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Alzheimer's Disease at the Molecular Level

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Editorial

Alzheimer's disease (AD) is a deadly neurological condition that has no known origin or cure. It is predominantly a disease of old age, and it has become a major issue as people's life expectancies have increased. Massive loss of neurons and disruption of synaptic function are hallmarks of Alzheimer's disease, which begins in the hippocampus, a part of the cortex that is critical for the development of new memories. Genetics just plays a little role. In the senior population, Alzheimer's disease is the most prevalent cause of progressive dementia.

It is a long-term neurodegenerative disease that causes increasing impairments in cognitive skills such as memory, judgement, decision-making, spatial orientation, and language. Familial AD is a term used to describe a small percentage of cases, roughly 5% of the total. These are caused by well-defined, albeit rare, gene mutations, with mutations in the b-amyloid precursor protein gene (APP) on chromosome 21 being the first to be discovered. Only one risk gene, Apo lipoprotein, which is found on chromosome 19, has been definitively identified.

All of the genetic abnormalities and risk factors are linked to aberrant synthesis or clearance of the amyloid b-peptide (Ab), a tiny peptide that is a primary constituent of the senile plaques that are diagnostic of Alzheimer's disease. The amyloid hypothesis, which initially proposed Ab as a causal factor in AD, is now largely accepted [1-5].

Profound modifications of cytoskeletal proteins

Since the onset of Alzheimer's, it has been known that brain degeneration in AD is characterised by the accumulation of aberrant fibres in neuronal cell bodies (neurofibrillary tangles) and part of the altered neurites in senile plaques. The main components that make up these fibrous deposits were first discovered using electron microscopy in 1963 as pairs of 10 nm twisted filaments known as paired helical filaments. Antibodies to neuro filament proteins, specifically antibodies to phosphorylated epitopes of the high and middle molecular weight neuro filament polypeptides, were found to identify the PHF deposits in subsequent immuno-cytochemical experiments. Antibodies produced directly from isolated PHFs, on the other hand, did not react with neuro filament proteins and were quickly discovered to identify the microtubule-associated phosphoprotein. As a result, nearly every polyclonal and monoclonal antibody to mammalian tau was shown to identify some or all PHF-containing neurons and plaque neurites in AD brains. Furthermore, tau and PHF antibodies frequently detect a widespread pattern of dystrophic cortical neurites that is not restricted to plaques. The existence of neurofibrillary tangles in the cortex appears to be linked to the occurrence of these widespread "neuropil threads" or "curly fibres" [2,4].

Amyloid precursor protein (APP)

The APP gene is found on chromosome 21, and its multiple expression is linked to Down's syndrome as well as an elevated risk of Alzheimer's disease. Autosomal dominant mutations in the APP gene cause some inheritable types of AD, causing either greater secretion of Ab or increased secretion of the longer, more toxic version Ab(1–42). APP is a transmembrane protein with 770 residues that has been post-translationally modified. Its function is unknown. It is cleaved by a-secretase between residues in the extracellular domain in the middle of the segment that makes up Ab in the dominant "non-amyloidogenic" pathway. The APPs-a N-terminal fragment is released into the medium, whereas the C-terminal segment remains tethered to the membrane.

The amyloid b-peptide (AB)

Understanding the chemistry of AD is same to comprehending the chemistry of Ab. Ab is a 39- to 43-residue peptide that is cleaved from the C-terminal portion of the amyloid precursor protein, APP. Ab(1–40) and Ab(1–42) are the most prevalent pieces, with the latter being significantly more neurotoxic. The net charge is -3 because there are six negatively charged residues and three positively charged residues. The pKas (of the conjugate acids) of the three His residues are close to physiological pH. About 5.5 is the isoelectric point. Histidine residues are efficient copper ligands, and Ab has a high affinity for Cu(II). Cu(II) binding also lowers the pKa of a neighbouring amide group, bringing it into the physiological range [1,3].

Glutamate-mediated neurotoxicity

Glutamate excitotoxicity, caused by excessive NMDA receptor activation, is thought to have a role in neuronal death in Alzheimer's disease and other neurodegenerative diseases. Glutamate is the central nervous system's principal excitatory neurotransmitter, and a healthy level of glutamate-receptor activation is required for appropriate brain function. Metabotropic glutamate receptors, which are G-protein-coupled, and ionotropic glutamate receptors, which are ligand-gated ion channels, are the two types of glutamate receptors. The latter are divided into three groups based on their susceptibility to synthetic agonists: NMDA, a-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA), and kainate receptors [6].

Inhibition of cholinesterase activity in the brain

The neurotransmitter acetylcholine is rapidly destroyed by the hydrolytic activity of cholinesterases after its release into the synaptic cleft. AChE is the most significant enzyme involved in acetylcholine hydrolysis in the human brain. Butyrylcholinesterase (BChE) can also hydrolyze acetylcholine in the brain, according to new data, and may play a role in cholinergic transmission. The inhibition of these enzymes increases the concentration of acetylcholine in the synaptic cleft, which is believed to improve cholinergic transmission and alleviate cholinergic deficiency. Several randomised, double-blind, placebo-controlled studies have found that cholinesterase inhibitors have beneficial benefits on cognitive and functional symptoms, as well as behavioural problems in Alzheimer's disease [2].

Treatment strategies for b-amyloid and tau

The amyloid cascade hypothesis: The amyloid cascade theory, which claims that Ab, a fragment of the amyloid precursor protein, plays a crucial role in the aetiology of Alzheimer's disease, is the most widely accepted explanation. The so-called b- and g-secretases proteolytically generate Ab from APP. The accumulation of b-amyloid in the brain is thought to start a chain reaction that leads to neuronal malfunction, neurodegeneration, and dementia [1,3,5].

Inhibition of Ab-aggregation: Another possible method for developing novel and causative therapies for Alzheimer's disease is to prevent the

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production of the anticipated toxic oligomeric aggregates of Ab using small compounds. Metal ions such as Cu^{2+} and Zn^{2+} may play a role in Ab aggregation and toxicity mitigation. After 9 weeks of therapy with clioquinol, an antibiotic and Cu/Zn chelator that crosses the blood–brain barrier, brain Ab deposition in APP-transgenic mice was significantly reduced.

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Conflict of Interest

The authors reported no potential conflict of interest.

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