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EDITORIAL

Proteomics in neurodegenerative disease: unlocking hidden therapeutic targets

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Neurodegenerative disorders like Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis are among the most formidable biomedical challenges of our era. Despite decades of high-intensity research efforts, disease-modifying treatments remain out of reach, with our current treatments primarily focused on symptomatic management (1). One of the primary reasons for this therapeutic plateau is the multifaceted neurodegenerative pathophysiology, driven by heterogeneous genetic, molecular, and environmental factors. Traditional reductionist approaches, focusing on an individual candidate protein or pathway, have been unable to account for this complexity (2). Proteomics in this context comes across as a revolutionary tool that holds the promise of revolutionizing our understanding of disease processes and drug discovery.

Proteomics offers unparalleled potential for mapping the dynamic protein map of the nervous system. While genomics or transcriptomics only predicted potential protein expression, proteomics uncovers the functional reality of the cell, post-translational modifications, protein-protein interactions, and signaling cascades directly culpable for pathology. Profiling thousands of proteins in brain tissue, cerebrospinal fluid, and even blood is now feasible with advances in mass spectrometry, protein labeling, and bioinformatics (3). This holds the promise of uncovering early diagnostic biomarkers, something badly needed, as neurodegeneration begins long before clinical symptoms are evident. For instance, proteomic screening has already pinpointed new biomarkers such as neurofilament light chain, synaptic proteins, and markers for oxidative stress that have the potential to outperform conventional methods for disease detection at early stages.

Beyond diagnostics, proteomics offers a point of entry into the identification of hidden therapeutic targets. By defining broken signaling pathways and deranged protein networks, proteomics enables researchers to move away from beaten-path targets such as amyloid-β or α-synuclein. Early evidence suggests that the necroptosis, autophagy, mitochondrial injury, and neuroinflammation pathways may be systematically interrogated through proteomic profiling (4). Drug–target interaction proteomics also provides an interface for the detection of off-target effects and lead drug optimization, which reduces the bench-to-bed translational pipeline.

The intersection of proteomics with other "omics" platforms, genomics, metabolomics, and transcriptomics, under systems biology, is very significant. The convergent approach has the promise of providing multidimensional disease signatures,

boosting patient stratification, and paving the way for precision medicine of neurodegeneration (5). Such strategies are especially relevant in the face of the rampant heterogeneity of neurodegenerative diseases, for which one-size-fits-all therapies will be destined to fail.

Nevertheless, challenges persist. Brain proteomics is limited by tissue availability, post-mortem degradation, and cellular heterogeneity. Translating laboratory findings into clinically valuable biomarkers requires validation in large, diverse cohorts and standardization of proteomics protocols (6). Also, computational intensity of big data analytics emphasizes the importance of consortia involving neuroscientists, clinicians, and data scientists (7).

But the course is clear. Proteomics is no longer a sidebar; it is at the forefront of the neurodegenerative disease research horizon. By illuminating previously intractable biology, proteomics promises sooner diagnosis, novel targets for drugs, and more focused therapeutic strategies. For a field long plagued by therapeutic failures, proteomics represents a welcome change in paradigm, one that may at long last begin to unlock meaningful clinical advancement.

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