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Thematic Minireview Series on the Molecular Basis of Alzheimer Disease*

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Alzheimer disease (AD)[2] is a debilitating neurodegenerative disorder that directly affects millions of people and indirectly affects the lives of tens of millions of others who must deal with many years of cognitive decline of their loved ones. This devastating disorder, for which no cure is available at present, now strikes someone in America every 71 s. With the current aging population, AD is becoming an ever-increasing social burden for the health care system and national economy in addition to the emotional burden for the immediate family members. AD is pathologically characterized by the presence in the brain of senile plaques containing amyloid-β (Aβ) and neurofibrillary tangles containing Tau. Although these pathological hallmarks were recognized more than a 100 years ago (1–3), only within the past decade have real advances been made in determining the molecular and biochemical basis of AD. This thematic minireview series deals with the current knowledge of the biochemistry of the molecules involved in AD with a view toward understanding the pathobiology of and potential treatments for AD. The first section starts with a discussion of the metabolism and function of the amyloid precursor protein (APP) and plaque formation in AD. The subsequent sections (to be published in later issues) deal with the formation of amyloid oligomers; fibrillization, degradation, and neurotoxicity of Aβ; Tau mutations in AD-like diseases; the association of apoE with AD; and mouse models for AD.

The first four minireviews of this thematic series deal with the metabolism and function of APP and how these may affect AD. The first minireview, "Amyloid Precursor Protein Trafficking, Processing, and Function" by Gopal Thinakaran and Edward H. Koo, discusses the biology of APP and its relatives APLP1 and APLP2, with a particular focus on trafficking through the secretory, endocytic, and recycling pathways. The potential function of APP as a trophic, cell adhesion, or receptor molecule is presented with a discussion of the role of APP in the development of the nervous system and synapse structure. The next minireview, by Sarah L. Cole and Robert Vassar, "The Role of Amyloid Precursor Protein Processing by BACE1, the β-Secretase, in Alzheimer Disease Pathophysiology," initiates a detailed discussion of the processing of APP by BACE1, the enzyme that generates the N terminus of Aβ. The initial identification of the BACE1 enzyme, only 10 years ago, other possible biological roles for BACE1, and the putative development of inhibitors for this ideal target based on its crystal structure round out this review. "Intramembrane Proteolysis by γ-Secretase" by Harald Steiner, Regina Fluhrer, and Christian Haass then develops the story of the elusive nature of the γ-secretase, the enzyme complex made of four subunits, which releases Aβ by cleavage of APP C-terminal fragments. Presenilin, the catalytic subunit, is presented both as an interesting protease that hydrolyzes its substrates in a non-aqueous environment and as the bearer of mutations in familial AD. Of particular interest is the discussion of γ-secretase as a potential target for pharmaceutical intervention and where the prospects currently stand. Phosphorylation is, of course, a main regulatory theme in any biological system, and it certainly holds form for consideration of regulation of APP as detailed in the minireview "Regulation of Amyloid β-Protein Precursor by Phosphorylation and Protein Interactions" by Toshiharu Suzuki and Tadashi Nakaya. The normal function of APP has been hard to pin down, but this minireview carefully outlines the trafficking, transport, and regulation of APP by phosphorylation, with a focus on what the C-terminal fragment may be doing. Taken together, these reviews highlight the known features of APP function, metabolism of APP, the enzymes that cleave it to produce Aβ, and aspects of the physiological regulation of APP processing and Aβ production. The targeting of inhibitors toward certain of these steps to reduce the Aβ load provides optimism for eventual treatment of AD itself.

The next section of this series discusses what is believed to be the pathogenic product of APP cleavage, Aβ, in terms of its fibrillization, toxicity, and degradation. In "Structural Classification of Toxic Amyloid Oligomers," Charles G. Glabe considers various "prefibrillar" forms of Aβ and proposes that conformationally sensitive antibodies might be the best means now for classifying structural types of Aβ oligomers, rather than size. The importance of Aβ degradation as a natural or medicinal means of regulating Aβ levels is discussed in "The AβCs of Aβ-cleaving Proteases" by Malcolm A. Leissring. This minireview evaluates a multitude of Aβ-degrading enzymes that are now known and points to the possibilities of targeting or utilizing this inherent proteolytic activity in the treatment of AD. "Amyloid β-Protein Assembly and Alzheimer Disease" by Robin Roychaudhuri, Mingfeng Yang, Minako Hoshi, and David B. Teplow ranges from a description of the pathway of assembly of Aβ into soluble oligomers and protofibrils to the toxic effects of these assemblies via membrane effects, metals and reactive oxygen species, mitochondrial interactions, and ultimately apoptosis of neurons. Bruce A. Yankner and Tao Lu

* This minireview will be reprinted in the 2008 Minireview Compendium, which will be available in January, 2009.

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[2] The abbreviations used are: AD, Alzheimer disease; Aβ, amyloid-β; APP, amyloid precursor protein.

consider the pathobiological role of Aβ in the minireview "Amyloid β-Protein Toxicity and the Pathogenesis of Alzheimer Disease." Effects of Aβ oligomers in synaptic physiology, cognitive deficits, Tau interactions, and microglial inflammation lead to novel suggestions for treatments.

This 11-part series on AD will be concluded by a discussion of Tau etiology, the important role of apoE in mediating effects of AD, and the contribution of mouse models toward understanding AD pathology. The other side of the Aβ/Tau coin is critically examined in "Tau Mutations in Neurodegenerative Diseases" by Michael S. Wolfe. The role and putative mechanism(s) of aberrant Tau are discussed with an emphasis on splicing of Tau isoforms. The well known genetic association between apoE4 and AD is explored at the molecular level by Ning Zhong and Karl H. Weisgraber in "Understanding the Association of ApoE4 with Alzheimer Disease: Clues from Its Structure." The emerging information on the structure, stability, domain interactions, and aggregation of apoE isoforms is put in context of neuronal vulnerability, transgenic mice, and AD patients. Finally, no discussion of modern biomedical research would be complete without consideration of genetics and appropriate transgenic mouse models. "Relevance of Transgenic Mouse Models to Human Alzheimer Disease" by Debbi A. Morrissette, Anna Parachikova, Kim N. Green, and Frank M. LaFerla does that very well with a discussion of the advantages and disadvantages of current mouse models and where this approach will move in the future.

An understanding of the basic biochemistry of the key players in AD may ultimately provide a framework for developing drugs or other treatments to alleviate the severe pathology these molecules can cause in the elderly. Whether these treatments come as enzyme inhibitors, peptide aggregation blockers, trafficking modulators, lipoprotein mimics, or even Tau antagonists is unknown at this time. We are at a stage in the development of our knowledge of the molecular basis of AD where many people believe that we are poised on the brink of significant breakthroughs; we now need to achieve these next steps before we forget where we are walking.

REFERENCES

1. Alzheimer, A. (1906) *Neurolog. Centralbl.* **23,** 1129–1136
2. Alzheimer, A. (1907) *Centralbl. Nervenheilkunde Psych.* **30,** 177–179
3. Stelzmann, R. A., Schnitzlein, H. N., and Murtagh, F. R. (1995) *Clin. Anat.* **8,** 429–431