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Targeting Cell Signalling Pathways: Novel Targets for Alzheimer's Disease

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Abstract

Alzheimer's is the most common cause of dementia and is associated with the selective damage of brain regions and neural circuits critical for memory and cognition. Alzheimer's disease (AD) is mostly affecting the aging population. Progressive accumulation of Amyloid beta results in the formation of Ab oligomers and fibrils which are the principal components of the plaque. No pharmacological therapies have been success to prevent the disease progression. We need to identify novel biological markers to diagnose the early symptoms of AD. The Hedgehog (Hh) pathway is a major regulator of many fundamental processes in vertebrate embryonic nervous system development. Previous studies have demonstrated that Shh signalling is activated in adult organism after injury and is involved in tissue repair mechanisms. Targeted inhibition of Shh signalling cascade may be effective in the treatment and prevention of many types of human cancers as well as AD.

Introduction

Alzheimer's disease is a brain disorder named after German physician Aloes Alzheimer, who first described it in 1906. Alois Alzheimer described the case of Auguste D, recording an ante-mortem history of impaired memory, problems of speech, paranoia and delusional ideation [1]. The post-mortem revealed an atrophied brain, and for the first time neurofibrillary tangles were detected and described. The disorder became better known as Alzheimer's disease, and is the most common cause of dementia in the elderly population of the world. Since the early finding by Alois Alzheimer the cause(s) for the disease remain unclear and at present the disease can only be definitively diagnosed post mortem. The identification of a biological marker(s) of Alzheimer's disease would have utility in helping to diagnose the disease and to monitor and measure disease associated changes. The biological marker(s) could potentially lead to the development of new drug treatments and an early and accurate diagnosis of Alzheimer's disease.

Alzheimer's Disease Epidemiology

By the estimation of US Census Bureau data is that, between 2000 and 2020, the number of peoples living to 100 years or more will raised by over 200% and the number of people surviving to 90-95 years will double. From an epidemiologic perspective, the Baltimore Longitudinal Study of Aging (1985-1998) found that the incidence rates of AD increased with age from an estimated 0.08% per year in the 60-65-year age group to an annual estimated incidence of 6.48% in the ≥85-year age group [2].

AD is estimated to have cost the world $604 billion in 2010 alone [3]. These costs are staggering, particularly in light of predictions that the worldwide number of AD cases, currently estimated at 36 million, will triple by 2050 [3].

Risk Factors

Aging is the primary risk factor in Alzheimer's disease. However other risks factors include decreased reserve brain capacity, gross brain shrinkage, low mental achievement in early life, and minimal level mentally taxing occupations, followed by latter life reduced mental and physical activity. Head injury has also been considered as a risk factor [4].

Hypercholesterolaemia, hypertension, atherosclerosis, coronary heart disease, smoking, obesity, and diabetes, are all linked to Alzheimer's disease dementia, as these are all considered to be vascular risk factors, affecting the effective supply of blood [5,6]. Evidence suggests that countering risks that predispose an individual to dementia include benefits derived through diet alteration that is increasing an intake

of homocysteine-related vitamins (vitamin B12 and folate); antioxidants, such as vitamin C and E; unsaturated fatty acids [5,7]. In a large population based twin study, heritability for sporadic Alzheimer's disease was high (79%) with the same genetic factors being as influential, irrespective of sex, and non-genetic risk factors such as environment [8].

Alzheimer's Disease Pathology

Alzheimer's disease pathology is characterised by the formation and accumulation of misfolded proteins in the form of plaques and tangles, in the brain.

Amyloid β

The formation of extracellular plaques is described by the amyloid cascade (also Aβ-protein) theory of plaque causing pathology [9,10]. Plaques which are arise when the amyloid precursor protein (β-APP) is cleaved by the beta-amyloid cleaving enzyme (BACE) to result the Aβ-42 type aggregations [11, 12].

The presenilin proteins (PS1 and PS2) are critical in the enzymatic cleavage of the APP, and subsequent release of β-APP. Specific mutations in the presenilin genes result in familial Alzheimer's disease (FAD), through an increase in APP cleavage, which causes an increase of β- amyloid [13]. FAD research has shown that the allele apolipoprotein E type 4 (APOE ε 4) increases the risk of late onset Alzheimer's disease [14]. The development of transgenic gene knockout animal models such as the APP swedish mutation and PS1 and PS2 mutations have elucidated the molecular mechanisms underlying plaque pathology [11,13,14]. The amyloid cascade theory is thought to be relevant to genetically inherited or predisposed people, whereby a ready mutation must exist [13]. However this theory does not explain the cause of sporadic Alzheimer's disease.

