Kristin Ducrest
Biochem 118-OSP Paris
Professor Doug Brutlag
11-15-02

Tackling Parkinson Disease with Bioinformatics and Genomics

Parkinson disease (PD) is a neurodegenerative disease characterized most commonly by resting tremor and muscle rigidity. Afflicting approximately one percent of the population over 50 year of age, PD is the second most prevalent neurodegenerative disease after Alzheimers. Diagnosis of PD is primarily clinical in nature, and symptoms include the above mentioned as well as bradykinesia and postural instability, and often characteristic postural abnormalities, dysautonomia, dystonic cramps, and dementia. In addition to these physical symptoms, mental changes in patients with PD also occur and include slowing of thinking, altered visual perception, depression, hallucinatory experiences, apraxia, and disinhibition. Progressive onset of the disease occurs in mid to late adulthood.[1]

Treatment of the disease could include the dopamine precursor L-DOPA, dopamine agonists, anticholinergic agents, or COMT inhibitors. Despite these various drugs, treatment with in general dopamine can lead to other neurological challenges. Since dopamine exists throughout the brain (even in patients with PD) at carefully monitored levels, treatment with dopamine can actually raise levels of dopamine elsewhere in the brain to devastating levels. Schizophrenia happens to be a neurological disease resulting from too much dopamine in the brain, and PD patients can actually exhibit schizophrenic behaviors if drug concentrations for treatment are too high.

In regard to the genetics beneath the manifestation of the disease, the inheritance pattern of PD has been a subject of great debate in past years, as the disease fails to demonstrate a

[1] Parkinson Disease; PD. *OMIM*.
<http://www. ncbi.nlm.nih.gov/entrez/dispomim.cgi?cmd=entry&id=168600>

specific pattern, and “parkinsonian” diseases are often erroneously included in such inheritance studies. Nevertheless, a familial component to inheritance is apparent, and the disease is often referred to as autosomal dominant due to identification of certain gene loci associated with this type of Mendelian inheritance. However, gene mapping efforts have resulted in data that have not been reproduced.

Furthermore, environmental factors are also posited to play a role in the emergence of PD, though which environmental factors are still vague at this time. This neurological disease, along with many others, might actually be in part a disease of vulnerability and not necessarily inheritability. Though the genes of an individual might contain the mutation(s) that could result in this disease, he might not express it phenotypically unless exposed to external factors that “jumpstart” the onset of the disease. Evidence also suggests that mitochondrial mutations might be involved in or even the cause of PD.

On a neurological level, PD involves selective neuronal death of dopaminergic neurons in the substantia nigra (SN) of the pons. Secondary neuronal death occurs in the basal ganglion. It is believed that the dysfunction of dopamine, a neurotransmitter present in high concentrations in the SN, or dopaminergic neurons in this region of the brain is the cause of motor problems that manifest as physical and diagnostic symptoms of the disease. Furthermore, the mental symptoms of decreased inhibition result most likely from the death of neurons in the frontal lobe of the brain, the region thought to function primarily in inhibition, organization, and coordination of communication between other regions of the brain. Surviving neurons in some cases of PD have been observed to contain intracellular inclusions, also called Lewy bodies. Much work needs yet to be done on the mechanisms, however, of neuronal selectivity.

Current research in endocrinology and neurology labs further investigate the idea of neuronal selectivity in the hopes of understanding the mechanism of the disease and subsequently developing improved treatments or a cure for patients suffering from PD. Many labs are focusing

on a neurotransmitter/neurohormone within the brain called somatostatin, whose function, among others, might involve protection of spared neurons.

One such lab in McGill University's Royal Victoria Hospital in the Endocrinology Department directed by Dr. Yogesh Patel tests neuronal cultures grown from neurons extracted from rat embryos with various neurotoxins associated with specific neurodegenerative diseases to isolate the role of somatostatin in these processes of neuronal selection.[2] As a student in this lab, I had the privilege of running several of the experiments, wherein the proposed role of somatostatin as a protective agent in spared neurons provided the inspiration for at least two of the four experiments.

Three of the four projects consisted of experiments testing the neurotoxicity of various proteins, each commonly correlated with specific neurological diseases, on both cortical and striatal cultures of neurons extracted from embryonic rats at approximately 14 days gestation. Proteins included NMDA, Prion, ß-Amyloid, and GP 41 associated with PD, Mad Cow Disease, Alzheimer's Disease, and HIV respectively.

Identification of levels of somatostatin as a product of both release and accumulation of neurons spared by the neurotoxins after treatment became the objective of one experiment in particular. Co-localization of somatostatin and NMDA receptors as well as cytokine expression also provided a means of comparing these neurons that survived immuno and those that did not. The fourth project, somewhat less related to the other three, tested the expression of NMDA receptors in post-partum rat brains. Rather than experimentation on neuronal cultures, this protocol involved treatment of coronal sections. Due to insufficient time and resources at present, much of the analysis of data acquired from the described experiments has yet to be performed.

