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Perspective

Unraveling the mechanistic complexity of Alzheimer's disease through systems biology

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Abstract Alzheimer's disease (AD) is a complex, multifactorial disease that has reached global epidemic proportions. The challenge remains to fully identify its underlying molecular mechanisms that will enable development of accurate diagnostic tools and therapeutics. Conventional experimental approaches that target individual or small sets of genes or proteins may overlook important parts of the regulatory network, which limits the opportunity of identifying multitarget interventions. Our perspective is that a more complete insight into potential treatment options for AD will only be made possible through studying the disease as a system. We propose an integrative systems biology approach that we argue has been largely untapped in AD research. We present key publications to demonstrate the value of this approach and discuss the potential to intensify research efforts in AD through transdisciplinary collaboration. We highlight challenges and opportunities for significant breakthroughs that could be made if a systems biology approach is fully exploited.

Keywords: Computational modeling; Integrative; Holistic; Complex systems; Risk genes; Transdisciplinary research

1. Introduction

Of the top five terminal diseases in the developed world, Alzheimer's disease (AD) is the only disease with no known etiology, treatment, or definitive premortem diagnosis and accounts for between 50 and 70% of all cases of dementia. At best, the few available treatment options only target symptoms of the disease. This overall dearth of options to treat and ultimately prevent the onset of AD lies primarily with the disease's heterogeneity and comorbidity. This high level of complexity creates the over-riding challenge of understanding the disease mechanisms that conventional research methodologies have to date been unsuccessful in unraveling.

Although many insights into possible mechanisms have been found through experimental research in classical molecular biology and genetics, including amyloid beta (Aβ) deposition [1–3], tau phosphorylation [4,5], metal ion dysregulation [6,7] and inflammation [8,9], we suggest a higher level of understanding will be made possible through adopting a more integrative and holistic "systems" approach. This will enable a more thorough appreciation of the disease mechanisms across the different system levels from genetic to cellular, through to brain tissue and up to the individual (organism) level. The anticipated outcome of this holistic approach will be the added bonus

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of a faster track of the translation process from in vitro studies to in vivo human biology.

This perspective introduces the reader to the emerging view that a systems biology approach is essential to enabling the much needed breakthroughs in AD research. Our aim is to challenge those working in the field of AD to consider new ways of approaching their research. We demonstrate how tools from systems biology have already been successfully integrated with conventional experimental studies across other disease modalities, cancer to date being the most widely studied. We provide examples of outcomes from a range of these studies to demonstrate how the use of a systems approach has been a key enabler for researchers to develop hypotheses that would have been otherwise unattainable. Our main point will be to argue that systems biology is the much sought after enabler in the field of AD research to address the challenge of gaining a deeper understanding of the mechanisms of AD, with the ultimate goal of more rapidly identifying new targets for both pharmacologic and nonpharmacologic interventions.

1.1. Why a paradigm shift in AD research is critical

1.1.1. The socio-economic cost

On a global scale, the cost of AD at a personal, social, and economic level is staggering. In 2013, the worldwide prevalence of dementia was estimated to be 44.35 million [10]. By 2030, this figure is expected to swell to 71 million and more than triple to 205 million by the middle of the century [10]. With expectations of a global population reaching 9.6 billion by 2050, this could mean that one person in every 47 will be living with dementia in less than four decades. These numbers are of epidemic proportion and, as many believe, are an underestimate of the true nature of the problem, with less than half of all cases of dementia in high-income countries, and fewer than 10% in low- and middle-income countries, being diagnosed [10].

In 2010, the annual cost of dementia to the global economy was reported to be in excess of US $604 billion [11]. It is clear that without a translatable understanding of the pathogenic mechanism of AD that enables both drug development and early detection, costs will surpass those associated with any other health condition.

1.1.2. Meeting the challenge

The over-riding challenge in understanding the mechanisms, and, therefore, cause of AD lies in its sporadic rather than Mendelian nature. Mutations in three genes, amyloid precursor protein and two presenilins (*PSEN1* and *PSEN2*), are the only definitively known genetic component of the disease [12]. However, these mutations are rare but predispose the individual to developing early-onset AD, which accounts for approximately 3% of all cases of AD. The sporadic and most common form, late-onset Alzheimer's disease (LOAD) [13,14], is also likely to have a complex pattern of genetic inheritance that has to date eluded detection. It is known that the presence of one or two copies of the ε4 allele in the apolipoprotein E gene (*APOE*, chromosome 19q13.2) increases an individual's susceptibility to LOAD [15]. It is possible that the relevant regulatory apparatus will have distributed control across the network, implying that a large number of genes will play a role and that conventional approaches guided by intuition will be less of a guide.

Over the past decade, genome-wide association studies (GWAS) have been evolving into an important tool for investigating the genetic architecture of human disease [16,17]. With access to data from the whole human genome, the ability to be able to simultaneously assess millions of single-nucleotide polymorphisms in thousands of samples has enabled a much higher level of understanding of the architecture and genetic variation of common disease. GWAS have also enabled the development of new technologies for capturing genetic information, novel study designs, and statistical methodologies [18,19]. Through these techniques and access to high-throughput human genetic data, we have begun to capture glimpses of some of the functionally relevant gene candidates that contribute to the genetic risk in sporadic AD.

GWAS have previously provided compelling evidence for 10 susceptibility loci for LOAD—*APOE*, *CLU*, *PICALM*, *CR1*, *BIN1*, *EPHA1*, *MS4A*, *ABCA7*, *CD33*, and *CD2AP* genes [20–23]. In addition, rare variants of the *TREM2* gene expressing the triggering receptor located on myeloid cells 2 have also been observed to represent novel risk factors for LOAD [24–26]. With the rapid evolution of genomic methods, the search for novel genetic risk factors will be further improved. International collaborative cohort studies generating large-scale meta-analysis of GWAS is crucial to this success. Such a study by the International Genomics of Alzheimer's Project has recently detected 11 novel susceptibility loci for AD following the meta-analysis of 74,046 individuals [27]. Some of these genes highlight the importance of molecular pathways previously hypothesized to increase risk of AD. In addition, the existence of novel pathways underpinning AD has also been suggested, necessitating further analyses.

It is, therefore, evident that a whole-system approach is essential to explore the full range of regulatory motifs involved in the cascade of events at the molecular and cellular level that ultimately lead to the abnormal build-up of Aβ and tau, two hallmark proteins involved in AD pathogenesis. By adopting a systems approach to both viewing and studying AD not only will highly significant risk genes for LOAD be teased out from the vast quantities of "omics" data sets available [14], but potentially new pathways will be revealed with functions previously not thought to be related to AD. Pharmaceuticals targeting only the Aβ pathways have yet to demonstrate efficacy [28] and hence there is an urgent need to consider in parallel other possible pathways contributing to the etiology of AD.