EDITORIAL

Molecular Psychiatry special issue: advances in Alzheimer's disease

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Since our inception we have published 380 articles on Alzheimer's disease (AD) in Molecular Psychiatry. AD has been a topic of great relevance to us and it is a great pleasure to present this special issue dedicated to AD. Putting this extraordinary issue together our focus was clearly on AD, but we also added some compelling papers related more broadly to aging.

The strongest genetic risk factor for AD is the epsilon4 allele of Apolipoprotein E (APOE4). This special AD issue starts with a thought-provoking Comment by Chen et al. on potential vascular-meningeal lymphatic" components of APOE4-mediated Alzheimer disease and their therapeutic implications [1, 2]. In a Perspective, Wainberg et al. provide an overview of recent studies in mouse models, human tissue models, and population cohorts that collectively suggest that many of the hallmarks of AD, like amyloid beta production and neuroinflammation, can arise as a protective response to acute infection that becomes maladaptive in the case of chronic infection [3]. In an outstanding review, Hampel at el. cover the evidence highlighting a differentiated interaction of distinct amyloid-beta (Abeta) species with other AD-related biological mechanisms, such as tau-mediated, neuroimmune, and inflammatory changes, as well as a neurochemical imbalance and they also discuss the data-driven rationale for Abeta-targeting therapeutic strategies in the early treatment of AD [4]. In their Expert Review, Cisbani & Rivest remind us that traditionally the brain had been seen as an immune-privileged organ; however, this concept evolved with the discovery of microglia about 100 years ago, and much has been discovered in terms of neuro-immune interactions [5]. Indeed, the brain harbors its own innate immune system that senses the environment and quickly responses to changes, and re-establishes parenchymal homoeostasis. Innate immunity has been the focus of many new directions to understand the mechanisms involved in the etiology of brain diseases, especially AD. Unfortunately, immune-based therapies have not been particularly successful. Cisbani & Rivest present both sides of the innate immunity story in AD, with a particular emphasis on the beneficial properties of innate immune cells [6]. In their Immediate Communication, Tsatsanis et al. used transcriptomic data from a large neuropathologically characterized patient cohort and showed that the acute phase protein lactoferrin (Lf) is the key predictor of amyloid pathology [7]. In vitro studies showed that an interaction between APP and the iron-bound form of Lf secreted from activated microglia diverted neuronal APP endocytosis from the canonical clathrin-dependent pathway to one requiring ADP ribosylation factor 6 trafficking. By rerouting APP recycling to the Rab11-positive compartment for amyloidogenic processing, Lf increased neuronal Abeta production. Their work shows that Lf may be a novel pharmacological target for AD that not only modulates APP processing but provides a link between Abeta production, neuroinflammation, and iron dysregulation.

Our regular articles in this issue start with a systematic review and meta-analysis of the complement cascade in AD Krance et al. [6]. Following that interesting systematic review, Park et al. examined the roles of proteinopathy in AD by studying anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase, which is crucial for the tau-mediated AD pathology [8]. They showed that ALK caused abnormal accumulation of highly phosphorylated tau in the somatodendritic region of neurons through its tyrosine kinase activity and that ALK activation in neurons impaired Stx17-dependent autophagosome maturation and this defect was reversed by a dominant-negative Grb2. In a series of experiments, including Drosophila melanogaster and the triple-transgenic AD (3xTg-AD) mice models, as well as RNAseq and measuring ALK levels in the brains of AD patients showing autophagosomal defects. Based on their results they proposed that aberrantly activated ALK is a bona fide mediator of tau proteinopathy that disrupts autophagosome maturation and causes tau accumulation and aggregation, leading to neuronal dysfunction in AD.

Arroyo-Garcia et al. tested the hypothesis that decreased gamma power and fast-spiking interneurons (FSN) synchrony precede amyloid plaque deposition and cognitive impairment in App(NL-G-F) knock-in mice (App(NL-G-F)) [9]. They provided evidence that impaired FSN spike-gamma coupling is one of the earliest functional impairment caused by the amyloidogenic pathology progression, and proposed that it is a potential cause for the degradation of gamma oscillations and consequent cognitive impairment. They further suggest that therapeutic approaches should be aimed at restoring normal FSN spike-gamma coupling and not just removal of Abeta.