The sortilin related receptor 1 (SORL1), is a neuronal sorting receptor, APP processing is control by this. SORL1 works by directing APP into the recycling pathway, and thus away from enzymatic cleaving by BACE and the presenilin proteins. When BACE and the presenilin proteins cannot act on APP Aβ production is reduce. However, where an under expression of SORL1 does occur, then APP to BACE a direct transit occurs there, which causes Aβ production. SORL1 may be the first gene that is linked to sporadic Alzheimer's disease because there is no known reduction in SORL1 in FAD [15]. In the brains of Alzheimer's disease patients and in the brains of individuals with mild cognitive impairment levels of SORL1 have been shown to be reduced [15,16].

Clusterin is a chaperone protein that involved in the production of Aβ. A recent genome wide association study in patients with Alzheimer's disease found that clusterin was associated with the severity and progression of Alzheimer's disease [17].

The identification of specific genes which are thought to confer the risk of Alzheimer's disease is important. However, there remain problems with the identification of a specific risk gene is that a single gene will only confer a low level of risk [9]. To overcome this by analysing the genome for risk associated genes genome wide array studies have attempted. However, the role of Alzheimer's disease changes varies from one person to another.

Amyloid cascade hypothesis

The hypothesis proposes that there is a primary imbalance between Aβ production and its subsequent clearance, with increased Aβ production in familial disease and decreased Aβ clearance in sporadic disease. hippocampal function may inhibit by Aβ oligomers and Aβ oligomers also impair the synaptic function, as well as leading to inflammation and oxidative stress caused by the aggregation and depositing of Aβ. These processes combine to impair neuronal and synaptic function with resulting neurotransmitter deficits and cognitive symptoms. Tau pathology with tangle formation is regarded as a downstream event, but could contribute to neuronal dysfunction and cognitive symptoms.

Tau

It is the second major hallmark of Alzheimer's disease related changes in the brain are intracellular formations called neurofibrillary tangles (NFTs). NFTs are primarily composed of paired helical filaments (PHF). Tau protein is the major component of the NFTs, tau is a microtubule associated protein (MAP) [18], which binds with microtubulin to provide structural stability to a cell. Dissociation of the tau protein from the microtublin leads to unbounded tau protein aggregation [19]. The reason for the aggregation is explained by the tau hypothesis [19].

Under normal conditions, tau which is a soluble protein undergoes phosphorylation and dephosphorylation, thus forming insoluble aggregates. An imbalance in this dynamic results in increased levels of abnormally hyperphoshorylated tau (P-tau 181, P-tau 199, P-tau 231, P-tau 396, P-tau 404), which in turn sequesters normal tau and other MAPs (MAP1 and MAP2) [20]. Hyper phosphorylated tau aggregates into PHF, and form tangle. Parallel to the process of tangle formation is the disassembly of microtubules. The combined effect of tangle formation and disassembly of microtubules is that they compromise normal neuronal and synaptic function [21]. According to the amyloid cascade hypothesis it is the increase in concentration levels of Aβ that trigger the changes in tau thus leading to the formation of NFTs.

Alim et al. [22] have shown that the protein α-synuclein (aberrant forms of which are core components of lewy body based pathologies, known as synucleinopathies), like tau is involved in microtubule assembly, serving as a binding for the tublin protein. However this binding ability is lost when α-synuclein becomes mutated and result the tubulin aggregation (as well as α-synuclein). As microtubule function is necessary for normal neuronal and synaptic function, dysfunction of the

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microtubules may be central in neurodegeneration [22]. The pathological marker of Alzheimer's disease severity is the number of neurofibrillary tangles.

Animal models & post mortem studies

Support from the transgenic gene knockout animal model (AM) the P301L human tau mutation transgenic mouse model has been shown to produce tangles [10]. The core symptoms have a neurobiological basis, with the aggregation of amyloid plaques and neurofibrillary tangles, both developing independently of one another, and with differing patterns of distribution [10,23].

