Biological Systems: Open Access

Fu, Biol syst Open Access 2016, 5:1
DOI: 10.4172/2329-6577.1000148

Mini Review Open Access

Genomics Reveals Similar and Dissimilar Pathogenesis between Alzheimer`s and Parkinson`s Diseases

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Rec date: Sep17, 2015; **Acc date:** Dec 09, 2015; **Pub date:** Dec 17, 2015

Abstract

Despite decades of intensive research, the pathogenesis of neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD), is still not fully understood. Latest genomics technology offers a new perspective on this issue. Yet, the genomics-based approach to pathogenesis identification is a new technology at the incipient stage. In this communication, we summarize the current progress along this line and report the commonality and difference in pathogenesis between AD and PD revealed by this approach.

Background

Understanding the cause and mechanisms of a disease often requires intensive human efforts, especially for diseases with complex etiology like neurodegeneration. The latest genomic technology coupled with advanced bioinformatics has promised a high-throughput approach that can quickly identify disease-affected genes and pathways. Pathogenesis describes the origin and development of a disease, namely, the biological mechanisms that, driven by underlying etiology, lead to the disease. In neurodegenerative diseases, the degeneration or death of neurons is the effect rather than the cause. As their causes remain elusive, the analysis of pathogenesis is an effective means to investigate their causes. In fact, study of neuroscience based on genomics is an insightful approach since a large portion of the mammalian genome is dedicated to brain function [1].

We investigated the pathogenesis of two most common neurodegenerative diseases, Alzheimer's disease (AD) and Parkinson's disease (PD). AD, first described by Alois Alzheimer in 1906, is a progressive neurodegenerative disease characterized by cognitive deterioration together with behavioral disturbances and declining activities of daily living [2], and it is the most common cause of senile dementia. Microscopically, AD is characterized by extracellular amyloid plaques and intraneuronal neurofibrillary tangles [3]. Amyloid plaques are dense deposits of amyloid-beta (Aβ) protein, whereas neurofibrillary tangles are the aggregates of hyperphosphorylated tau protein. Accumulations of amyloid fibrils are believed to be neuro-toxic, cause loss of neurons and synapses in the cerebral cortex and certain subcortical regions, and result in gross atrophy of the affected areas [4]. However, deposition of amyloid plaques does not correlate well with neuron loss [5]. In one clinical trial, an experimental vaccine was found to clear the amyloid plaques, but it did not have any significant effect on dementia [6], suggesting that neurofibrillary tangles could play a more important role than amyloid plaques in the pathophysiology of AD. Next, let us consider the second most common neurodegenerative disease, PD, which first described by James Parkinson in 1817, is a movement disorder characterized by bradykinesia, rigidity, and resting tremor. It is well established that this disease is caused by the loss of neurons in the substantia nigra pars compacta (SNpc), which in turns leads to dopamine deficiency in the nigrostriatal pathway [7]. The pathological hallmark of PD is Lewy bodies, which are abnormal aggregates of proteins found inside nerve cells and containing mainly α-synuclein [8].

The initial cause and biological mechanisms that account for the pathogenesis are particularly interesting because they hint at optimal clinical management at the early stage. Historically, causality investigation is an important scientific problem. Many statistical and computer science techniques have been developed for construction of causal models that configure the causal relationships among a set of given variables as a network or graph. In this way, the pathogenic mechanisms correspond to the root part of the causal model.

A necessity in causal modeling is the temporal order among the variables. In the process of unraveling complex pathophysiology, a well-known dilemma, known as the chicken or egg causality dilemma often arises when the temporal order of two correlated events is unknown. To illustrate the dilemma, consider this example. In PD, mitochondrial dysfunction can induce synuclein aggregation, whereas over-expression of synuclein can cause mitochondrial fragmentation [9,10]. So one can raise the question of which process comes first. Unfortunately, the clinical gene expression data available for analysis often lack temporal order. Prior knowledge on the causal gene network would fall short since this knowledge does neither necessarily apply to an abnormal diseased state nor to ensemble genomic behavior.

Advance in Genomics-Based Pathogenesis Analysis

Researchers have begun to investigate the pathogenesis of a disease based on genomics data. To overcome the above mentioned causality dilemma, temporal staging is part of the research protocol. For instance, a well-known study focused attention on incipient AD in an attempt to study its pathogenesis [11]. In this study, incipient AD was defined by the criterion: MMSE (Mini Mental Status Examination) in the range of 20-26; the significant genes were identified by testing the correlation of each gene's expression with MMSE and NFT (neurofibrillary tangle) scores; and the significant biological process

categories were identified using EASE software (the Expression Analysis Systematic Explorer [12]). EASE can identify enriched biological themes that are more comprehensible than a gene interaction network.

