Calculating gene and protein connections in a Parkinson's disease model

February 22 2009, by Nicole Giese

Researchers have created an algorithm that meshes existing data to produce a clearer step-by-step flow chart of how cells respond to stimuli. Using this new method, Whitehead Institute and Massachusetts Institute of Technology scientists have analyzed alpha-synuclein toxicity to identify genes and pathways that can affect cell survival. Misfolded copies of the alpha-synuclein protein in brain cells are a hallmark of Parkinson's disease.

A novel approach to analyzing cellular data is yielding new understanding of Parkinson's disease's destructive pathways.

Whitehead Institute and Massachusetts Institute of Technology (MIT) scientists have employed this new computational technique to analyze alpha-synuclein, a mysterious protein that is associated with Parkinson's disease.

Cells are constantly adapting to various stimuli, including changes in their environment and mutations, through an intricate web of molecular interactions. Knowledge of these changes is crucial for developing new treatments for diseases. To decipher how a cell responds to various stimuli, laboratories worldwide have been turning to new technologies that produce vast amounts of data. Such data typically exists in two major forms: genetic screen data (the results from deleting a gene from a cell's genome and seeing what observable traits appear in the cell) and information on the cellular levels of messenger RNA (mRNA, which is the template for proteins).

Historically, these two types of data have largely been analyzed independently of each other, revealing only glimpses of the cell's internal workings. Each type of data is actually biased toward identifying different aspects of cellular response, something that researchers had not realized until now. However, the new algorithm, known as ResponseNet, exploits these biases and allows for combined analysis.

In this combined analysis, both data types are integrated with molecular interactions data into a diagram that connects the experimentally identified proteins and genes. While this typically results in an extraordinarily complicated diagram, sometimes jokingly referred to as a "hairball", ResponseNet is designed to whittle the hairball down to the most probable pathways connecting various genes and proteins.

Esti Yeger-Lotem, a postdoctoral researcher in the laboratories of Whitehead Member Susan Lindquist and of Ernest Fraenkel at MIT's Biological Engineering department and co-author of the Nature Genetics article, says that by analyzing those probable pathways, a systems view of the cellular response emerges. "This allows for a more complete understanding of cellular response and can reveal hidden components of the response that may be targeted by drugs," she says.

According to Laura Riva, a postdoctoral researcher in MIT's biological engineering department and one of the designers of the algorithm, ResponseNet is potentially very useful for researchers.

"It is a powerful approach for interpreting experimental data because it can efficiently analyze tens of thousands of nodes and interactions," says Riva, who is also a co-author on the article. "The output of ResponseNet is a sparse network connecting some of the genetic data to some of the transcriptional data via intermediate proteins. Biologists can look at the network and understand which pathways are perturbed, and they can use it to generate testable hypotheses."

To demonstrate ResponseNet's capabilities, Yeger-Lotem entered the data from screens of 5,500 yeast strains (*Saccharomyces cerevisiae*). These strains are based on a yeast model that creates large amounts of the protein alpha-synuclein, thereby mimicking the toxic effects of alpha-synuclein accumulation in Parkinson's disease patients' brain cells.

Ernest Fraenkel, Assistant Professor of Biological Engineering at MIT, says that the alpha-synuclein data are an excellent test case for the algorithm, which has lead to new insights from existing data.

"The connection between alpha-synuclein and Parkinson's disease is enigmatic," says Fraenkel. "We have wonderful data from the yeast model, but despite this richness of data, so little is known about what alpha-synuclein really does in the cell."

Using these data, ResponseNet identified several links between alpha-synuclein toxicity and basic cell processes, including those used to recycle proteins and to usher the cell through its normal life cycle.

Surprisingly, ResponseNet also tied alpha-synuclein toxicity to a highly-conserved pathway targeted by cholesterol-lowering statin drugs and another pathway targeted by the immunosuppressing drug rapamycin.

To confirm ResponseNet's links and to test how these two pathways could affect alpha-synuclein toxicity, researchers added either rapamycin or the statin lovastatin to yeast model cultures. When the researchers added a low dose of rapamycin to the yeast model, the drug was toxic to the yeast. When lovastatin was added, the yeast reduced their growth rate, an indicator that the yeast had gotten sicker. However, when researchers added the molecule ubiquinone (also known as coenzyme Q10 or CoQ10), which is farther downstream in the statin network and possibly undersynthesized in alpha-synuclein-containing yeast, ubiquinone modestly suppressed alpha-synuclein toxicity.

All of these results validated the hypotheses based on ResponseNet's network.

"ResponseNet provides a wealth of new information," says Lindquist, who is also a Howard Hughes Medical Institute investigator and a professor of biology at MIT. "Some of the things we have found offer a promise to speed the development of new therapeutic strategies for Parkinson's disease. For the sake of the patients involved, let's hope they hold true in a human brain."

More information: "Bridging high-throughput genetic and transcriptional data reveals cellular responses to alpha-synuclein toxicity", *Nature Genetics*, online February 22, 2009

Source: Whitehead Institute for Biomedical Research