Sun et al. performed conceptually interesting work questioning the traditional belief that in AD cerebral Abeta deposits are derived from the brain itself [10]. Using a bone marrow transplantation model to investigate the contribution of blood cell-produced Abeta to AD pathogenesis, they found that bone marrow cells (BMCs) transplanted from APPswe/PS1dE9 transgenic mice into wild-type (Wt) mice at 3 months of age continuously expressed human Abeta in the blood, and caused AD phenotypes including Abeta plaques, cerebral amyloid angiopathy (CAA), tau hyperphosphorylation, neuronal degeneration, neuroinflammation, and behavioral deficits in the Wt recipient mice at 12 months after transplantation. Based on their results, they suggest that blood cell-produced Abeta plays a significant role in AD pathogenesis, and the elimination of peripheral production of Abeta might potentially decrease brain Abeta deposition, thereby representing a novel therapeutic approach for AD.

The special issue continues with multiple remarkable articles. Fei et al. showed that degradation of formaldehyde (FA) by formaldehyde scavenger-NaHSO3 or coenzyme Q10 reduced Abeta aggregation and ameliorated the neurotoxicity, and improved the cognitive performance in APP/PS1 mice [11]. Their study provided evidence that endogenous FA is essential for Abeta self-aggregation and that scavenging FA could be an

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effective strategy for treating AD. Eysert et al. provided evidence that the Alzheimer's genetic risk factor FERMT2 (Kindlin-2) controls axonal growth and synaptic plasticity in an APP-dependent manner [12, 13]. In our Image section article, Lemoine et al. conducted a detailed study of amyloid, tau, and astrocyte pathology in the autosomal-dominant Alzheimer's disease variants AbetaPParc and PSEN1DE9 [14]. Although Presenilin 1 (PS1) has been extensively studied in neurons, Ledo et al. addressed the role of PS1 in microglia, which is incompletely understood [15]. They reported that microglia containing phospho-deficient mutant PS1 display a slower kinetic response to micro injury in the brain in vivo and the inability to degrade Abeta oligomers due to a phagolysosome dysfunction. In an Alzheimer's mouse model containing phospho-deficient PS1 their experiments showed severe Abeta accumulation in microglia as well as the postsynaptic protein PSD95. Their results demonstrated a novel mechanism by which PS1 modulates microglial function and contributes to Alzheimer's -associated phenotypes. Chopra et al.'s paper showed that microRNA-298 reduces levels of human amyloid-beta precursor protein (APP), beta-site APP-converting enzyme 1 (BACE1) and specific tau protein moieties [16]. In a mouse model, Yang et al demonstrated that chondroitin 6-sulphate is required for neuroplasticity and memory in ageing [17]. Ng et al's work revealed that adiponectin (APN) levels were reduced in the brain of AD patients and in a mouse model containing five familial AD mutations (5xFAD) [18]. They then crossbred 5xFAD mice with APN(-/-) mice to generate APN-deficient 5xFAD (5xFAD;APN(−/−)). APN deficiency in 5xFAD mice accelerated amyloid loading, increased cerebral amyloid angiopathy, and reduced insulin-signaling activities. Treatment with adipoRon (APN receptor agonist) improved neuronal insulin-signaling activities and insulin sensitivity in vitro and in vivo. Chronic adipoRon treatment improved spatial memory functions and significantly rescued neuronal and synaptic loss in 5xFAD and 5xFAD;APN(−/−) mice and lowered plaque and Abeta levels in AD mice. AdipoRon also exerted anti-inflammatory effects by reducing microglial and astrocytes activation as well as suppressing cerebral cytokines levels. Moreover, the microglial phagocytic activity toward Abeta was restored after adipoRon treatment. Those results indicated that adipoRon exerts multiple beneficial effects providing important therapeutic implications.

