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Review

Current status and future directions of gene expression profiling in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a common age-associated neurodegenerative disorder. Motor symptoms are the cardinal component of PD, but non-motor symptoms, such as dementia, depression, and autonomic dysfunction are being increasingly recognized. Motor symptoms are primarily caused by selective degeneration of substantia nigra dopamine (SNDA) neurons in the midbrain; non-motor symptoms may be referable to well-described pathology at multiple levels of the neuraxis. Development of symptomatic and disease-modifying therapies is dependent on an accurate and comprehensive understanding of the pathogenesis and pathophysiology of PD. Gene expression profiling has been recently employed to assess function on a broad level in the hopes of gaining greater knowledge concerning how individual mechanisms of disease fit together as a whole and to generate novel hypotheses concerning PD pathogenesis, diagnosis, and progression. So far, the majority of studies have been performed on postmortem brain samples from PD patients, but more recently, studies have targeted enriched populations of dopamine neurons and have begun to explore extra-nigral neurons and even peripheral tissues. This review will provide a brief synopsis of gene expression profiling in parkinsonism and its pitfalls to date and propose several potential future directions and uses for the technique. It will focus on the use of microarray experiments to stimulate hypotheses concerning mechanisms of neurodegeneration in PD, since the majority of studies thus far have addressed that complicated issue.

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder afflicting about 1% of people over age 55. The cardinal signs of the disease are motor in nature and include resting tremor, bradykinesia, rigidity, and postural instability. These motor symptoms primarily result from selective degeneration of substantia nigra dopamine (SNDA) neurons in the midbrain.

Recently, there has been a rediscovery of the fact that PD is not merely a specific disorder of SNDA neurons, but a more systemic neurological disease that affects multiple levels of the neuraxis, including the cortex, amygdala, brainstem, peripheral autonomic nervous system (sympathetics and parasympathetics), and the enteric nervous

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system (ENS) lining the gastrointestinal (GI) tract. Symptoms are similarly varied and encompass multiple non-motor features, including cognitive impairment, dementia, depression, sleep disturbance, autonomic instability, and digestive dysfunction (Adler, 2005; Barone et al., 2009; Martinez-Martin et al., 2007; Poewe, 2007; Temlett and Thompson, 2006).

Development of symptomatic treatments for motor and non-motor symptoms, as well as any potential disease-modifying (neuroprotective) therapies, is dependent on an accurate and comprehensive understanding of the pathogenesis and pathophysiology of PD. The majority of studies addressing such issues have been hypothesis-driven 'candidate-mechanism' approaches. Scientifically, this approach is the only way to test and delineate specific mechanisms of disease and therapeutic intervention; however, it is an approach that is necessarily limited by previous experience and current scientific understanding. In some cases, it may engender asking questions that are the most answerable, not necessarily the most relevant. The search for unique and unexpected factors impacting the pathophysiology of PD and many other diseases has led to the development of systems approaches that attempt to assess function on a broader level in the hopes of gaining greater knowledge concerning how individual components fit together as a whole.

One such method is gene expression profiling, which has been touted as a way of generating new hypotheses concerning the pathogenesis of Parkinson's disease, enhancing diagnostic accuracy, improving predictions about progression and prognosis, and predicting disease in asymptomatic individuals (Miller and Federoff, 2006; Papapetropoulos et al., 2007). For example, one recent experiment used SNDA neuron expression profiling to search for novel genetic loci for vulnerability to PD and reported an association, although two subsequent studies failed to replicate the finding (Elstner et al., 2009; Guella et al., 2010; Vilarino-Guell et al., 2010). So far, the majority of studies have been performed on the midbrain and striatum in postmortem samples from PD patients and animal models of parkinsonism (Bassilana et al., 2005; Bossers et al., 2009; Duke et al., 2007; Grunblatt et al., 2004; Hauser et al., 2005; Miller et al., 2004, 2006; Moran et al., 2006; Papapetropoulos et al., 2006; Sutherland et al., 2009; Zhang et al., 2005). More recently, studies have targeted enriched populations of dopamine neurons (as opposed to tissue pieces) and have begun to explore extra-nigral neurons and peripheral tissues (Cantuti-Castelvetri et al., 2007; Meurers et al., 2009; Mutez et al., 2010; Scherzer et al., 2007; Simunovic et al., 2009, 2010; Stamper et al., 2008; Yacoubian et al., 2008). This review will provide an overview of gene expression profiling in parkinsonism and its pitfalls to date and propose several potential future directions and uses for the technique. It will focus on the use of microarray experiments to stimulate hypotheses concerning the causes of PD, since the majority of studies thus far have addressed that complicated issue.

