

Enabling Technologies 2003 Workshop Summary

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Summary of Recommendations

Overview

The first day of Enabling Technologies 2003 focused on the natural history of Alzheimer's disease, fundamental cell biology, and mechanisms of neurodegeneration. On the second day, workshop participants reviewed the current status of biomarkers and experimental therapies, discussed the regulatory considerations that make the development of biomarkers and therapies for Alzheimer's disease so challenging, and explored ways to advance scientific consensus on key issues. The final session of the workshop presented a sampling of enabling technologies involving protein interaction networks, methods for tracking cellular and subcellular processes, and the use of RNA interference as a tool for discovery and therapy development.

Research Priorities re: Natural History of AD

The disease process begins at least five years before the appearance of cognitive symptoms, and the initial pathologies most likely involve changes in synapse function rather than cell death. The relationship between disease stage and the appearance of A β plaques and various products of APP metabolism (A β oligomers, protofibrils, C-terminal fragments) needs to be clarified. There is a need to define when "early AD" happens in terms of synapse loss. Imaging studies aimed at early synaptic dysfunction could be a useful strategy here. The role of aging needs much more extensive investigation, for example through broad-based genomic and proteomic screens around the transition point between normal aging and prodromal AD. Also worth pursuing are studies to see whether such alterations might be linked to DNA damage. Another priority is to understand the anatomical pattern of neurodegeneration by searching for genes with region-specific expression (such as CalDAG-GEFs and DUBs). Finally, participants agreed it is essential to be able to distinguish between the basic pathophysiology and the main modulatory risk factors. This would open up new possibilities to attack modulatory risk factors and delay onset of AD by a decade or more, with a big impact on incidence.

Research Priorities re: Mechanisms of Neurodegeneration

Sporadic AD is most likely a syndrome, with multiple pathways converging on a final common disease process. Studies in both humans and mice indicate that there must be pathways preceding and possibly independent of A β and tau that contribute to the pathogenesis of AD. These must be identified and targeted. A high priority should be to understand how ApoE modulates disease risk. Other candidates include variants of the BDNF gene, cell cycle genes, DUBs (involved in degrading protein aggregates), CalDAG-GEFs, and MHC I (both involved in learning and memory).

The interaction of the immune system with the central nervous system also deserves investigation, e.g. studies of MHC I molecules in human AD brain and experiments crossing mouse models of neurodegenerative diseases with mice lacking specific immunological genes. An emerging and understudied area is how cells compensate for losses of gene function caused by aging, DNA damage, toxins, etc.

Other major knowledge gaps include:

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the cell biology of A β ; in the context of synaptic function, how can a small peptide come out of a membrane and affect the synapse?

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the biology of the C-terminal fragment (CTF); it is produced at the same time as A β and therefore may be equally suspect as a cause of neurodegeneration.

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the role of chaperone proteins in A β folding (or misfolding) and degradation. Another fundamental question is whether neuronal dysfunction is a consequence of an internal mechanism gone awry or of an external toxic agent. Cell and slice culture models should be developed to help answer this question.

Workshop participants stressed the importance of referring back frequently to the human condition, e.g. is MCH I expressed in human brain and is this altered in AD? What about other genes involved in region-specific synaptic function? There is a temptation to test hypotheses in transgenic mice, but such testing requires constant reality checks.

Research Priorities re: Biomarkers, Therapies, Regulatory Consensus

Previous workshops emphasized the importance of validated biomarkers for presymptomatic AD. There is a great need for studies following apparently healthy people who are at-risk of AD to collect biological samples and perform brain imaging and neuropsychological tests, followed by gene expression or protein assays once some of the subjects have developed AD. Include some current biomarker candidates such as isoprostanes and sulfatides, which distinguish very mild dementia from controls. The underlying biology must evolve to support biomarker studies. A working group could assess existing standards for sample collection, storage, and evaluation, and make recommendations that would boost the power of longitudinal studies by enabling multiple centers to pool their samples and data.

A very high priority is to develop an expert consensus on a validated surrogate marker for AD and work to gain FDA acceptance of this surrogate marker. Drug targets are also needed. One way of approaching this goal is to consider establishing a "Virtual Drug Development Pipeline" based on the process used by the Hereditary Disease Foundation.

Research Priorities: Enabling Technologies

Tandem affinity purification coupled with mass spectrometry (TAP-MS), which has been used with great success in drawing an expanded protein interaction map for APP processing, should be used to build interaction maps for other proteins. For drug screening, the field needs in vitro models (cell cultures, slice cultures) based on mechanisms of neuronal dysfunction and death. New tools, such as siRNA and imaging methods that record the activity of individual synapses could be harnessed to probe the effects of genes on neuronal signaling, synaptic function, and cell death.

Recommendations

1. Conduct mechanistic studies to determine what A β oligomers do in the synaptic cleft: how do they affect calcium metabolism and synapse function when applied from outside

to normal slices of brain tissue or when the oligomers are produced within cells in slices from transgenic mice? Study the effect of oligomers on all measurable synaptic properties.

2. Identify modifying genes in the backgrounds of existing mouse strains; or, beginning with one strain of transgenic mice, study out-bred mice that have at least a 10-fold difference in amyloid deposition. A critical need for this project and for analyses of future transgenic strains is consensus on the relevant pathological and behavioral phenotypes.

3. Continue screening mutant mice for neurodegenerative phenotypes and identify loss-of-function mutations in their genes.

4. Find modifier genes in existing human populations. (A) In the Colombian kindred, the largest known, one PS mutation causes AD that varies in age of onset over a range of 30 years. What genes determine this difference? (B) Explore ways to conduct appropriate studies for gene modifiers of AD in people with Down syndrome.

5. Conduct more proteomic fishing expeditions to identify genes underlying the common aspects of idiopathic AD, HD, PD, and to verify whether DNA damage is a significant factor.

6. Re synaptic change: Cross MHC-I knockouts to APP transgenics, and also to other models relevant to AD, neurodegeneration, synapse activity, and learning.

7. Find new ways of studying the APP C-terminal fragment and try to import relevant mouse strains into mouse repositories.

8. Work towards a synthesis of the pathobiology, e.g. cell cycle, DNA repair, immune function.

9. Pursue new initiatives for literature/information management through the Alzforum, perhaps including a website for negative findings.

10. Fund a scientist solely to identify novel targets and candidate compounds in the literature, list and curate them, and make them available to the community through Alzforum. Continue tracking how candidates go through development and whether new leads from basic science are moved rapidly to drug discovery.

11. Create a virtual, non-profit "biotech" along the lines of the Hereditary Disease Foundation to proactively develop drug targets and shepherd them through the development process.

12. To improve diagnosis at the national level, find ways to bring centers across the country up to the level of the expert centers known for predicting accurately who will convert from MCI to AD, so that standardized skills and procedures are in place to identify subjects once more promising treatments are at hand for prevention trials.