Searching for Common Protein Networks in Neurodegenerative Disorders

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1 Introduction

Neurodegenerative disorders (NDDs) consist of several distinct categories of diseases and each manifests its own unique symptoms. However, the diseases share several common features, especially aggregation and deposition of abnormal proteins [1, 3]. The objective of our research is to understand any common molecular pathogenic mechanisms in the sense of protein-protein interaction network by integrating the data from two-hybrid systems and microarray gene expression profiles.

We have identified and collected known protein-protein interactions that are related to the pathogenic mechanisms and created reference maps for the well-known NDDs: Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Dentatorubral-pallidoluysian atrophy (DRPLA) and Prion disease [5]. The protein interaction maps are part of the KEGG database.

2 Method and Results

In this study, we collected two-hybrid system experimental data of human proteins from ProNet Online [6]. We found 39 relatively short additional paths consisting of not more than 12 proteins, starting and ending at proteins in the reference maps. We assigned the functions of 57 proteins involved in the additional paths from the biological process of Gene Ontology (GO) [4]. We found that the GO category of signal transduction was most abundant, followed by oncogenesis. We also mapped additional paths consisting of not more than 3 proteins from the reference maps and again signal transduction was most abundant but followed by DNA damage response.

For the next step, we mapped up-regulated AD-related genes and down-regulated AD-related genes of postmortem gene expression profiles of AD victims [2] to these reference maps expanded by the two-hybrid data. We found only a few genes in the microarray data were mapped to genes in the two-hybrid data or the reference maps. These genes include alpha-2-macroglobulin (A2M), excision repair cross-complementing rodent repair deficiency, complementation group3 (xeroderma pigmentosum group B complementing) (ERCC3), dynactin 1 (p150, glued homolog, Drosophila) (DCTN1) for up-regulated AD-related genes and tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide (YWHAB), mitogen-activated protein kinase kinase 1 (MAP2K1) for down-regulated AD-related genes. These two down-regulated genes and one of the up-regulated genes

are also close to each other in the network created from the two-hybrid data as shown in Figure 1. This network is related to insulin receptor signaling and protein phosphorylation.

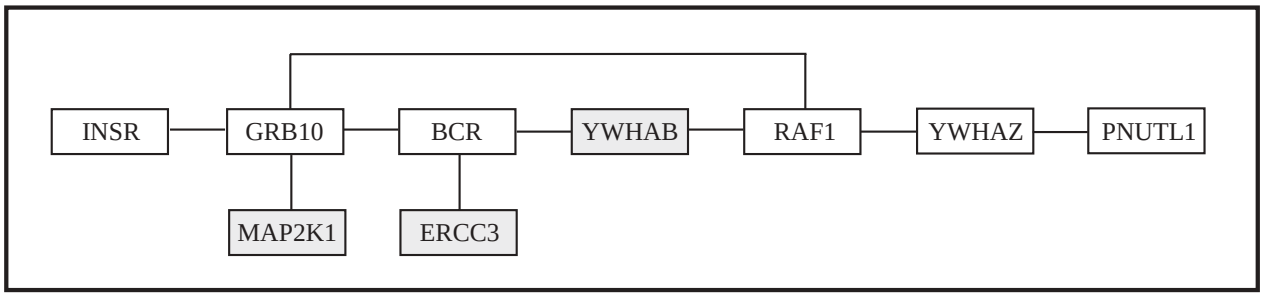

Figure 1: Network of proteins identified by the two-hybrid data.

3 Discussion

In Figure 1, YWHAB binds to BCR (break point cluster region) and RAF1 (v-raf-1 murine leukemia viral oncogene homolog1). Both genes are commonly annotated in the biological process of GO as oncogenesis, signal transduction and protein phosphorylation. On the other hand, YWHAB is not yet annotated in the biological process of GO, but we expect it is involved in a similar biological process as BCR and RAF1. Therefore, by such analysis of neighbor proteins in the network, biological functions may be uncovered for unknown genes.

Genes that are differentially expressed in AD [2] are also detected in other NDD maps such as ALS, HD and DRPLA. These genes may be involved in common molecular mechanisms in NDDs. There are additional microarray data that come from transgenic mouse models. We plan to use ortholog relations and map differentially expressed mouse genes to the network of human proteins in order to find common proteins and paths in NDDs.

References

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