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Unbiased Approaches to Biomarker Discovery in Neurodegenerative Diseases

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Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and frontotemporal dementia have several important features in common. They are progressive, they affect a relatively inaccessible organ, and we have no disease-modifying therapies for them. For these brain-based diseases, current diagnosis and evaluation of disease severity rely almost entirely on clinical examination, which may be only a rough approximation of disease state. Thus, the development of biomarkers—objective, relatively easily measured, and precise indicators of pathogenic processes—could improve patient care and accelerate therapeutic discovery. Yet existing, rigorously tested neurodegenerative disease biomarkers are few, and even fewer biomarkers have translated into clinical use. To find new biomarkers for these diseases, an unbiased, high-throughput screening approach may be needed. In this review, I will describe the potential utility of such an approach to biomarker discovery, using Parkinson's disease as a case example.

Introduction

The two most prevalent neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD). As of 2010, > 35 million people worldwide suffered from dementia, with the vast majority due to AD (Wimo and Prince, 2010). Similarly, as of 2005, > 4 million people worldwide suffered from PD (Dorsey et al., 2007). Moreover, risk for both of these neurodegenerative diseases increases with age, with both of these diseases projected to double in numbers over the next two decades (Dorsey et al., 2007; Wimo and Prince, 2010). As a consequence, the economic burden associated with these incurable, neurodegenerative diseases is enormous and continues to grow (Dorsey et al., 2013; Kowal et al., 2013; Wimo and Prince, 2010).

It is increasingly recognized that to tackle this looming crisis, we need better tools, including tools for the early recognition and precise measurement of these diseases (Marek et al., 2008; Mueller et al., 2005; Perrin et al., 2009; Sherer, 2011). Thus, several large efforts to develop biomarkers—objective, proxy indicators of pathophysiological state or therapeutic response—have been recently launched in AD (Weiner et al., 2013) and in PD (Marek et al., 2011).

Launching an effort neither dictates the methodology nor ensures success, however, and a high-throughput, unbiased screening approach may be needed to successfully find and develop biomarkers for neurodegenerative diseases. To provide concrete examples that may illustrate more broadly applicable ideas, this review will focus on the development of PD biomarkers. Specifically, I will point out areas of need for PD biomarkers, discuss existing biomarkers in PD, and make a case for an unbiased screening approach to the development of new biomarkers. I will then discuss various methods that could be applied in this type of approach, highlighting successes in other fields and evidence for their potential in PD. Finally, I will suggest concrete measures that may accelerate the pace of biomarker discovery in PD and beyond.

Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disease first described clinically by James Parkinson nearly 200 years ago (Parkinson, 1817). The defining motor features of PD—bradykinesia accompanied by various other features such as resting tremor, hypertonia, or postural instability—cause considerable morbidity (Hughes et al., 1992). In addition, both the personal and societal tolls of cognitive impairment and dementia due to PD have been increasingly recognized (Pressley et al., 2003). Indeed, over 80% of patients with longstanding PD will develop dementia (Buter et al., 2008; Hely et al., 2008; Mayeux et al., 1992). Altogether, the United States national economic burden of PD is estimated to have exceeded $14 billion in 2010 (Kowal et al., 2013).

Approximately 100 years after the first clinical description of PD, a characteristic cytoplasmic eosinophilic inclusion body was demonstrated in neuropathological studies of PD patient brains by Frederick Lewy (Lewy, 1912), and this pathognomonic inclusion body subsequently came to bear his name (Trétiakoff, 1919). In the 1990s, Lewy bodies were reported to consist largely of the protein alpha-synuclein (Spillantini et al., 1997), and pathological forms of this protein are now strongly implicated in the development of PD (Desplats et al., 2009; Luk et al., 2012; Polymeropoulos et al., 1997; Singleton et al., 2003). While some Mendelian genetic causes, as well as some common genetic variant risk factors, for PD are known (reviewed in Trinh and Farrer, 2013), for the most part, PD remains a sporadic, idiopathic disease, diagnosed during life on clinical grounds.

At present, the gold standard for PD diagnosis is the neuropathological finding of dopaminergic neurodegeneration accompanied by the presence of alpha-synuclein-containing

Lewy bodies (Dickson et al., 2009). However, clinical diagnosis during life agrees with neuropathological diagnosis at autopsy only 70%–80% of the time (Hughes et al., 1992). In PD, like in AD, amyotrophic lateral sclerosis, frontotemporal dementia, and other neurodegenerative diseases, no disease-modifying therapies are available, despite nearly two decades of failed trials (Olanow et al., 2008; Rascol et al., 2011b).