In a very provocative article, Morales et al. show that cerebral accumulation of Abeta can be accelerated after exposing mouse models of AD to Abeta seeds by different peripheral routes of administration, including intra-peritoneal and intra-muscular [19]. Interestingly, animals receiving drops of brain homogenate laden with Abeta seeds in the eyes were efficiently induced. In contrast, oral administration of large quantities of brain extracts from aged transgenic mice and AD patients did not have effects in brain pathology. This work highlighted the role of peripheral tissues and body fluids in AD-related pathological changes. In other words, could AD start by being transmitted from peripheral tissues into the brain?

Five papers cover alterations in brain cells grown in culture that were derived from AD patients. Ryu et al. report that neural progenitor cells and astrocytes differentiated from late-onset Alzheimer's disease (LOAD) patient-derived induced pluripotent stem cells exhibit multiple inter-related bioenergetic alterations including: changes in energy production by mitochondrial respiration versus glycolysis, as a consequence of alterations in bioenergetic substrate processing and transfer of reducing agents, reduced levels of NAD/NADH, diminished glucose uptake and response rates to insulin (INS)/IGF-1 signaling, decreased INS receptor and glucose transporter 1 densities, and changes in the metabolic transcriptome [20]. Their data confirm that LOAD is a "multi-hit" disorder and provide evidence for innate inefficient cellular energy management in LOAD that likely predisposes to neurodegenerative disease with age. Brookhouser et al. demonstrated that a APOE 2 variant (APOE2) mitigates disease-related phenotypes in an isogenic human induced pluripotent stem cell (hiPSC)-based model of Alzheimer's disease [21]. This is noteworthy as Velez et al. had previously reported that APOE2 allele delays age of onset in Alzheimer's disease caused by the PS1 E280A mutation [22]. Perez et al. showed loss of function of peptidase pitrilysin metallopeptidase 1, a mitochondrial protease involved in mitochondrial precursor processing and degradation, induces proteotoxic stress and Alzheimer's disease-like pathology in human cerebral organoids [23]. Ghatak et al. provided evidence that nitroSynapsin ameliorates hypersynchronous neural network activity in Alzheimer hiPSC models [24]. Alic et al. utilized an intriguing model of developing trisomy 21 cerebral organoids to study patient-specific AD-like pathology. Their work revealed BACE2 as a gene dose-sensitive AD suppressor in human brain [25, 26].

On the genetic front, Nitsche et al. show that nearly all AD-associated-genes are evolutionarily old and did not originate later in evolution than not-AD-associated-genes; however, the gene-structures of loci, that exhibit AD-associated changes in their expression, evolve faster than the genome at large [27]. Therefore, they conclude that AD-related genes show accelerated evolution. AD with psychosis (AD + P) affects ~50% of individuals with AD, and results in poor outcomes and greater degree of cognitive impairment and depressive symptoms. Although the estimated heritability of AD + P is 61%, genetic sources of risk were unknown. DeMichele-Sweet reported a genome-wide meta-analysis of 12,317 AD subjects, 5445 AD + P [28]. Results showed common genetic variation accounted for a significant portion of heritability. Two loci, one in ENPP6 and one spanning the 3'-UTR of an alternatively spliced transcript of SUMF1, had genome-wide significant associations with AD + P. Stocker et al. investigated the ability of an AD polygenic risk score (PRS) and APOE status to predict clinical diagnosis of AD, vascular (VD), mixed (MD), and all-cause dementia in a community-based cohort prospectively followed over 17 years and secondarily across age, sex, and education strata [29, 30]. The PRS enriched the ability of APOE to discern AD with stronger associations than to VD, MD, or all-cause dementia in a prospective community-based cohort. Wagner et al. studied frontotemporal dementia (FTD), a clinically and genetically heterogeneous disorder, and investigated the spectrum of genetic causes and assessed the genotype-driven differences in biomarker profiles, disease severity, and clinical manifestation by recruiting 509 FTD patients from different centers in Germany, where individuals were clinically assessed including biomarker analysis [31].

