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Toxicogenomics and PD; Is there a possible role?

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ABSTRACT

PD is a neurodegenerative disease with progressive pathology. The role of genetics and environmental exposure has been supported by many researches. One of the problems facing PD treatment is that clinical picture is delayed until severe degeneration occurs in the neurons. A need for early detectors of PD has been increased after the discovery of many candidate neuroprotectant agents where early detection would mean early intervention and a possible better prognosis. Toxicogenomics is a field combining both the toxic exposure with gene expression changes. Such technique would be perfect to conditions like PD where both genetics and toxicology is intermingled. The enthusiasm for toxicogenomics application in PD should not prevent further steps to validate this technique before using it in clinical practice.

KEYWORDS

PD;
Toxicogenomics;
Biomarkers;
Genes;
Environment;
Early diagnosis.

INTRODUCTION

Parkinson's disease (PD) is one of the common neurodegenerative diseases. It is characterized by a progressive pathological degeneration of the dopaminergic neurons. PD patients have a presymptomatic phase in which there is continuous damage to the neurons without clinical manifestations[1].

When entering clinical stage, the PD patient will be losing about 70% of his neurons[2]. This great neuronal damage seems to be irreversible with little chance of improvement. Moreover, symptomatic therapies are not satisfactory as regards their complications and the quality of life offered to the patient[3,4].

Causes of PD; the gene toxin interplay

Many researches have been made to find out the exact cause of idiopathic PD cases. But, till now no one can decide a specific causation[5].

Two factors have been linked to PD. The first one is genetic cause and the second one is toxic exposure. It seems that certain genetic changes increase the liability of risky group to the effects of environmental factors like pesticides and heavy metals[6].

Genes play a big role in PD. Although this role is maximized in familial type, they still have their influence on the idiopathic type[7]. Genes that has been linked to causative mechanisms of neurodegeneration include (α-synuclein (SNCA), parkin, leucine-rich repeat kinase

2 (LRRK2), PTEN-induced putative kinase 1 (PINK1) and DJ-1)[8].

New evidences suggest that genetic changes in PD may represent a 'responder- effect' to the damage[9]. For example, one hypothesis is that DJ-1 functions to detect and/or defend against oxidative stress associated with mitochondrial respiration[10].

Also, it seems that Pink1 and Parkin act together to regulate mitochondrial function. So, a change in these genes expression would suggest mitochondrial damage[11].

Trying to detect gene expression changes in PD proved to be useful, as many trials revealed detectable changes in gene expression patterns in Parkinsonian cases[12-14].

In human PD, an increase in striatal expression of ΔFosB and RGS9-2 was observed in postmortem brains of PD patients. This was confirmed on toxic mice model. However, it is till unknown at this time whether these changes are due to the toxic insult itself or a regional adaptation in the brain to the toxin[15].

Since apoptosis and oxidative stress represent two possible pathways in the pathogenesis of PD[11,16] many researches have targeted the genes that can be responsible for these pathways.

One gene group is that controlling molecular cell cycle program e.g. E2F-1. This pathway which is proved to be aberrantly activated in PD patients could be a target of monitoring or silencing in future trials[17].

Also the synapse related genes synapsin 1, syntaxin-binding protein 1, vesicle associated membrane protein 2 (VAMP2), synaptotagmin 4, and synaptogyrin 1 have shown measurable changes in their expression patterns in PD[18].

So, as we can see the pivotal role of genes - both in pathogenesis and as a marker of PD- is undeniable. Researches targeting these genes would help in improving modeling of PD in animals and also monitoring the disease in human cases.

The need of PD biomarkers

A biomarker would improve our knowledge about both the clinical and pathological parameters of a disease[19]. This is complicated in Parkinson's disease by a rather poor correlation between the underlying pathology and the subsequent clinical phenotype[20].

In case of PD the delayed clinical diagnosis would come after a long period of pathological degeneration of neurons[21]. This certainly limits the possible solutions a neurologist would have to improve his patient condition[22].

Finding specific biomarker that can shorten the gap between beginning of the disease and clinical diagnosis would help to increase the chances of better case prognosis[23].

Besides early diagnosis, biomarkers are needed to monitor drug safety, to identify individuals who are most likely to respond to specific treatments, to stratify presymptomatic patients and to quantify the benefits of treatments[19].

The establishment of biomarkers of PD pathology can improve drug development related to the disorder[24] as animal models have low predictive power for determining the efficacy of treatments in patients with sporadic PD[25].

Toxicogenomics as PD biomarker

Toxicogenomics is defined as 'the study of the relationship between the structure and activity of the genome (the cellular complement of genes) and the adverse biological effects of exogenous agents'[26].

One major concern of toxicogenomics is to characterize changes in gene expression after exposure to toxic substances. Such exposure invariably results, either directly or indirectly, in characteristic changes in gene expression[27]. These gene expression changes may sometimes be the cause or in other cases the consequence of the early stages of a toxic response[28].

Since it integrates gene expression patterns with environmental exposure, toxicogenomics seems the ideal candidate to deal with risk assessment in a case like PD. As shown previously the interplay between genes and environment is so obvious in PD.

Gene expression analysis would improve monitoring of high risk groups as well as early diagnosis of PD patients. Detecting the changes at gene levels may take the diagnosis potential to a step earlier than the pathology[29]. This condition would be perfect for the neuroprotection administration.

In fact, many researches have been made targeting gene expression analysis. Although results seem promising, certain points should be taken in consideration

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before accepting toxicogenomics as biomarker:

1 Significance of gene expression changes must be validated; this would involve reproducibility of assays across different laboratories, species, individuals or tissues.
2 Defining 'normal' gene expression as it is an ever changing condition[30,31].
3 Choosing the gene groups which will be the perfect candidates for microarray analysis.

CONCLUSION

Toxicogenomics seems to be the perfect biomarker for PD. This new technique would offer earlier diagnosis of the disease which would give us the opportunity of better treatment conditions. The enthusiasm towards this approach should not cover the potential caveats that should be treated before accepting toxicogenomics in the clinical field.

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