Alzheimer's Disease: From Molecular Mechanisms to Psychobiological Perspectives

A myriad of neurodegenerative diseases (NDs), epitomized by Alzheimer's disease (AD), Parkinson's disease and Huntington's disease, currently impacts the elderly of every nation and appears to be increasing in frequency. Whereas there are symptomatic treatments for these disorders, no disease progression altering drugs are available and numerous have failed in clinical trials over the recent years. In this special issue (SI), we invited scientists with basic and clinical medical and psychology backgrounds to contribute by submitting articles focused on common molecular mechanisms that underpin the development of NDs, and particularly AD that generally impacts people greater than 60 years of age and accounts for 60 to 80 percent of dementia cases. Whereas AD is clinically characterised by a loss of cognitive functions, so too are many other common and well-studied NDs as well. From a clinical trial and scientific perspective, it is important to differentiate them early in their course, as both their development and potential response to treatment almost certainly differ. An emphasis was requested in this SI on potential molecular pathways leading to AD, its pathology, diagnosis – particularly by new biomarkers, management strategies, plus a psychological perspective of patients in terms of their ability and challenges to take advantage of potential behavioural strategies that may offset or limit later ND onset. Contributions from scientists that highlight these broad topics were highly desired in their review articles. Our aim was to develop a SI that is of significant interest to not only scientific researchers, but also to educators and physicians with interests in NDs with respect to psychology as well as healthy aging.

Regen et al., provide a review article on the parallel development of neuroinflammation and AD - as microglial activation, a hallmark of neuroinflammation, is seen across most acute and chronic neuropsychiatric conditions [1]. With a growing knowledge of the multiple functions of microglia in maintaining homeostasis and surveying the brain for alterations, microglial activation is increasingly discussed in the context of disease progression and pathogenesis of AD. Appropriately, orchestrated microglial functioning is an essential requirement underpinning its scavenging role and the optimal local activation of the brain’s innate immune cells to respond to and resolve a broad array of insults – whether induced by a bacterial infection or a misfolded protein. Activation of microglia results in a transient, severely altered microenvironment to duly remove the initiating insult and then suitably start the healing process. This not only entails a series of secreted cytokines, chemokines and generation of reactive oxygen/nitrogen species, but is time-dependently accompanied by an anti-inflammatory phase that additionally involves an increased turnover/production of neuroprotective endogenous substances such as retinoic acid (RA), as recently shown in vitro. Regen et al., discuss findings linking unresolved microglial activation and AD and speculate that microglial malfunction, which brings about changes in local RA concentrations in vitro, may underlie AD pathogenesis and precede and/or facilitate the onset of AD. Thus, chronic “innate neuroinflammation” may provide a valuable target for preventive and therapeutic strategies for AD [1].

Mantzavinos et al., shed light on biomarkers for AD diagnosis in their article as a dramatic increase in the population with dementia is expected in coming decades, and thus, the establishment of novel and innovative methods with the potential to offer accurate and efficient detection of AD in its early stages is desperately needed [2]. The aim of their study has been to investigate, evidence risk factors that affect and increase AD progression over time - especially in cases with no significant memory impairment present. Several potential markers are discussed with relevance to oxidative stress, metal ions, vascular disorders, protein dysfunctions and alterations in key mitochondrial populations. A multiparametric model of Alzheimer’s biomarkers is presented in line with the latest classification of the disease [2].

Echeverria et al., provide an article focused on vascular endothelial growth factor (VEGF) as a potential neuroprotective cytokine that promotes neurogenesis and angiogenesis within the brain [3]. In animal models, environmental enrichment and exercise, two non-pharmacological interventions that appear beneficial in potentially decreasing the progression of AD and depressive-like behavior, have been reported to enhance hippocampal VEGF expression and neurogenesis. The stimulation of VEGF expression appears to promote neurotransmission and synaptic plasticity processes such as neurogenesis. It is thought that these VEGF actions in the brain may underlie its potentially beneficial therapeutic effects against psychiatric and other neurological conditions. In their review, evidence linking VEGF deficits with the development of AD as well as the potential role of VEGF signaling as a therapeutic target for neurodegenerative conditions are discussed [3].

