin protein. GSK-3 plays a central role in neuronal plasticity and memory. It also promotes both inflammation and apoptosis. So, GSK-3 is the potential emerging target for the treatment of AD [5].

Immunotherapy has triggered a new area for development of Alzheimer's therapeutics by recruiting an immune response against beta-amyloid (Aβ). Previous finding suggest that monoclonal antibodies against synthetic Aβ peptide can keep the peptides from aggregating into neurotoxic fibrils and can dissolve already formed amyloid. Active and passive immunization studies in transgenic mice models of AD show that antibodies against Aβ peptide are effective in reducing Aβ levels and plaque pathology, as well as attenuating cognitive deficits in animal models of AD sometimes associated with adverse reactions. Blocking the β-secretase cleavage site of APP using antibodies which interfere with APP-BACE interaction Aβ peptide formation can be reduced [6].

Scyllo-Inositol, is a naturally occurring compound present in the body, has shown promising therapeutic potential for AD, because it is an orally available natural compound that penetrates into the brain and coats the surface of amyloid β-proteins (Aβ) to inhibit their lateral stacking into toxic amyloid fibrils both *in-vitro* and *in-vivo*. A study on TgCRND8 mice shows that over express human APP, bearing two familial AD mutations, treatment with scyllo-inositol resulted in reduced Aβ pathology, a rescue of spatial memory and an increase in survival in transgenic animals. It is currently in phase II clinical trials for AD. Phase I clinical trials have shown that scyllo-inositol is well tolerated, with no significant adverse effects at all doses tested. Orally administered scyllo-inositol is able to cross into the CNS at levels that were therapeutically effective in animal models of AD [7].

γ-Secretase is an important enzyme required for the proteolytic cleavage of amyloid precursor protein (APP) to generate Aβ, the major component of plaques found in brains of AD patients. Different classes of γ-secretase inhibitors have been explored to block the cleavage of APP and the generation of toxic Aβ. Various *in vitro* and *in vivo* studies have demonstrated that the key components of the γ-secretase complexes such as Nicastrin and APH-1 are capable of modulating γ-secretase substrate recognition and Aβ production. Different classes of γ-secretase inhibitors have been explored to block the cleavage of APP and the generation of toxic Aβ, however, they also block the γ-secretase cleavage of Notch to generate Notch Intracellular domain (NICD), a critical signaling molecule. Thus, γ-secretase, and its subunits in particular, continue to be one of the prime targets for the development of amyloid based AD therapies [8].

As it is evidenced that AD, like Type 2 diabetes mellitus (T2DM), is an insulin resistance disease. It is associated with significant deficits in insulin and insulin-like growth factor (IGF) and receptor gene expression, and impaired insulin/IGF receptor binding in brain. These abnormalities worsen as AD progresses, and correlate with cholinergic dyshomeostasis. A study on intracerebral injection of streptozocin causes neurodegeneration and cognitive impairment was ameliorated by treatment with insulin sensitizer drugs. Therefore, the potential insulin sensitizer agents that target T2DM and AD, may possibly be the differently targeted mechanisms of neurodegeneration [9].

Inhibition of tau is another important emerging target in AD. In sporadic AD, mitochondrial dysfunction results in over-crowding of endosomal-lysosomal pathway leads both to nucleation of tau aggregation and decreased capacity of this pathway to clear tau oligomers. Targeting tau aggregation and disaggregation of oligomers offers the potential to alter the rate of disease progression by facilitating clearance of the constituent monomers through the more efficient proteasomal pathway and bypassing the endosomal-lysosomal pathway [10].

Another important target in AD is metabolic disturbance of insulin. In AD, patients without diabetes showed marked reduction in insulin signaling and IGF-I (insulin like growth factor-1) signaling pathway. At serum level, IGF-1 levels have been reported to be altered in AD, and it was suggested that the changes in IGF-1 serum level may play a role in disease pathology and progression. The level was found to be high in initial stages, low at more advanced stages of AD. Thus, IGF-1 plays an important therapeutic and emerging target in AD [11].

AD is also characterized by low cerebral metabolic rate of glucose that leads to catharsis. Ketosis is characterized by an increase in circulating ketone bodies (β-hydroxybutyrate, acetoacetate and acetone) which is produced by the body from fat stores under conditions of low glucose like fasting. The neuroprotective potential of ketone bodies has very well demonstrated in animal models of several neu-

rodegenerative conditions. So targeting low cerebral metabolic rate of glucose by induction if ketosis represents a promising therapeutic approach in AD [12].

Bibliography

1. Kumar A., *et al*. "A review on Alzheimer's disease pathophysiology and its management: an update". *Pharmacological Reports* 67.2 (2015): 195-203.

2. Kumar A and Singh A. "A review on mitochondrial restorative mechanism of antioxidants in Alzheimer's disease and other neurological conditions". *Frontiers in Pharmacology* 6 (2015): 206.

3. Anand R., *et al*. "Therapeutics of Alzheimer's disease: Past, present and future". *Neuropharmacology* 76 (2014): 27-50.

4. Mondragón-Rodríguez Siddhartha., *et al*. "Tau Amyloid Beta and Deep Brain Stimulation: Aiming to Restore Cognitive Deficit in Alzheimer's disease". *Current Alzheimer Research* (2016).

5. Eldar-Finkelman H. "Glycogen synthase kinase 3: an emerging therapeutic target". *Trends in Molecular Medicine* 8.3 (2002): 126-132.

6. Carrera Ivan., *et al*. "Validating Immunotherapy in Alzheimer's Disease: The EB101 Vaccine". *Current Pharmaceutical Design* 22.7 (2016): 849-858.

7. Tanaka K., *et al*. "Scyllo-Inositol, a Therapeutic Agent for Alzheimer's Disease". *Austin Journal of Clinical Neurology* 2.4 (2015): 1040.

8. Slavica Krantic. "From Current Diagnostic Tools and Therapeutics for Alzheimer's Disease Towards Earlier Diagnostic Markers and Treatment Targets". *Current Alzheimer Research* 14.1 (2017): 1-5.

9. Somang Kan.g, *et al*. "Agmatine ameliorates type 2 diabetes induced-Alzheimer's disease-like alterations in high-fat diet-fed mice via reactivation of blunted insulin signaling". *Neuropharmacology* 113 (2017): 467-479.

10. Wischik CM., *et al*. "Tau-aggregation inhibitor therapy for Alzheimer's disease". *Biochemical Pharmacology* 88.4 (2014): 529-539.

11. Philip P Ostrowski., *et al*. "Meta-Analysis of Serum Insulin-Like Growth Factor 1 in Alzheimer's Disease". *PLoS One* 11.5 (2016): e0155733.

12. Klaus W Lange., *et al*. "Ketogenic diets and Alzheimer's disease". Food Science and Human Wellness (2016).

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