Following systematic research on post mortem brains of Alzheimer's disease patients, Braak and Braak, have shown how the disease may progress topographically with respect to time. The brain regions involved are the medial temporal cortex, hippocampus, and entorhinal cortex, anterior cingulate gyrus (as well as disruption of the neocortex) - while other areas are unaffected - prominently cerebral and cerebellar cortex. This topographically predictive nature of aggregation is thought to be a five to six stage process whereby the first three stages are preclinical, with symptomatic or clinically diagnosable symptoms becoming prominent from stages III onwards. The symptoms of amnesia are thought to be due to the hippocampus being affected and thus producing early changes in memory, and ultimately the progression to the final stage, where the neocortex is affected [23,24].

Recent studies indicated that in the majority of cases, tangle formation precedes amyloid deposits [25,26]. This is contrary to the amyloid cascade theory, which explains tangle formation as a result of amyloid plaque formation [9]. Support for this view is found in the novel creation of the "3xTgAD APP Swedish mutation," "PS1" & "P301L" animal models [10,11] which have shown amyloid deposition, as an event which precedes tangle formation, and thereby revealing a temporal and spatial distribution of tau pathology following amyloid deposition. Combination of the APP swedish mutation and "P301L" models have yielded both sets of pathologies; with amyloid considered the more pathogenic feature of the two, and therefore more liable to cause dementia.

Other aetiological hypotheses

Oxidative stress: Oxidative stress is considered to be a hallmark of neurodegenerative diseases also induce damage to various biological macromolecules in an uncontrolled manner. One consideration is that the plaques and tangles rather than being critical in the initiation or pathology of the disease are potentially acting as an antioxidant defence, that is a protective action. Therefore the subsequent appearance of Aβ deposits and tau hyperphosphorylation is a consequence of this defence [27]. Nunomura and colleagues have shown in animal model study that oxidative damage precedes the pathological changes associated with Alzheimer's disease [28].

Inflammation: Brain regions affected by Alzheimer's disease are known to contain increased neuroinflammatory mediators (cytokines and microglia) through increased inflammatory cascades [29]. However this is unknown that this is a natural response to control inflammation or an out of control immune process. Using COX-1 and COX-2 drugs the Alzheimer's disease Anti-inflammatory prevention Trial (ADAPT) looked into the role of NSAIDs in people vulnerable to dementia, but the trial was cancelled due to cardiovascular risks [30].

Cholinergic hypothesis: The cholinergic hypothesis of Alzheimer's disease suggests that destruction of the cholinergic pathway in the basal forebrain results in a reduction of cholinergic neurons, which release the neurotransmitter acetylcholine [31,32]. These neurons project to the hippocampus and neocortex, which are implicated in both memory disturbance and cognitive symptoms [31]. Enzyme acetylcholine esterase (AChE) degraded Acetylcholine (Ach). Compared to mild patients Levels of this enzyme are reduced in moderate and severe Alzheimer's disease patients; cholinesterase inhibition improves neurotransmitter function and provides relief of Alzheimer's disease symptoms [32].

Sonic hedgehog signalling pathway: The Hedgehog (Hh) gene was discovered by Christiane Nusslein-Volhard & Eric F. Weischaus [33] in 1980 in their screen for mutations that disrupt the Drosophila larval body plan [33].

Sonic hedgehog (Shh) protein is a signalling protein of Hedgehog family. When Shh binds to its receptor Patched-1 (PTCH1), PTCH1 cannot interact with the transmembrane protein Smoothened (SMO), resulting in activation of transcription factor GLI. The activated GLI regulates expression of many target genes that control cell growth, survival, and differentiation in a wide variety of cells, including neurons [34]. Shh signalling is vital during embryonic development. Previous studies have demonstrated that SHH signalling is activated in adult organism after injury and is involved in tissue repair mechanisms [35].

Shh signals have diverse functions; they may act as morphogens in the dose-dependent induction of distinct cell fates within a target field, or may act as a mitogen in the regulation of cell proliferation controlling the form of developing organs [36]. The crucial developmental function of SHh signalling is illustrated by the dramatic consequences in human foetus, with defects in the Shh signalling pathway resulting in fetuses with brain, facial and other midline defects such as holoprosencephaly (failure of forebrain development) or microencephaly, cyclopia, absent nose or cleft palate [37,38]. In adults, the Hh pathway remains active and is involved in regulation of tissue homeostasis, continuous renewal and repair of adult tissues, and stem cell maintenance [39].