Ahmad et al. review the current status and future perspective of nanotechnology based on theranostic approaches in AD management [4]. Currently, approved AD drugs are not curative and act by mitigating AD associated symptoms. There is broad consensus that improvements in treatment outcome would benefit from early disease diagnosis, a greater scientific understanding of the time-dependent pathological process that occurs in AD brain and drug targeting across the blood-brain barrier to achieve optimal therapeutic CNS concentrations. Nanotechnology based diagnostic tools, drug carriers and theranostics offer the potential for highly sensitive molecular detection, effective drug targeting and their combination. Over the past decade, significant research has moved this area forward and we have reached the point where its application to AD could remarkably impact the outcome of therapy. Along this line, various nanoparticles from both organic and in-organic nano-material sources are under investigation for AD. A review article by Ahmad et al., discusses the potential of nanoparticles in early detection of AD, effective drug targeting to brain and theranostic (diagnosis and therapy) approaches to AD’s management.

Extending the above theme, an article by Leszek et al., further explores nanotechnological development of biocompatible nanoparticles and the potential of using nanoparticles for both drug carrier and imaging contrast agents to aid the diagnosis and treatment of AD [5]. If appropriately positioned and innovatively applied, advances of nanotechnology...
have the potential to offer huge opportunities in early-stage diagnosis and improved treatment of AD. Biocompatible nanoparticles hold promise as targeted delivery systems for drugs to overcome biological barriers and to minimize the adverse effects. For example, biocompatible nanomaterials with enhanced optical and magnetic properties may provide them the features of useful alternative contrast agents to support early-stage diagnosis. Given the complex biochemical environment of the central nervous system and the multiple current challenges in AD, it is increasingly clear that focused innovative research on the application of nanomaterials and nanotechnology can likely overcome many of these challenges and aid translational.

Ahmad et al. provide an insightful in silico-updated overview on the commonalities in biological pathways, genetics and cellular mechanisms between AD and other NDs [6]. Many biological pathways underpinning AD, as well as selected aspects of pathophysiology and genetics show commonalities with other NDs, such as Parkinson’s disease, Amyotrophic lateral sclerosis, Huntington’s disease, Prion Disease and Dentatorubral-pallidoluysian atrophy. In this regard, the sharing of common features, such as molecular mechanisms, may provide insight into the disease prevention and development of effective therapies. In their review, a brief description of the pathophysiology, clinical symptoms and available treatments is explored - with special emphasis on AD. To date, effective treatment for each of these disorders is lacking. Nevertheless, studies concentrating on commonalities in biological pathways, cellular mechanisms and genetics may provide scope to researchers to identify novel common targets for disease prevention and development of effective drugs across disorders [6], in much the same manner that drugs found effective in the degenerative disease of type 2 diabetes mellitus are now being applied to AD and other NDs.

Gupta et al. overview that underscores the importance from a therapeutic/diagnostic perspective of microRNAs (miRNAs) in AD [7]. miRNAs are endogenous, ∼22 nucleotide, non-coding RNA molecules that function as post-transcriptional regulators of gene expression. miRNA dysregulation has been observed in cancer and increasingly so in neurodegenerative diseases – particularly in AD, Parkinson’s disease, Huntington’s disease, and amyotrophic lateral sclerosis – as neuronal degradation and death are key hallmarks in each of these. Additionally, abnormalities in metabolism, synapse generation/maintenance and axonal transport are associated with these disorders with an increasing number of published studies demonstrating the importance of miRNAs in regulating these key factors. Gupta et al., review, the roles of different miRNAs (including miR-9, miR-107, miR-29, miR-34, miR-181, miR-106, miR-146a, miR132, miR124a, miR153) in disease pathogenesis as a time-dependent understanding of the expressions and activities of such miRNAs may aid in the development of sensitive approaches to detect and manage AD [7].

In closure, we end this editorial by thanking Prof. Debmoy Lahiri, the Editor-in-Chief, as well as Ms. Asma Shahid, the Senior Manager Publications, along with all the contributing authors who have enthusiastically responded to our request by contributing to this special issue of Current Alzheimer Research. We additionally extend our gratitude to the peer reviewers for the time and expertise that each altruistically provided by editing and revising individual contributions to a consistently high level to allow completion of this SI. As a result of the combined efforts of this scientific team - noteworthy for their wide-ranging proficiency across such a wide scope of science and technology - the present issue provides to both a broad range of scientists and lay readers a hopefully valuable source for promising developments that are being innovatively applied to the AD field to positively impact those suffering from neurological disorders.

REFERENCES


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