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Review article

Alzheimer Disease: Clues from traditional and complementary medicine

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ABSTRACT

Despite modern medicine's incredible innovation and resulting accumulation of valuable knowledge, many of the world's most problematic diseases such as Alzheimer Disease (AD) still lack effective cures and treatments. Western medicine has revealed many genetic, cellular, and molecular processes that characterize AD such as protein aggregation and inflammation. As the need for novel and effective treatments increases, researchers have turned towards traditional medicine as a resource. Modern, evidence based research examining traditional and complementary remedies for AD has generated promising results within the last decade. Animal based products inhibiting cellular toxicity, anti-inflammatory nutraceuticals such as omega-3 fatty acids, and plant based compounds derived from herbal medicine demonstrate viability as neuroprotective treatments and possible application in developing pharmaceuticals. Analysis of antioxidant, anti-inflammatory, and neuroprotective phytochemicals used in various traditional medicines around the world reveal potential to ameliorate and prevent the devastating neurodegeneration observed in AD.

1. Alzheimer Disease (AD): general views

Alzheimer, a progressive neurodegenerative disease an affliction of the elderly, is the most common form of dementia, affecting over 150 million patients.[1] Advances in research and technology have increased our quality of life and achieved increased longevity. Unfortunately, increased longevity is accompanied by elevated incidences of age-related diseases such as Alzheimer Disease (AD). AD is the sixth leading cause of death, and a leading cause of dementia amongst aged populations in the USA. It is a progressive neurodegenerative disorder, characterized by the prevalence of extracellular Aβ plaques and intracellular neurofibrillary tangles, derived from the proteolysis of amyloid precursor protein and hyperphosphorylation of microtubule-associated protein ***tau*** respectively. Multiple biological processes such as depletion or insufficient synthesis of neurotransmitters, oxidative stress, and abnormal ubiquitination are linked to neurodegenerative diseases.[2] (Fig. 1) AD has received substantial attention as researchers seek to understand associated debilitating cognitive decline and dementia in patients. Despite mounting research, using simpler animal models such as the fruit fly, *Drosophila*, and the tiny round worm, *Caenorhabditis elegans*, molecular mechanisms that underlie pathology of AD still remain unclear.[3] As one of the most complicated neurodegenerative diseases, AD is still an unsolved social and medical problem without effective treatment.[3–5]

Understanding and modulating chronic activation of innate inflammatory responses could lead to new approaches for preventing and treating AD. Formation of neurofibrillary tangles and misfolding of amyloid-β peptides are reasonably clear as the devastating basis of neurodegeneration in AD.[2,3] However, the role of neuroinflammation has only been recently identified as an important component. Experimental, genetic, and epidemiological data have revealed the immune system's active role as a disease promoting factor.[1] Binding of misfolded and aggregated proteins to receptors on microglia and astroglia may trigger an innate immune response, setting off a cascade of inflammation in the brain which in effect contributes to disease progression. Several genes associated with misfolding of proteins and inflammatory responses have been identified. External factors such as diabetes and obesity that exacerbate inflammatory processes may also contribute to disease

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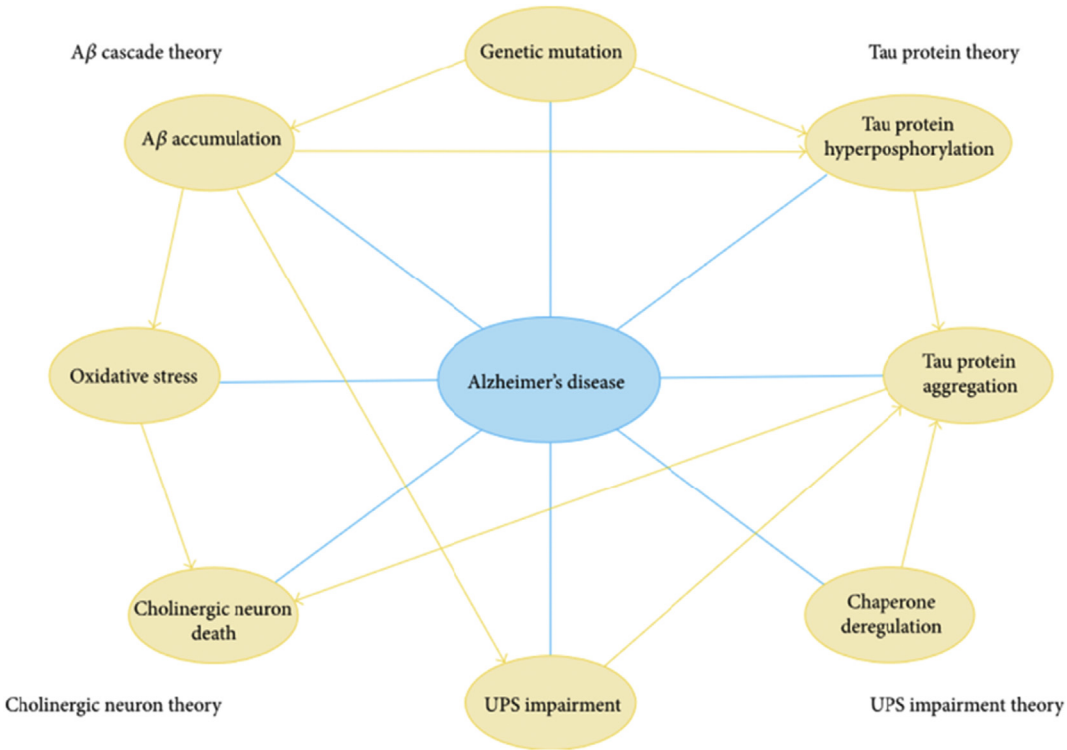