Hedgehog signalling is initiated by the binding of hedgehog ligand to Patched (Ptc), which is a 12-transmembrane protein receptor [39]. Downstream of Smo is a multi-protein complex known as the Hedgehog signalling complex (HSC), which comprises the transcription factor Cubitus interruptus (Ci), the serine/threonine kinase Fused (Fu), the kinesin-like molecule

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Costal 2 (Cos2) and the Supressor of fused (Sufu). Cos2 also binds to protein kinase A (PKA), protein kinase CK1 (formerly casein kinase 1) and GSK3. Ptc represses Smo preventing the activation of Hedgehog signalling in the absence of Ligand [39]. The HSC is bound to microtubules/membranes and associates with Smo through Cos2. The full length form of Ci is prevented from nuclear translocation through interactions with Sufu and Cos2.

To produce a repressor form of Ci, a portion of full length Ci is proteolytically cleaved, which enters the nucleus leading to the inhibition of Hedgehog target gene expression. Proteolytic processing of Ci is mediated by PKA, CK1 and GSK3. In the presence of Hedgehog, the inhibitory effects of Ptc on Smo are relieved and the HSC is freed from microtubules and membranes.

Smo becomes phosphorylated by PKA and CK1 and PKA, CK1 and GSK3 are released

from Cos2, precluding the generation of the repressor from of Ci. Full length Ci is no longer inhibited by Sufu and is therefore free to enter the nucleus to induce the transcription of Hedgehog target genes.

The up-regulation of Shh signals is involved in brain stroke and even multiple sclerosis. Our previous study showed that a clear activation of the Shh pathway has been demonstrated in glioblastoma and medulloblastoma, but not clearly enough in neuroblastoma, suggests different embryological aetiology of these tumours, as they are neuroepithelial in origin, while neuroblastoma derives from the neural crest. This embryological difference might in part explain the differences in the involvement of the Shh demonstrated in our previous study for these three malignant tumours of the nervous system [40].

To our knowledge, however, there is still no investigation of Shh signalling and its relationship with neurogenesis in Alzheimer's disease brains. Some previous study found an increased level of Shh signalling in the hippocampi of APP23 mice and AD patients. The elevation of Shh signalling accelerates NSCs or GPCs into division and differentiation, resulting in an increase in the number of immediate GPCs in response to elevated Shh level [41].

Shh signalling inhibition may be effective in the treatment and prevention of many types of human cancers as well as Alzheimer's disease.

Diagnosis & Clinical Symptoms of Alzheimer's Disease

Classification and diagnostic criteria

The classification and the criteria used to diagnose dementia and Alzheimer's disease is set out in the Diagnostic and Statistical Manual of Mental Disorders (4th ed, text revision, DSM-IV-TR) (APA) and the International Statistical Classification of Diseases and Health -related Problems, 10th revision (ICD-10) (WHO, 2007).

The ICD-10 defines Alzheimer's disease as "a primary degenerative cerebral disease of unknown etiology with characteristic neuropathological and neurochemical features. The disorder is usually insidious in onset and develops slowly but steadily over a period of several years." (WHO). The DSM-IV-TR does not use the term Alzheimer's disease, and instead uses dementia of the Alzheimer's type (DAT). DAT is a manifestation of "early deficits in recent memory followed by the development of aphasia, apraxia, and agnosia after several years (APA). The ICD-10, classifies Alzheimer's disease as early and late onset.

The first step in finding a diagnosis is obtaining the patient history. During this time, the physician will determine what symptoms are present, when they began, and how they have progressed over time. The family history of illness is also pertinent. The physician will perform a physical examination, including blood tests and urinalysis. This is done to rule out other potential causes of dementia, such as hormone imbalance, vitamin deficiency, and urinary tract infections. Brain scans may also be performed to exclude tumours, cerebrovascular accidents, traumatic brain injury, and infections. These scans are also helpful in identifying the characteristic tangles and plaques seen in AD. Structural imaging scans, including magnetic resonance imaging (MRI) and computed tomography (CT), provide information about the shape and volume of the brain. Functional imaging allows the physician to determine how effectively the brain cells are working. A functional MRI or positron emission tomography (PET) scan can be used.

Clinical symptoms

AD progresses gradually and can last for decades. There are three main stages of the disease, each with its own challenges and symptoms.