Since incipient AD was defined based on the MMSE criterion, this definition requires the assumption that cognitive impairment is proportional to pathological change. The analysis based on incipient AD would also need the assumption that incipient disease exhibits early biological changes that lead to late disease. It seems clear that without temporal staging, it would be difficult to conduct an analysis on pathogenesis, since temporal precedence is a necessary element for causal analysis.

Methodologically, the incipient-stage analysis requires the criterion for incipient diseases that may be inaccurate at the molecular level. The pathways identified in incipient diseases are not necessarily the cause of the disease. In addition, the incipient-stage analysis would have to use a smaller selected group of experimental subjects with incipient diseases, and hence a smaller sample size.

Recently, our research team has developed a new method that can identify upstream genomic processes from gene expression data [10]. Here a genomic process refers to a statistically significant biological theme that represents specific functional characteristics shared by a group of genes in a functional system category, as identifiable by EASE. Unlike the incipient-stage analysis [11], the upstream analysis is applicable to the data of all experimental subjects associated with various, mixed yet unknown or hidden temporal stages of the disease concerned. Lack of temporal precedence information in non-temporal data will prohibit causal analysis. However, as an exception to this rule, this advanced upstream analysis method has a unique advantage in its ability to analyze the data collected at single points in time that are not classified by temporal stages, whether given or assumed. For pathogenesis analysis, the top cluster of upstream genomic processes is considered as most likely pathogenic. This advanced method has been validated on both simulated and real experimental data, with its principle formally proven.

Pathogenesis of Neurodegenerative Diseases

Here we look at the mechanisms of pathogenesis of two most important neurodegenerative diseases, AD versus PD. The upstream analysis is compared with the incipient-stage analysis in this regard. The genomic data concerning AD were obtained from the NCBI GEO database in the public domain with the series accession number GSE1297 at the platform GPL96 (Affymetrix Human Genome U133A Array) (Blalock et. al. [11]), whereas the genomic data concerning PD were obtained from the same source with the series accession number GSE8397 at the same platform (Moran et. al. [13]).

The incipient-stage genomics-based analysis of AD revealed a new model of pathogenesis that highlighted the activation of tumor suppressor pathways [11]. Multiple tumor suppressor genes related to cell cycle regulation were identified in incipient AD. The activation of tumor suppressor pathways at the early stage of the disease suggests their important role in the pathogenesis of AD. Specifically, the tumor suppressor response could induce protein aggregation and result in NFTs. On the other hand, oncogenesis was identified as a significant biological process in AD as a whole but not particularly in incipient AD. Thus, cancer formation could be a down-stream effect if the tumor suppressor mechanism fails.

In contrast, the upstream gene-expression analysis of AD identified the cell cycle as the top biological process in up-regulated genomic activities. This result suggests that the up-regulation of the cell cycle control is a key event in the pathogenesis of AD. In this analysis, the biological process of the cell cycle is associated with genes related to cell division control such as cyclin and CDC proteins and with some genes related to tumor suppression such as the p53 tumor suppressor protein and the Retinoblastoma protein. The analysis also found that various transcriptional factors were activated, including zinc finger proteins and tumor suppressors. Like the incipient-stage analysis, the upstream analysis also identified oncogenesis as a downstream process, which is considered non-significant in the pathogenesis of AD.

It has been hypothesized that neurodegeneration, similar to cancer, is a disease caused by problems in cell cycle control and a phenomenon called cell cycle re-entry, characterized by increase in DNA content and re-expression of cyclin B1, was found in primary neurons, leading to tau phosphorylation seen in AD [14]. According to this theory, the cell cycle control is perhaps a more important biological mechanism than tumor suppression in the pathogenesis of AD, despite substantial overlap in associated genes.

Overall, for up-regulated biological process categories, the incipient-stage analysis and the upstream analysis of AD yielded closely related but somewhat different results on the basis of the same ontology (i.e., biological process categories). In particular, the incipient-stage analysis did not identify the cell cycle as a significant biological process, but it identified other process categories intersecting with the cell cycle process in terms of associated genes. For repressed gene activities, both analysis methods identified the transport and protein metabolism as relevant to AD pathogenesis.