Fig. 1. The multifaceted molecular pathology of AD. AD has been linked to many possible causes on genetic, molecular, and cellular levels. Each node in this figure represents a possible cause of AD. These causal events may work in concert and form an intricate cross-talking network, eventually resulting in neuronal death among patients.[6]

progression. Thus, evidence indicates that the pathology of AD extends beyond its effects on neurons, and is closely related to immunological mechanisms and neuroinflammation.[7]

Immune reactions that may contribute to progression of AD however are not entirely clear. The immune system plays a complex role in progression of neurodegenerative disorders, exhibiting both neurodestructive and neuroprotective responses. The destructive or protective mechanisms are dependent on the relative numerical and functional dominance of effector or regulatory T cells. Immune responses may exhibit different migratory, regulatory, and effector functions after being triggered by misfolded and aggregated proteins and cell-specific stimuli. This in turn alters glial and neuronal behaviors that affect neuroinflammation and neuronal survival, altering the disease course. Consequently, the discovery of these destructive or protective immune mechanisms could lead to development of novel treatments by targeting therapeutic pathways that affect neuronal survival and slow disease progression.[8]

2. Utilizing animal models

Our elderly population is rapidly growing, and as needs for novel therapeutics and methods of preventing AD escalate, analysis from an evolutionary perspective may prove valuable. In searching for answers and treatments, considering why AD exists and how it has evolved may expand our understanding of disease pathology.[9] Due to the complex nature of immune and genetic mechanisms involved in AD, using certain animal models has advantages. Turning to a known model, Lee et al (2014) acknowledge that the fruit fly *Drosophila* is one of the oldest and most powerful genetic models, and a novel source of insights into numerous biological processes. *Drosophila* has emerged as a model system to analyze human diseases, which now include several that affect the nervous system. Due to genomic similarity between *Drosophila* and humans, neurodegenerative disease models that employ *Drosophila* exhibit various human-disease-like phenotypes (Fig. 2). As a result there is rapid and cost-effective in vivo genetic modifier for screening and drug evaluation. These models reveal many disease-associated genetic factors that facilitate the identification of potentially useful drugs.[10]

Despite numerous advantages of *Drosophila*, its usage in evaluating traditional medicines is relatively new. Thus *Drosophila* can now be introduced for analyzing neurodegenerative diseases modeled after examples that demonstrate successful application of *Drosophila* models in evaluating traditional medicines.[10] Development of new genomic technologies has potential to advance animal model research even further.[10,11] When viewing animal models of disease and treatment, the fruit fly is often the first species to be examined. However, an even simpler model is becoming equally popular.[3] Model organisms, such as the nematode, *C. elegans*, offer a complementary approach to numerous questions. *C. elegans* is advantageous for several reasons to analyze AD and other neurodegenerative diseases in depth. Like their mammalian counterparts, these nematode worms possess complex conserved biochemical pathways. Gene mutations that correlate with AD possess worm counterparts in *C. elegans*. These include an amyloid precursor protein related gene, apl-1, a ***tau*** homolog, ptl-1, and presenilin homologs, such as sel-12 and hop-1. With neuronal connectivity in *C. elegans* established, it is now advantageous as a model for learning and memory impairments that occur during AD.[3]

Earthworms, an emerging model, have been widely used as sources of food and medicine in the practice of traditional medicine. Forging a new research direction recently has resulted from analyses of innate immunity. While interest in and recognition of earthworms' beneficial properties stems from ancient cultures, earthworms are now being examined in modern medicine for their biomedical potential, advancing how we understand innate

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