Innovative imaging methods are highlighted in multiple articles in this special issue, including four papers by Agneta Nordberg's group at the Center for Alzheimer's Research, Karolinska Institutet in Stockholm, Sweden (Kumar et al. [32], Sala et al. [33], Chiotis et al. [34], and Bucci et al. [35]) and two papers by Rosa-Neto's group at McGill, Montreal, Canada [36, 37]. Kumar et al. used BU99008, a novel astrocytic positron emission tomography (PET) ligand targeting imidazoline-2 binding sites (I_2BS) on astrocytes, to demonstrate for the first time that this ligand can visualize reactive astrogliosis in postmortem AD brains and proposed a multiple binding site [super-high-affinity (SH), high-affinity (HA) and low-affinity (LA)] model for BU99008, I2BS specific ligands (2-BFI and BU224) and deprenyl in AD and control (CN) brains [32]. Comparative autoradiography studies reinforced their findings, showing higher specific binding for (3)H-BU99008 than (3)H-Deprenyl in sporadic AD brain compared to CN, implying that they might have different targets. Their results indicate that BU99008 could detect I_2BS expressing reactive astrocytes with good selectivity and specificity and hence be a potential attractive clinical astrocytic PET tracer for gaining further insight into the role of reactive astrogliosis in AD. Sala et al. studied the mismatch between cerebrospinal fluid (CSF) and PET and amyloid-beta biomarkers occurs in up to approximately 20% of preclinical/prodromal Alzheimer's disease individuals [33]. Their results

suggest that there are two alternative pathways ("CSF-first" vs. "PET-first") toward established amyloid-beta pathology, characterized by different genetic profiles and rates of amyloid-beta accumulation. In conclusion, CSF and PET amyloid-beta biomarkers provide distinct information, with potential implications for their use as biomarkers in clinical trials. Chiotis et al. examined [^{18}F]THK5317 imaging as a tool for predicting prospective cognitive decline in Alzheimer's disease [33]. Their study subjects underwent baseline neuropsychological assessment, PET imaging with [^{18}F]THK5317, [^{11}C]PIB and [^{18}F]FDG, magnetic resonance imaging, and in a subgroup cerebrospinal fluid (CSF) sampling, with clinical follow-up after a median 48 months. Their findings support a temporal dissociation between tau deposition and cognitive impairment, and suggest that [^{18}F]THK5317 predicts future cognitive decline better than other biomarkers. Bucci et al. studied a subset of 282 patients, who had had at the same time PET investigations with amyloid-β and tau tracers, CSF sampling, and structural magnetic Resonance Imaging (MRI) [35]. They showed that while results for amyloid-β were similar using CSF or imaging, CSF and imaging results for tau and neurodegeneration were not interchangeable. PET tau positivity was superior to CSF p-Tau181 and PET amyloid-β in predicting cognitive decline in the AD continuum within 3 years of follow-up. Therriault et al. used imaging tools to show that APOE4 potentiates the relationship between amyloid-beta and tau pathologies [36]. Alsop using imaging, Kang et al. provide evidence that amyloid-beta modulates the association between neurofilament light chain (NFL) and brain atrophy in Alzheimer's disease [37]. Their findings further support the use of NFL as a neuronal injury biomarker in the research framework of AD biomarker classification and for the evaluation of therapeutic efficacy in clinical trials.

Calsolaro et al. also examined imaging of non-neuronal brain cells [38]. ^{11}C-BU99008 is a novel PET tracer that enables selective imaging of astrocyte reactivity in vivo. To explore astrocyte reactivity associated with Alzheimer's disease, older, cognitively impaired (CI) subjects and age-matched healthy controls (HC) underwent 3 T magnetic resonance imaging (MRI), ^{18}F-florbetaben and ^{11}C-BU99008. The amyloid (Abeta)-positive CI subjects had higher ^{11}C-BU99008 uptake relative to HC across the whole brain, but particularly in frontal, temporal, medial temporal and occipital lobes. This proof-of-concept study provides direct evidence that ^{11}C-BU99008 can measure in vivo astrocyte reactivity in people with late-life cognitive impairment and AD. Their results confirmed that increased astrocyte reactivity is found particularly in cortical regions with high Abeta load. In an interesting twist, Moriguchi et al. examined tau and (Abeta) accumulations in the brains of patients with major depressive disorder (MDD) and healthy controls using PET with a tau radioligand, [^{11}C]PBB3 and an Abeta radioligand, [^{11}C]PiB [39]. Mean cortical [^{11}C]PBB3 standardized uptake value ratios (SUVR)s in MDD patients were significantly higher than those of healthy controls. These values were higher in MDD patients with psychotic symptoms than in those without any. The authors suggest that tau depositions may underlie MDD, and especially in patients with psychotic symptoms.

