Alzheimer's & Dementia 12 (2016) 65-74

Alzheimer's & Dementia

Perspective

Could ecosystem management provide a new framework for Alzheimer's disease?

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Abstract Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder that involves a plethora of molecular pathways. In the context of therapeutic treatment and biomarker profiling, the amyloid-beta (Aβ) peptide constitutes an interesting research avenue that involves interactions within a complex mixture of Aβ alloforms and other disease-modifying factors. Here, we explore the potential of an ecosystem paradigm as a novel way to consider AD and Aβ dynamics in particular. We discuss the example that the complexity of the Aβ network not only exhibits interesting parallels with the functioning of complex systems such as ecosystems but that this analogy can also provide novel insights into the neurobiological phenomena in AD and serve as a communication tool. We propose that combining network medicine with general ecosystem management principles could be a new and holistic approach to understand AD pathology and design novel therapies.

Keywords: Alzheimer's disease; Amyloid-beta peptide; AD therapy; Ecosystem management; Eutrophication; Spatiotemporal dynamics; Aβ alloform; Network medicine; Communication

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, affects the human brain and causes severe memory loss and behavioral changes. Despite some promising drug candidates targeting AD, clinical trials, however, remain unsuccessful due to a lack of efficacy or safety issues [1]. Current treatment is still limited to the alleviation of disease symptoms without the arrest or reversion of the underlying disorder. This lack of success reflects the general failure to fully comprehend the neurobiology of AD and the underlying pathogenesis. As multiple biochemical pathways are affected in AD, it is conceivable that targeting only one disease pathway might have an overall negligible effect as other disease mechanisms and pathways could still play a dominant role.

The main molecular hallmarks of the disease are the formation of amyloid plaques and neurofibrillary tangles

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http://dx.doi.org/10.1016/j.jalz.2015.07.491

(NFTs), which ultimately result in neuronal dysfunction and neuronal cell death [2]. In addition to the deposition of the amyloid-beta (Aβ) peptide and the hyperphosphorylation of tau, AD pathology also includes neuronal degeneration, an impaired microvasculature, a dysfunctional blood brain barrier, neuroinflammation, mitochondrial deterioration, oxidative stress, cytoskeleton disintegration, and epigenetic changes [3]. Although the amyloid cascade hypothesis is still influential to explain the pathophysiology of AD, alternative views consider tau as the main driving force of AD [4] or deem that several pathogenic features of AD can be interpreted as amyloid-independent alterations of synaptic plasticity, endolysosomal trafficking, cell cycle regulation, and neuronal survival [5]. Another hypothesis suggests that AD results from accelerated neural and cognitive decline in the vulnerable, aged brain due to microvascular failure and decreased angiogenesis [6]. In most cases, AD thus results from the interplay between certain susceptibility genes, environmental factors, and lifestyle contributors [7]. Therefore, it is essential that drug development strategies not only address the complexity of a single disease component (e.g. Aβ, tau, neuroinflammation…) but also address the multifactorial nature of this disease and the dynamics of the various interacting disease-contributing factors [8]. Developing new therapeutic strategies is indispensable as AD incidence is predicted to nearly triple by 2050 if no cure becomes available [9].

In an effort to approach AD from a different angle, we postulate that a similar complexity can be observed in complex systems such as ecosystems, which can be defined as networks of interactions among species and their environment [10]. In ecosystems, the relative abundance of the composing species is continuously molded by environmental conditions affecting the relative population growth of species, priority effects (i.e. order of emergence or arrival of species [11]), and biotic interactions among species [12]. As a result, community structure may change over time, and the resulting trajectories may lead to different equilibria or oscillations [13] that, in turn, will determine the functions and services provided by the system (e.g. productivity, efficiency of biochemical cycles, and resistance against invasive species). Similarly, the temporal dynamics in the composition of disease factors may also be governed by inter- and intra-molecular interactions, changes in environmental conditions, and priority effects [14]. The end point of the evolution of a complex system may be deterministic (e.g. the formation of plaques in AD, the eutrophication of a lake, ecological succession toward a climax forest after a fire…), but the route to get there may not be. For instance, some elderly people retain a normal cognitive function despite having a high amyloid load in their brain, whereas others show severe cognitive decline with little Aβ deposition [15]. There could also be different end points, some of which may be preferable over others (e.g. turbid vs. clear water states in lakes, tree savannah vs. grass savannah). Finally, the stochastic nature of community trajectories should be investigated as order of arrival (priority effects) or small initial deviations followed by positive feedbacks could reduce the predictability of responses [13]. Based on these insights from ecosystem ecology, we postulate that a better knowledge of the interplay between the drivers that determine variation in the temporal trajectories of disease-contributing factors, by minimizing or avoiding trajectories that are associated with toxicity and neurodegeneration, may render AD treatment more effective.

This perspective article explores the parallel that exists between the complexity of the molecular interactions within AD and the complex architecture of direct and indirect interactions in ecosystems (Fig. 1). We propose that insights from ecology, community assembly theory, and ecosystem management principles, in particular, (Box 1) might provide novel useful insights into AD pathogenesis and could serve as a guiding principle for innovative therapy design. Moreover, this framework provides an additional opportunity to establish a dialog between researchers, medical experts, industrial partners, and the lay public (patients and caregivers) using more familiar observable natural events as proxies for molecular and cellular events in AD. The power of such a communication strategy is nicely illustrated with the cover image of the November 2014 issue of this *Journal*, which depicts the North American woodpecker. As described in the editorial, the "woodpecker model" provides a comparative mind-set to gain more insight into the link between traumatic brain injuries and the subsequent development of neurodegenerative diseases [17].

2. Comparison of Aβ behavior in AD with general ecosystem principles

As the idea originated from the viewpoint of bench scientists investigating the role of Aβ in AD, we have used the Aβ peptide as an example to showcase some of the commonalities between AD complexity and ecological principles. The main driving force for writing this perspective is the emerging picture of increasing complexity for Aβ aggregation, whereby Aβ dynamics at different levels play a crucial role in AD [14]. Yet, that picture remains incomplete as all therapeutic intervention strategies that target Aβ production, accumulation, or clearance have failed hitherto and there is still no means to cure or even halt the disease [3]. This fact alone provides strong support for the development of a combination therapy to tackle AD. Thus, this ecosystem paradigm should not be limited to Aβ as a disease-contributing factor, but similar analogies can be envisioned with other disease components (e.g. tau, neuroinflammation…) that can be combined in more complex models.

Ecosystems can be perceived at different levels in the context of AD: the brain, the extracellular space, or