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Emerging Mechanisms in Alzheimer's Disease and Their Therapeutic Implications

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Alzheimer's disease (AD) constitutes a massive and growing health care burden that is destroying the cognitive function of more than 5 million individuals in the United States and 25 million individuals worldwide. Today, therapeutic options are limited to approaches with mild symptomatic benefit and devoid of disease-modifying regimens. Given the unprecedented medical need, there is a growing societal recognition of the urgency to advance AD therapy to a level where options to slow, halt, or reverse the disease become available. Increasing resources from governmental and nongovernmental organizations are being devoted to developing disease modification for AD, with the U.S. National Plan to Address Alzheimer's Disease being a lead example.

The successful development of new therapies must be based on convincing molecular and cellular understanding of AD pathophysiology. The current collection of articles includes discovery science and therapeutic development, with an emphasis on new directions in the field of AD research.

Genetic analysis provides an unbiased human-specific methodology for understanding the basis for AD. Rare high-penetrance autosomal dominant mutations in amyloid- β ($A\beta$) precursor and presenilin genes have been recognized for decades as causative in some early onset cases. The existence of these mutations been interpreted as verifying the central role of $A\beta$ peptide, which accumulates in plaques of AD brain, as a trigger for the disease. Pimenova *et al.* (1) review recent advancements in the understanding of late-onset AD derived both from large-scale genome-wide association for common alleles of small effect size in AD risk and from next-generation sequencing studies to identify rarer alleles of moderate to large effect size. A key lesson from this work has been a growing appreciation of the contribution of genetic variation in myeloid cell lineage function to late-onset AD risk.

The majority of attempts to modify AD progression reaching late-stage clinical trials have focused on lowering $A\beta$ peptide levels, either by immunological removal or inhibition of production. The repeated failures and the ongoing hopes for anti-amyloid antibodies are discussed by van Dyck (2), with a focus on the rationale to intervene earlier in AD using such methods. Inhibition of $A\beta$ production has been attempted by inhibition of either β - or

γ -secretase enzymes, as discussed by Voytyuk *et al.* (3). As with anti-amyloid antibody approaches, the potential benefit of such interventions is likely to be greatest in earlier or presymptomatic stages of disease before the process triggered by A β accumulation progresses to complex signaling and cellular events no longer sensitive to A β lowering.

Insights into the physiology of interstitial fluid flow through the brain have uncovered new mechanisms in A β peptide dynamics. As reviewed by Boespflug and Iliff (4), glymphatic flow along perivascular spaces is a major determinant of A β clearance. Because this system is strongly modulated by sleep and also by aging, it provides a basis for the age-dependence of AD, as well as highlighting potential interventions based on sleep behavior.

AD pathology includes neurofibrillary tangles of hyperphosphorylated tau protein as well as A β plaque. The progression of tau pathology, after being triggered by A β accumulation, is recognized to correlate better than A β levels with the symptoms in AD. Recent activity in understanding tau pathology includes a focus on its spread through the brain, which is reflected in the anatomical patterns of Braak staging. Templated, prion-like misfolding and cell–cell transmission of tauopathy have now been documented in multiple experimental settings, as reviewed by Ayers *et al.* (5). It is hypothesized that interfering in cell–cell transfer via anti-tau antibodies may slow or halt disease, an approach that is entering trials for AD-related degenerative conditions (6).

The genetic risk factor with the largest burden and effect size is apolipoprotein E allele inheritance, as identified 25 years ago (7). Decades of apolipoprotein E research have identified multiple actions of the polypeptide in brain, which are reviewed by Zhao *et al.* (8). Many mechanistic hypotheses for apolipoprotein E allele–specific action in AD relate to A β metabolism, though recent data also document a role in tau pathology (9).

Cognitive dysfunction in AD is most closely related to synaptic dysfunction and synaptic loss (10), and therefore understanding synaptotoxic events triggered by A β and/or tau is central to pathophysiology (11). In part, A β may exert synaptotoxic actions indirectly through microglia and complement (12). Critically, direct neuronal actions are also well documented, and efforts have been made to define molecular “acceptor” sites for A β species on neurons, as reviewed by Purro *et al.* (13). One such site is cellular prion protein (14) and its pharmacologically targetable coreceptor metabotropic glutamate receptor 5 (15,16).

Definitions of AD are based on the co-occurrence of A β and tau pathologies, so linking these molecules may hold the key to successful intervention for AD. A therapeutic target with such potential is Fyn kinase, as discussed by Nygaard (17). This kinase is highly expressed in the brain, is activated downstream of A β oligomer receptors, and can be blocked with existing pharmacological tools (18). One Fyn kinase inhibitor is now in a multicenter phase 2 trial to assess disease modification in AD (NCT02167256).

As noted above, recent genetic approaches to defining AD mechanisms have been most notable for highlighting the role of myeloid cell function in modulating risk. Of several genes, *TREM2* variation has attracted the most attention in AD risk (19,20). As reviewed by Condello *et al.* (21), the gene product functions in the plasma membrane of brain microglia. The proper function of *Trem2* appears necessary to protect neurons from the damaging

effects of A β accumulation, and modern optical imaging techniques have aided cell biological definition. Therapeutic approaches that exploit understanding of the role of *TREM2* remain to be developed, but have exciting potential.

Multiple lines of research define crucial sequential aspects of the extended development of AD pathophysiology triggered by A β . Therapeutic intervention at several molecular sites tailored to the stages of AD may provide the synergy to halt AD progression in the future. As individual novel treatments demonstrate efficacy in future clinical trials, combination therapy can be expected to make the most significant impact on AD clinical management.

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