

Book Review

Athena Andreadis*

Department of Cell Biology, University of Massachusetts Medical School, Worcester, MA, USA

Current Hypotheses and Research Milestones in Alzheimer's Disease, edited by Ricardo Maccioni and George Perry, Springer Science+Business Media, 2009, ISBN: 978-0-387-87994-9.

As the title clearly indicates, this book presents various theories and approaches to dissecting some of the myriad aspects of Alzheimer's disease (AD). It contains twenty chapters under eight conceptual headings. The "chapters" are formalized expansions of presentations at the Renāca conference of 2007, organized by the International Center for Biomedicine, the academic home of one of the editors (Maccioni).

As the editors note in their introduction, AD is the most prevalent cause of dementia, the fourth largest cause of death in developed countries and still impossible to either predict or cure, despite an enormous amount of research on it. And, as in all biomedical fields whose relevance and profitability attracts over-size egos and ambitions, a perennial problem in the field is that there has been little attempt to reconcile "pet" theories that will undoubtedly prove in hindsight to be inputs into common pathways or processes that result in equivalent cellular outcomes. The problem is exacerbated by the intrinsic complexities of the brain and its functions. The editors half-jokingly refer to "baptists, tauists or agnostics" – the insider names for those who are respective proponents of amyloid- β ($A\beta$), tau or "other" as the major causative agents of AD.

True to its objective, the book presents papers that cover most hypotheses and tastes: $A\beta$, tau and the cytoskeleton, oxidative stress, neuroinflammation, cere-

brovascular pathology and infection, general molecular and cellular pathways, biomarkers and cognitive neurology. Known and suspected culprits discussed in the articles range from the molecular (tau truncation and phosphorylation, $A\beta$ processing, tau and $A\beta$ misfolding, LEARN) to the cellular (mis-localization of cytoskeletal elements in the axon, possible action of $A\beta$ on the plasma membrane, involvement of microglia and astrocytes in neurodegeneration) to the organismic (the pleiotropic effects of neuroinflammation, brain blood supply) to the medical (prion-like genesis, re-activation of latent HSV, cortical disconnection).

The focus is firmly on AD, with a few excursions into adjacent diseases such as Parkinson's and Creutzfeldt-Jakob. The authors are aware of recent paradigm shifts and have incorporated them in their thinking and work: the grudging recognition that the amyloid cascade hypothesis is incomplete whereas tauopathies are the obligatory downstream portion of AD; the gradual realization that the events committing neurons to degeneration occur early and affect synaptic plasticity; the near-consensus that the toxic species involved seem to be oligomers of $A\beta$ and tau, whereas neurofibrillary tangles and senile plaque fibrils may be neutral or even protective. One hypothesis that is not explored in the book is the theory that neurodegeneration may be triggered by an aberrant attempt of the neuron to re-enter the cell cycle.

Equally crucial is the explicit admission that no mouse model so far completely recapitulates the progression of human AD, and that the species difference partly extends to molecular/cellular aspects. Such insights are crucial not only to understanding what triggers the process, but also for designing effective countermeasures. For example, a reagent that removes senile plaques or tangles may cause additional harm by recycling fibrils into actively toxic oligomers (as seems to be the conclusion from amyloid vaccine trials on humans).

*Address for correspondence: Athena Andreadis, Ph. D., Associate Professor, Cell Biology, University of Massachusetts Medical School, Department of Cell Biology, 55 Lake Avenue North, Worcester, MA 01655, USA. Tel.: +1 508 856 1414; Fax: +1 508 856 2484; E-mail: Athena.Andreadis@umassmed.edu.

Lacking is a conclusion that summarizes 1) how the various pathways might mesh and feed into the neurodegenerative process; 2) what has been tested *in vitro* versus in cells versus *in vivo*; 3) what has been tested/observed only in mice (versus recapitulating human aspects), and how uniform the results have been; and 4) what new and unique insights each of the papers brings to the question. Lacking such a synthesis, the book remains no more than the sum of its parts. As such it follows the letter of its title but does not fulfill its promise and will be out of date by the time of its

publication, an all-too common fate of such efforts.

What does come across is how much we still need to figure out and the crucial importance of details when we try to translate basic knowledge into medical applications. The other points that come across forcefully are how inadequate our current pharmacological arsenal is, how little advance there has been in designing reagents that might be effective in preventing, delaying or curing this devastating disease, and how crucial it is to have the correct paradigm for such efforts to have a chance of success.