Yet another interesting development in this field, as described by Dr. William Langston of Stanford University, involves the posited role of neurotrophic factors as agents that stimulate nonfunctioning neurons and protect them from the damage incurred by the neurodegenerative

[2] New Hope of Cure for Parkinson's Disease. <http://www.mcgill.ca/relseases/2000/april/patel>

process. It is plausible that such agents could actually rejuvenate damaged or nonfunctioning neurons. Since research indicates that many neurons in the brains of PD patients have not yet died but are simply no longer functioning, treatment with these compounds could conceivably bring patients back out of their symptomatic states. Not only could these neurotrophic factors slow the onset of the PD, but they could actually have the potential to reverse the symptoms of patients in the later stages of the disease.[3] A current trial being conducted presently involves the growth factor GDNF. While this prospect is promising, it is still in the early experimental stages and has yet to be proven effective or to be fully understood.

From yet another perspective, current research in bioinformatics has also offered promising insight into the treatment of neurodegenerative diseases such as PD. The field of bioinformatics is one that must be further developed, as genomics and stem cell research provide the possibility of cures to inherited, genetic, or acquired diseases that were before seen as incurable. At present, technology in this domain has grown to an impressive aptitude: genomes can be entirely sequenced, inherited and genetic diseases can be diagnosed merely on the basis of genetic evaluation, stem cells can be grown to regenerate damaged tissues. As research in this science continues, the possibility exists to treat individuals with crippling and fatal diseases in ways far more remarkable than current protocol, treatment which often aims at relieving patients of their symptoms.

Stem cell research, though currently banded in the United States, has proven to be a promising method of treatment in neurodegenerative diseases, specifically with the potential in the reversal of parkinsonian symptoms. At Cedars-Sinai Medical Center in Los Angeles, Dr. Michael Levesque reports that stem cell treatment has entirely reversed the progression of PD in one particular patient treated with his own neural stem cells. This method of therapy consists of removing neural stem cells from the brain of a patient, directing the differentiation of these stem

[3] FCA: Interview: Dr. William Langston. <http://www.caregiver.org/interciews/langstonC.html>

cells into dopaminergic neurons, and finally reimplanting the cells into the brain of the patient.[4] With stem cells originally from the patient, reimplantation does not generate problems with immunosupression or rejection of the transplantation. The differentiated cells of the transplant, thus, continue to produce dopamine at appropriate levels, essentially replacing the diseased part of the brain.

Another example of success with stem cell research comes from Emory University School of Medicine, where at implantation of retinal cells into the brains of PD patients has been shown to dramatically improve motor function.[5] As with the transplant aforementioned, this retinal method uses cells from the patient himself, requiring no subsequent use of immunosupressants. According to follow-up studies of the six patients treated at Emory University School of Medicine, the patients demonstrated an average motor function improvement of fifty percent. This method of treatment, therefore, offers another possibility of reversal of the devastating symptoms of PD.

Further research indicates that a significant difference in response to stem cell treatment exists on the basis of stem cell origin, that is, therapy with adult stem cells results in more promising outcomes compared to therapy with embryonic stem cells. According to an article entitled "Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model" published in *Proceedings of the National Academy of Science*, only half of the rats treated with mouse embryonic stem cells received a benefit.[6] This statistic is much less impressive than other information regarding the potential of adult stem cell transplants. Furthermore, this same source cited a death rate of twenty percent among these rats treated with mouse embryonic stem cells, all a result of ensuing brain tumors. This form of

---

[4] Stem Cell Report – Spring 2002. <http://www.stemmcellresearch.org/stemcellreport/scr-02spring.htm>
[5] "Retinal Cell Implants Improve Parkinson's." *New Scientist*. 18 April 2002.
[6] L.M. Bjorklund et al. "Embryonic stem cells develop into functional dompaminergic neurons after transplantation in a Parkinson rat model." *Proc. Natl. Acad. Sci.* 19 Feb 2002.

treatment with embryonic stem cells clearly requires more research before it can feasibly be applied to a human population where stem cell research is permitted.

Finally, gene therapy has also proven through experimentation to yield promising results in rats with Parkinson induced symptoms. Considerable restoration of motor function, specifically normal limb movement, was observed after the injection of two corrective genes into the region of the brain most significantly affected by the disease.[7] Rats with Parkinsonian lesions found in only one hemisphere of the brain showed complete reversal of motor function symptoms, while rats with complete dysfunction of neurons in the SN received only minimal benefits from the treatment. Thus, some dopaminergic neurons must still be present in the brains of the diseased individuals for this method of corrective gene therapy to reap significant results.

The challenges posed by PD are now being tackled by innovative and promising methods of treatment, a result of research development in the new domains of science such as Bioinformatics and Genomics. Though clarification of neuronal mechanisms and disease expression need still to be determined, recent findings in experimental medicine reveal the potential for developing cures for these formerly incurable diseases. Whether through treatment with neurohormones or neurotrophic factors, whether through stem cell research or gene therapy, research continues to expand the boundaries of medical possibility.

[7] D. Kirk et al. "Reversal of motor impairments in parkinsonian rats by continuous intrastriatal delivery of L-dopa using rAAV-mediated gene transfer." *Proc. Natl. Acad. Sci*. 2 April 2002.