Early-stage alzheimer's disease

This mild stage, which usually lasts 2 to 4 years, is often when the disease is first diagnosed. In this stage, family and friends may begin to realize that there has been a decline in the patient's cognitive ability. Common symptoms at this stage include (Alzheimer's Association 2010):

A. Difficulty retaining new information

B. Difficulty with problem solving or decision making. Patients may start to have trouble managing finances or other instrumental activities of daily living.

C. Personality changes. The person may begin to withdraw socially or show lack of motivation.

D. Difficulty expressing thoughts

E. Misplacing belongings or getting lost.

Moderate alzheimer's disease

Lasting 2 to 10 years, this is longest stage of the disease. Patients often experience increased difficulty with memory and may need help with activities of daily living.

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Severe alzheimer's disease

In this final stage of the disease, cognitive capacity continues to decline and physical ability is severely impacted. This stage can last between 1 and 3 years. Due to the family's decreasing ability to care for the patient, this stage often results in nursing home or other long term care facility placement. Common symptoms appearing in this stage include (Alzheimer's Association 2010):

A. Loss of ability to communicate.

B. Inability to function physically.

Pharmacotherapy

Current treatments for Alzheimer's disease are used to reduce the cognitive decline. The central role of these drugs is to stabilize and thus minimise disruption of two key neurotransmitters, acetylcholine (ACh) (the cholinergic hypothesis of Alzheimer's disease), and glutamate. AChE inhibition is used to protect the cholinergic neurons and glutamate [43]. The interaction of glutamate with the N-methyl-D-aspartate (NMDA) receptor is important in the workings of memory and learning. In Alzheimer's disease an increase in glutamate activity results in NMDA receptor being excessively activated which may lead to neurodegeneration [43].

Consequently memantine, an NMDA antagonist, is used to counter the loss or damage of NMDA receptors due to excess glutamate excitation in Alzheimer's disease patients. Memantine is considered to overall reduce burden of care on the carer, as well as clinically reversing and improving memory and global cognition, reducing behavioural disturbances, and improvement in the quality of life [44,45].

A number of treatments are also used to alleviate neuropsychiatric symptoms, including anti-depressants and anti-psychotics. Anti-psychotics are largely used to treat agitation, aggression and psychosis.

Biomarkers are extremely useful in the measurement of efficacy of drugs, which can be measured during clinical trials. Biomarkers are also important in helping to reveal novel therapeutic areas which may not have been previously considered.

Biomarkers for alzheimer's disease

For Alzheimer's disease there is a clear and present challenge to diagnose the disease as early as possible. Advances in Alzheimer's disease research have allowed treatments to be translated in to potential novel treatments which specifically aim to reduce the disease pathology and to modify disease progression. These have included anti- Aβ drugs, e.g. Aβ immunotherapies, secretase inhibitors and Aβ aggregation inhibitors.

For any disease modifying drug to be effective in the early stages of the disease there is a need to identify such patients possibly at earliest stage of the disease, where the pathology caused by neuronal damage has not manifested as dementia [46]. One way of achieving this goal is to detect and identify biomarkers for Alzheimer's disease. A biomarker of any disease would ideally allow for the measurement of the pathological process associated with a disease, whether or not it was linked to any direct pathology. Therefore a biomarker could be used to determine whether the disease is or is not present and be part of the clinical diagnosis process, and whether any potential therapies for the treatment of the disease are effective.

In Alzheimer's disease research there is a need to identify whether there are specific biological bases for these symptoms. This would provide therapeutic targets for pharmacological developments [10]. The primary sources of potential experimental biomarkers of Alzheimer's disease are blood (serum and plasma), and the cerebrospinal fluid (CSF), and brain imaging techniques.

The need to identify biomarkers of Alzheimer's disease is of great importance as to date the diagnosis of the disease can only be confirmed post mortem, and to date there are no robust and reliable biomarkers that can be used to identify the high sensitivity and specificity levels of the currently used clinical diagnosis.

For managing AD Substantial advances have been made in characterizing pre-dementia stages of AD, such as MCI, and improving the diagnostic and therapeutic options available. Our ability to find the 'cure' for AD ultimately depends not only on having an accurate view of the cellular and molecular processes but also on having optimal biomarkers to enable early diagnosis. There is an urgent need to develop clinically useful neuro-imaging and other biomarkers for the early detection of AD.

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