Insulin Resistance Intrudes AKT2's Protective Effects Against Neural Apoptosis

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Introduction

Alzheimer's disease is the sixth leading cause of death in the United States, accountable for an estimated 500,000 deaths in 2010 [1]. While it seems to affect individuals quite arbitrarily, there has been some question in the past about the role of diet in its development. In this abstract, we will look at the role of insulin resistance in neural apoptosis as noted in Alzheimer's disease. The primary gene of focus will be AKT2, a kinase responsible for phosphorylating several important proteins, but most relevantly FOXO1 as it contributes to neural apoptosis [2]. Identifying kinase-substrate interactions and phosphorylation can yield uncertain results, but this relationship was previously confirmed using PDK1-PHKI embryonic stem cells [3]. AKT2 is activated by insulin [4], and it has been found that AKT2 plays a crucial role in preventing oxidative-stress-induced apoptosis [5]. The levels of AKT2 in patients with Alzheimer's disease are therefore relevant to addressing theories that relate Alzheimer's disease to diabetes mellitus, insulin resistance, and the ultimate cause of Alzheimer's disease.

Methods

We downloaded the dataset reference series GSE28146 from the National Center for Biotechnology Information (NCBI) website [6]. The data obtained was derived from a study that analyzed laser-captured hippocampal CA1 gray matter from FFPE hippocampal sections of subjects at varying stages (incipient, moderate, severe) of Alzheimer's disease. Two sample sets were compared; one of a group of seven patients with severe Alzheimer's and a control group of eight patients with no Alzheimer's. Genes that expressed differently between the two groups were calculated using a student T-test with a p-value of less than 0.01 through the computer program R. This left us with a list of up-regulated genes, and a list of down-regulated genes. We then used the Cytoscape plugin BiNGO to further analyze our results. The first output showed that the down-regulated gene list was not significant for representations of gene ontology (GO) categories. The second output showed that there were several GO categories that were significantly overrepresented within our list of up-regulated genes. Our team members then each set out to individually investigate genes within that list. Genecards and String were used frequently to help direct theories regarding the genes' relations to Alzheimer's disease pathophysiology.

Results

In total there were 36 genes found to be both significantly up-regulated in the severe Alzheimer's disease group and within significantly overrepresented GO categories. From these categories, I focused on AKT2. The high levels of the protein noted in patients with severe Alzheimer's disease supports existing theories that insulin resistance is a relevant aspect of the disease.

Conclusion

Further investigation to determine the role of ATK2 in promoting neural cell survival is needed. Other members of the ATK family may also be noteworthy mechanisms of Alzheimer's disease, particularly ATK3. Very little is known about this gene, but it has been noted at high levels in brains of healthy individuals and conversely, mice with reduced levels of ATK3 have presented with smaller brains [7].

Keywords: ATK, FOXO1, phosphorylation, insulin resistance, apoptosis, Alzheimer's disease

References:

1. http://www.alz.org/alzheimers_disease_facts_and_figures.asp
2. http://www.genecards.org/cgi-bin/carddisp.pl?gene=SH3RF1
3. http://www.sciencedirect.com/science/article/pii/S0092867407007751
4. http://www.ncbi.nlm.nih.gov/pubmed/9620559
5. http://www.ncbi.nlm.nih.gov/pubmed/21303257
6. http://www.ncbi.nlm.nih.gov/sites/GDSbrowser?acc=GDS4136
7. http://www-06.all-portland.net/bst/032/0350/0320350.pdf

I am a recent graduate from Community high school in Ann Arbor, MI, and will be attending the University of Michigan this fall. I came to the summer computational biology camp organized by miRcore almost exactly a year ago, and have been coming to the weekly volunteer meetings ever since. In high school I played field hockey, coached an elementary school Academic Games team, was heavily involved in my school's student government and GIDAS (genes in diseases and symptoms- an outreach of miRcore!) club, and this past year was thrilled to participate in Huron high school's Health Sciences program. Next year, I will be in the University of Michigan's Health Sciences Scholars Program.
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