When applied to PD, the upstream genomics-based analysis confirmed the current misfolded protein theory about the pathogenesis of PD, and provided new insights as well [10]. Interestingly, this analysis discovered that RNA (ribonucleic acid) metabolism pathology was a potential cause of PD. This finding is supported by recent research that highlights the role of RNA metabolism in PD [15]. Here we omit the pathogenesis analysis of PD based on incipient-disease genomics since no study conducting this analysis can be found in the literature.

With regard to down-regulated genomic behavior, the transport mechanism was identified as a significant biological process that occurred at the early stage of both AD and PD. This is not a coincidence since the transportation of the neurotransmitters inside and across neurons is a universal behavior in a nervous system such as the brain. In the literature, endoplasmic reticulum dysfunction is proposed as a potential cause for loss of dopaminergic neurons [13].

Moreover, protein metabolism was identified as a significant down-regulated biological process in AD (at the early stage) but not in PD. While both diseases are caused by the aggregation of special abnormal proteins, the repression of protein metabolism seems to have a greater impact on the pathogenesis of AD than PD.

Conclusion

The genomics-based incipient-disease analysis done in a previous study indicated that the transcriptional and tumor suppressor responses played an important role in the pathogenesis of AD, whereas the latest genomics-based upstream analysis showed that dysfunction in cell-cycle control was a culprit. The finding by the upstream analysis

supports the theory of cell cycle re-entry in neurons of AD. By contrast, neither the cell cycle control nor the tumor suppressor response is responsible for the pathogenesis of PD according to the genomics-based upstream analysis. Instead, the pathogenesis of PD could be attributed to misfolded protein and RNA metabolism. In terms of down-regulated gene activities, the transport biological process is repressed in both AD and PD. However, down-regulation of protein metabolism appears to be more prominent in the pathogenesis of AD than in PD. Our understanding of the pathogenesis of a disease at the genomic level can accelerate the development of more accurate and effective diagnosis and treatment methods at the cellular and molecular levels. It is anticipated that this research strategy will become increasing important in the near future.

References

1. Boguski MS, Jones AR (2004) Neurogenomics: at the intersection of neurobiology and genome sciences. Nat Neurosci 7: 429-433.
2. Burns A, Byrne EJ, Maurer K (2002) Alzheimer's disease. Lancet 360: 163-165.
3. Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J (2004) The importance of neuritic plaques and tangles to the development and evolution of AD. Neurology 62: 1984-1989.
4. Wenk GL (2003) Neuropathologic changes in Alzheimer's disease. J Clin Psychiatry 64 Suppl 9: 7-10.
5. C Schmitz, BP Rutten, A Pielen, S Schafer, O Wirths, et al. (2004) Bayer, Hippocampal neuron loss exceeds amyloid plaque load in a transgenic mouse model of Alzheimer's disease, The American journal of pathology 164: 1495-1502.
6. Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, et al. (2008) Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. Lancet 372: 216-223.
7. Dauer W, Przedborski S (2003) Parkinson's disease: mechanisms and models. Neuron 39: 889-909.
8. Davie CA (2008) A review of Parkinson's disease. Br Med Bull 86: 109-127.
9. Exner N, Lutz AK, Haass C, Winklhofer KF (2012) Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. EMBO J 31: 3038-3062.
10. LM Fu, KA Fu (2015) Analysis of Parkinson's disease pathophysiology using an integrated genomics-bioinformatics approach, Pathophysiology: the official journal of the International Society for Pathophysiology/ISP 22: 15-29.
11. EM Blalock, JW Geddes, KC Chen, NM Porter, WR Markesbery, PW Landfield (2004) Incipient Alzheimer's disease: microarray correlation analyses reveal major transcriptional and tumor suppressor responses, Proc Natl Acad Sci U S A 101: 2173-2178.
12. Hosack DA, Dennis G Jr, Sherman BT, Lane HC, Lempicki RA (2003) Identifying biological themes within lists of genes with EASE. Genome Biol 4: R70.
13. Moran LB, Duke DC, Deprez M, Dexter DT, Pearce RK, et al. (2006) Whole genome expression profiling of the medial and lateral substantia nigra in Parkinson's disease. Neurogenetics 7: 1-11.
14. McShea A, Lee HG, Petersen RB, Casadesus G, Vincent I, et al. (2007) Neuronal cell cycle re-entry mediates Alzheimer disease-type changes. Biochim Biophys Acta 1772: 467-472.
15. Lu B, Gehrke S, Wu Z (2014) RNA metabolism in the pathogenesis of Parkinsons disease. Brain Res 1584: 105-115.