The intractability of PD to attempts at disease-modifying therapy is likely multifactorial. One factor, though, that extends to our current conception of all the adult-onset neurodegenerative diseases, may be the advanced stage of pathophysiology at the time of clinical diagnosis (Berg et al., 2014). Specifically, it is estimated that at the time of clinical PD diagnosis, ~50% of substantia nigra dopaminergic neurons may already be lost (Fearnley and Lees, 1991). Moreover, in recent years, a number of prodromal features for PD have been recognized; two that have received much attention are hyposmia (impairment in one's sense of smell) and REM behavior disorder (RBD; inability to suppress movements during dreaming) (Berg et al., 2014). For example, individuals suffering from hyposmia may have a 5-fold increased risk of developing PD (Ross et al., 2008a), and ~40% of RBD patients may develop PD or related neurodegenerative diseases over 10 years (Postuma et al., 2009; Schenck et al., 1996). With the advent of these data has come the recognition that there is a prodrome indicative of onset of a pathophysiological cascade of events, and that this prodrome may predate formal diagnosis of a neurodegenerative disease by years or even decades (Berg et al., 2014; Braak and Del Tredici, 2008).

Biomarkers in Neurodegenerative Conditions: Definitions and Needs

As defined by the Biomarkers Definitions Working Group convened by the National Institutes of Health (NIH), a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group, 2001). A key point in this definition includes the emphasis on objective measurement; this stands in contrast to the clinical context, in which many aspects of assessment may be to various extents subjective. An additional inherent assumption is that the surrogate biomarker indicator will be relatively easy to measure compared to the biological or pathogenic process itself.

In PD, both the objectivity and the ease inherent in biomarkers are attractive features. PD is a brain-based disease diagnosed and followed primarily on clinical grounds, with significant day-to-day and even hour-to-hour fluctuations in clinical presentation. As a consequence, PD presents challenges in both the establishment of diagnosis and the assessment of disease severity that would benefit from objective corroborative data.

As previously mentioned, neuropathological diagnosis is presently the gold standard for the determination of PD diagnosis (Dickson et al., 2009). However, for obvious reasons, in actual practice the diagnosis is made on clinical grounds. Clinical diagnosis is ~80% accurate in patients followed longitudinally with moderate symptoms (Hughes et al., 1992). In best-case scenarios, where the diagnosis is made by movement disorders specialists applying strict criteria, the accuracy may rise to 90% (Hughes et al., 2001). However, this accuracy may also fall substantially, to ~65%, in earlier stages of PD (Rajput et al., 1991). Because in PD there likely exists a long prodromal phase in which pathophysiological events are already in motion, a situation arises in which it is precisely in those patients in whom clinical diagnosis is difficult that there exists the greatest opportunity for therapeutic intervention.

A PD diagnostic biomarker could be used to corroborate or confirm clinical diagnosis. In addition, in the case of very robust markers, diagnostic biomarkers could be used to screen individuals for enrollment in clinical trials. Notably, such a diagnostic-biomarker-screened approach to clinical trial enrollment has recently been pioneered for clinical trials in AD (Kozauer and Katz, 2013), using two proteins—tau and amyloid-beta—measured in cerebrospinal fluid (CSF). A PD diagnostic biomarker that could be used in the earliest stages of disease would be particularly valuable.

Aside from biomarkers that could classify patients easily into PD versus other diagnostic groups, biomarkers providing an objective measurement for the assessment of PD severity would also be valuable in the clinical care of existing PD patients. These biomarkers of disease severity might prove particularly useful in a clinical trial context, even serving as potential surrogate endpoints. To date, PD clinical trials have relied on clinical endpoints such as timing of the need to start levodopa (e.g., Parkinson Study Group PRECEPT Investigators, 2007) or change in the clinical Unified Parkinson's Disease Rating Scale (e.g., Rascol et al., 2011a) to determine efficacy. After two decades of largely unsuccessful clinical trials (Olanow et al., 2008; Rascol et al., 2011b), it may be worth re-examining not just the therapeutic mechanisms that have been targeted, but also the ways that efficacy has been measured. That is, without fine-scaled, precise measures of disease severity, subtler benefits may have escaped detection. This biomarker goal is admittedly ambitious, and experience to date in AD has proved disappointing, but the ramifications of discovering and validating such a surrogate endpoint biomarker in any of the neurodegenerative diseases would be profound (Greenberg et al., 2013).

A third area in which biomarkers may be of particular utility in PD is in prognostication for various motor and nonmotor outcomes. A frequent question from the newly diagnosed PD patient is one about prognosis and expected disease course. Unfortunately, while population-level data suggest that certain demographic features (e.g., older age, associated comorbidities) may predict a more rapid rate of progression (Suchowersky et al., 2006), or certain motor phenotypes (e.g., lack of tremor) may associate with faster rates of decline (Marras et al., 2002), these data are not particularly informative for prognostic purposes on an individual scale. Prognostic biomarkers—analogous to a measure such as cholesterol level in assessing risk for cardiovascular events, or tumor estrogen receptor status in assessing prognosis in breast cancer—would therefore also address a significant unmet need in PD.

Biomarker discussions often separate markers into two conceptual categories, biomarkers of state and trait. Biomarkers of state are envisioned as indicators of current disease presence and severity, and biomarkers of trait as indicators of risk for disease or potential for various future outcomes. The first two