Further work in this issue examines the roles of tau in brain pathology. Monteiro-Fernandes at el. show that allosteric modulation of AMPA receptors counteracts Tau-related excitotoxic synaptic signaling and memory deficits in stress- and Aβ-evoked hippocampal pathology [40]. Wu et al. elegantly demonstrate that there is a requirement of brain interleukin-33 for aquaporin-4 expression in astrocytes and glymphatic drainage of abnormal tau [41]. Xu et al. studied the transcription factor EB (TFEB), a master regulator of lysosomal biogenesis, which plays an essential role in the lysosomal exocytosis of selected tau species and showed that TFEB regulates lysosomal exocytosis of tau and its loss of function exacerbates tau pathology and spreading [42]. In our cover article, Dickstein et al. meticulously examined brain and blood biomarkers of tauopathy and neuronal injury in humans and rats with neurobehavioral syndromes following blast exposure [43]. Thompson et al. using ultrasensitive immuno-assays to measure tau and neurofilament light chain (NfL) protein concentrations in 709 plasma samples taken from 377 individuals with prion disease during a 12-year prospective clinical study, alongside healthy and neurological control groups [44]. Their results suggest that plasma tau and NfL have potential to fill key unmet needs for biomarkers in prion disease: as a secondary outcome for clinical trials (NfL and tau); for predicting onset in at-risk individuals (NfL); and as an accessible test for earlier identification of patients that may have CJD and require more definitive tests (NfL). However, further studies should evaluate their performance directly in these specific roles. In a study of 70 individuals in a longitudinal assessment of familial AD (FAD). O'Connor et al. showed that plasma phospho-tau181 (p-tau181) concentration is increased in symptomatic and presymptomatic FAD suggests potential utility as an easily accessible biomarker of AD pathology [45].

Other major contributions to AD research presented in this issue include work by Xia et al. showing evidence that C/EBPβ is a key transcription factor for APOE and preferentially mediates APOE4 expression in AD [46]. Pentz et al. suggest that the human brain nerve growth factor (NGF) metabolic pathway is impaired in the pre-clinical and clinical continuum of AD [47]. In a large US national survey, Beydoun et al. documented that selected periodontal pathogen titers, factors, and clusters interacted mostly synergistically, with Helicobacter pylori (Hp) sero-positivity, to alter the risk of AD and all-cause dementia [48]. Those authors add that ultimately, a randomized controlled trial is needed in order to examine the effects of co-eradication of Hp and select periodontal pathogens on neurodegenerative disease. In an integrative brain transcriptome analysis, Panitch et al. linked complement component 4 and HSPA2 to the protective effect of APOE epsilon2 in AD [49]. Ou et al. used genetic, proteomic, and transcriptomic approaches to identify compelling genes that may represent potential drug targets for AD [50]. The work of Tian et al. demonstrated that the kidney physiologically clears Abeta from the blood, suggesting that facilitation of Abeta clearance via the kidney represents a novel potential therapeutic approach for AD [51]. The work of Magalhaes et al. al shows that protein inhibitor of STAT2 (PIAS2)-mediated blockade of interferon-beta (IFN-β) signaling can be a basis for sporadic Parkinson's disease dementia [51].

It is spectacular to see such outstanding work that truly advances the field of AD research published here. In our future issues, Molecular Psychiatry will continue to publish groundbreaking progress in AD research.

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ADDITIONAL INFORMATION

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