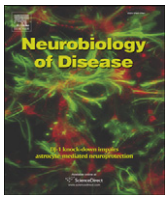
Neurobiology of Disease 35 (2009) 148–156

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Review

Chipping away at diagnostics for neurodegenerative diseases

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ARTICLE INFO

Article history:
Received 18 September 2008
Revised 16 February 2009
Accepted 19 February 2009
Available online 10 March 2009

Keywords:
Gene expression
Transcriptional profiling
Microarray
Biomarker
Blood
Biological fluids
Variation
Stability
Reproducibility
Validation
Parkinson's disease
Alzheimer's disease
Multiple sclerosis
SORL1
LR11
α-Synuclein

ABSTRACT

Biomarkers are needed to overcome critical roadblocks in the development of disease-modifying therapeutics for neurodegenerative diseases. Evolving genome-wide expression technologies can comprehensively search for molecular biomarkers and allow fascinating insights into the expanding complexity of the human transcriptome. The technology has matured to the point where some applications are deemed reliable enough for use in patient care. In the neurosciences, it has led to the discoveries of osteopontin in multiple sclerosis and *SORL1*/*LR11* in Alzheimer's, and recent studies indicate its potential for identifying neurogenomic biomarkers. Advances in pre-analytical and analytical methods are improving search efficiency and reproducibility and may lead to a pipeline of biomarker candidates suitable for development into future neurologic diagnostics.

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Available online on ScienceDirect (www.sciencedirect.com).

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doi:10.1016/j.nbd.2009.02.016

Introduction

Why does a neurologist need biomarkers?

Biological markers – biomarkers – are biologic indicators of disease or therapeutic effects, which can be measured through tests on blood and other biologic samples, and imaging tests. Biomarkers are needed to overcome critical roadblocks in the development of disease-modifying therapeutics for Parkinson's disease, Alzheimer's disease, and other common neurodegenerative diseases. Five major roadblocks involve early diagnosis, phase II and phase III clinical trials, and early drug development.

Roadblock 1

Diagnosis based on clinical exam delays detection until clinical deficits have already manifested, reflecting widespread underlying neuronal injury. Individuals at the earliest disease stages or at risk of disease with less complete neuronal damage, however, would be most responsive to a neuroprotective therapy. A simple laboratory biomarker could be used to identify individuals with high risk of developing neurodegeneration. These individuals could then be prioritized for in-depth evaluation with time and cost intensive, advanced clinical and neuroimaging instruments. Markers that identify high-risk individuals before a majority of neurons have been injured, combined with a risk-modifying or disease-modifying therapeutic could prevent the disease from ever manifesting (*risk marker* or *early diagnostic*).

Roadblock 2

In small phase II clinical trials, testing safety and tolerability of a compound is straightforward, however they lack power to detect slowing of disease progression based on clinical assessments alone. Therefore every compound has to go through large, costly and time-consuming phase III clinical trials to make decisions about its neuroprotective efficacy or failure. Markers that track the progression of neurodegenerative diseases in phase II clinical trials (*progression marker*) and that can serve as surrogates of therapeutic effect are needed to prioritize lead compounds for phase III clinical trials (*response marker*).

Roadblock 3

A third roadblock arises in phase III clinical trials. Entry diagnoses are based on a physician's assessment and clinical diagnostic scales, but even skilled neurologists misdiagnose common neurodegenerative diseases in up to 30% of cases. This dilutes the power of phase III trials. A diagnostic that increases the specificity of the differential diagnosis or aids in defining disease subtypes would allow enrolling a more homogeneous population, increase power to detect disease modification, and reduce costs (*diagnostic marker*).

Roadblock 4

The pharmaceutical industry seeks markers that are a direct measure of modulation of the biologic drug target and measure quantitative changes in response to dose. These *pharmacodynamic markers* accelerate go/no go decisions in early drug development.

Roadblock 5

Markers that predict serious adverse medication effects would be of similar benefit in the early drug development of disease-modifying therapeutics (commonly referred to as *pharmacogenomic marker*).

Scientific rationale

Looking through the dumps: what is the biological basis of biomarkers in body fluids of patients with brain diseases?

Body fluids such as blood, urine (Muthukumar et al., 2005), saliva (Li et al., 2004), and very recently cerebrospinal fluid (Izzotti et al., 2008) have been used for gene expression biomarker discovery. Non-neuronal cells and tissues such as fibroblasts, lymphoblasts, and muscle biopsies have also been explored. These analyses are based on the premise that biological fluids and non-neuronal cells can serve as surrogate substrates of select pathobiological and pharmacological processes in the brain. While clinical symptoms of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS) reflect preferential neuronal damage, DNA, RNA, and biochemical traits have been detected in peripheral cells. Genes causing familial AD are ubiquitously expressed (Schlossmacher et al., 1992; Citron et al., 1994), and skin fibroblasts from individuals carrying a familial AD mutation secrete excessive amounts of Aβ (Citron et al., 1994). Biochemical traits have been documented in blood cells of patients with AD (Schlossmacher et al., 1992; Ibarreta et al., 1998; Cecchi et al., 1999; Stieler et al., 2001; Tayebati et al., 2001; Scherzer et al., 2004a,b; Hye et al., 2005; Blandini et al., 2006; Mhyre et al., 2007). Dopamine biosynthesis/signaling and mitochondrial function appear perturbed in blood cells of patients with PD (Yoshino et al., 1992; Schulz and Beal, 1994; Nagai et al., 1996; Barbanti et al., 1999; Caronti et al., 1999; Caronti et al., 2001; Petrozzi et al., 2001). Lymphocytes of MS patients show biochemical changes (Kerlero de Rosbo et al., 1993; Mahad et al., 2003; Oki et al., 2004; Hallin et al., 2006; Vallittu et al., 2007). Blood cells of patients with Huntington's disease show perturbed mitochondrial function (Panov et al., 1999; Panov et al., 2005; Saft et al., 2005; Squitieri et al., 2006), apoptosis (Sawa et al., 1999; Maglione et al., 2006a,b), adenosine receptor