Global assessment of gene expression in postmortem samples from PD patients

Several microarray experiments have been performed using postmortem brain samples from PD patients. A feature all of the studies share in common is the ability to segregate samples into appropriate groups based on gene expression profile alone (Bossers et al., 2009; Cantuti-Castelvetri et al., 2007; Duke et al., 2007; Grunblatt et al., 2004; Hauser et al., 2005; Miller et al., 2006; Moran et al., 2006; Papapetropoulos et al., 2006; Simunovic et al., 2009; Sutherland et al., 2009; Zhang et al., 2005). Samples from PD patients are consistently differentiated from those obtained from matched control individuals without evidence of neurological disease. In addition, one study has suggested that expression profiles are disease-selective in that segregation is fairly consistent between PD, progressive supranuclear palsy (PSP), and frontotemporal dementia with parkinsonism (FTD-P) (Hauser et al., 2005). Distinction has also been made based on the presence or absence of dementia in PD (Stamper et al., 2008). Different brain regions (SN v. striatum; lateral v. medial SN) from PD patients can also be correctly categorized based on expression profile (Duke et al., 2007; Miller et al., 2006; Moran et al., 2006). Furthermore, there are strong gender-related differences in alterations of gene expression associated with PD (Cantuti-Castelvetri et al., 2007; Simunovic et al., 2010).

Clearly, PD affects gene expression in a global way in multiple cell types (discussed below). This is a very interesting finding, but its significance is not clear at present. Is it a pathological signature, like SNDA neuron loss or Lewy bodies? Does it provide clues to mechanisms of neurodegeneration? Is it a result of circuitry or neuronal activity changes? Is it a more complicated interaction, such as the way a PD patient responds to end-of-life issues, such as respiratory failure? There are a myriad of interpretive questions arising from this data, and they are not easily answered experimentally. A few will be highlighted below with consideration of potential next steps. Regardless, the data appear to indicate that PD affects global gene expression in a stereotypic way. Understanding the reasons for and implications of this broad-based change in transcriptional neuroanatomy would be extremely useful in understanding PD as a whole.

Analysis of individual transcripts and molecular pathways in gene expression data from PD

The ultimate utility of describing global alterations in gene expression in PD will be decided based on its therapeutic impact. For instance, will analysis of transcription profiles indicate an unexpected and effective target for a pharmacological or genetic intervention to retard the progression of PD or improve its treatment? With this in mind, analysis of expression data in PD has focused on examination of individual genes and related groups of genes with the idea being that an individual gene or concerted pathway might provide an opening for disease-modifying therapeutics.

Differences in individual genes have not been consistent between experiments. In fact, a recent meta-analysis of several PD microarray studies revealed that no individual gene showed reliably different expression among the 11 studies evaluated, even after a re-analysis of 6 of the datasets using a common method (Sutherland et al., 2009). The absence of a handful of dramatically altered transcripts has been somewhat disappointing from the perspective of rapid discovery and intervention, but is not surprising given the heterogeneous and complex nature of PD phenotypes.

It seems more intuitive to suspect it is not a single or handful of transcripts, but multiple differentially expressed genes that account for functional differences in PD. Additionally, it has been shown experimentally in several studies that examination of related gene sets (or pathways) produces more consistent results between experiments than does comparison of lists of individually different transcripts (Subramanian et al., 2005; Ye and Eskin, 2007). As such, this analysis technique seems a more powerful and sensitive method for overcoming biological variability (between individuals and series of individuals), experimental noise, and inter-laboratory differences that complicate and cloud the interpretation of microarray experiments.

In fact, analysis of concerted molecular pathways in gene expression data from PD patients has been more revealing, but correlation between individual studies remains poor (Sutherland et al., 2009). Those studies performed have tended to highlight previously hypothesized mechanisms of PD pathogenesis. For example, Grunblatt et al. in 2004 described decreases in protein modification and degradation pathways, energy metabolism, and signal transduction and increases in cytoskeleton, cell cycle, and stress pathways (Grunblatt et al., 2004). In a similar experiment, protein handling and degradation (ubiquitin pathways, chaperones), mitochondrial function, vesicle trafficking, and apoptotic pathways were implicated in substantia nigra from PD patients, but not