

Editorial

From Protein Misfolding to Dementia: Basic Research, Innovative Diagnosis and Early Biomarkers

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The Special Issue “From protein misfolding to dementia: basic research, innovative diagnosis and early biomarkers” presents some of the most recent discoveries on neurodegenerative diseases (NDs), focusing on protein aggregation and diagnosis. NDs are chronic and progressive in nature with a higher incidence as age increases. They present with a variety of clinical phenotypes that may overlap in the early stages. From a neuropathological perspective, the hallmark of NDs is the misfolding and accumulation of proteins. For instance, misfolded α -synuclein accumulates in Parkinson’s disease (PD), dementia with Lewy bodies (DLB) and other α -synucleinopathies; misfolded tau aggregates in corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and other tauopathies; misfolded beta-amyloid (A β) and tau accumulate in Alzheimer’s disease (AD); while TAR DNA-binding protein 43 (TDP-43) aggregates in amyotrophic lateral sclerosis (ALS) and Frontotemporal Lobar Degeneration (FTLD) [1,2]. The clinical diagnosis of NDs is very challenging, especially in the early stages, due to the lack of biomarkers tightly linked to the core pathology of these diseases. Furthermore, several pathological mechanisms of NDs are still not well understood, adding to the complexity of their study.

This issue contains review articles and original research on topics such as the neuropathology and pathophysiology of NDs, basic research, and innovative diagnostic approaches. Basellini *et al.* [3] provide a comprehensive review of the pathological mechanisms and changes occurring in extra-brain districts of patients with PD. Therefore, easily accessible tissues, including skin fibroblasts, sympathetic postganglionic neurons, peripheral blood mononuclear cells, fetal intestinal neurons, colonic hybrid cells, and colon and skin biopsies may be useful to improve the clinical diagnosis of PD. Understanding the molecular mechanisms underlying α -synuclein aggregation and its interactions with other molecules is essential to develop effective treatments. In this regard, Natalello *et al.* [4] highlight that current treatment options primarily focus on alleviating symptoms rather than targeting the underlying pathological mechanisms. Therefore, they suggest to exploit the structural properties and aggregation pathways of α -synuclein to pinpoint small molecules capable of modifying or impeding

disease progression. Dopamine and its oxidation products, particularly 3,4-Dihydroxyphenylacetaldehyde (DOPAL), which are extensively investigated in this article, are considered as promising candidates. They harbor the potential to hinder and reverse α -synuclein fibrillation, potentially leading (catalyzing) to the formation of α -synuclein oligomers with diverse structures some of which can be characterized by toxic properties. The aggregation properties of α -synuclein have been recently exploited to develop the Seed Amplification Assays (SAAs) which allowed the detection of minute amounts of misfolded α -synuclein in peripheral tissues of patients with PD, Multiple system atrophy (MSA), and DLB. The research article authored by Bellomo *et al.* [5] highlights the importance of refining and standardizing the experimental SAAs protocol for diagnostic applications, assessing the impact of several critical experimental factors, such as pH, presence of beads, and detergents. To this aim, cerebrospinal fluid (CSF) collected from a single hydrocephalic patient was seeded with varying recombinant α -synuclein aggregates and then subjected to SAA under different experimental conditions.

Basic *in vitro* and *in vivo* research studies are crucial to gain a deeper understanding of the pathways involved in NDs. Sarg *et al.* [6] demonstrate the presence of tau protein in the platelets, possibly in a highly fragmented form. Activated and dysfunctional platelets have been observed in patients with cognitive impairments such as AD and depression, and this study raises the possibility of using platelet tau levels as a potential diagnostic approach. In the context of AD, Polykretis *et al.* [7] extensively discuss the use of Raman-based techniques for disease diagnosis. These techniques provide information on proteins’ chemical and structural properties (e.g., beta-amyloid and tau), such as the tertiary arrangements, aggregations, pH dependence, and folding states. The authors suggest a great potential of these techniques to identify early-stage AD patients by screening easily accessible peripheral tissues. Alongside the study of human biological samples for research and diagnostic purposes, animal models are crucial to enhance our understanding of the biological mechanisms underlying NDs. Marín-Moreno *et al.* [8] review and discuss various mouse models employed in studying NDs, examining the advantages



and disadvantages of each model. Specifically, the authors highlight that the generated models do not entirely and faithfully replicate human pathologies. However, they suggest that combining ‘genetic’ and ‘pathway-focused’ models can yield significant insights, potentially paving the way for drug development strategies. These strategies must account for the phenotypical heterogeneity observed in clinical presentation of NDs. Various disease phenotypes may respond differently to therapeutic drugs. The paper by Villa *et al.* [2] systematically reviews the clinical phenotypes of patients with microtubule-associated protein tau (MAPT) mutations to explore genotype-phenotype correlation, focusing on the rarest clinical phenotypes and on those belonging to the FTL spectrum. The authors indicate various mutations associated with multiple phenotypes, showing no clear genotype-phenotype correlation in most cases. The effort to correlate individual mutations represents a significant step towards comprehending the substantial heterogeneity of clinical aspects associated with MAPT mutations. It is now evident that NDs may exhibit more intracerebral aggregates than those strictly associated with the pathology. These findings could somewhat challenge the concept of disease-specific biomarkers for NDs. In this regard, Moda *et al.* [9] present neuropathological evidence that the same protein aggregates can be detected in the brain of patients with different NDs. For example, secondary aggregates of TDP-43 are surprisingly found in a subset of AD brains, while aggregates of beta-amyloid are found in some PD brains. This suggests that, contrary to what we typically believe, the brains of patients with NDs may have copathologies that complicate the clinical and pathological picture. In addition, this highlights the need for multiple technical approaches to improve the diagnostic accuracy of NDs, some of which are mentioned in this special issue.

This editorial provides an overview of multiple perspectives to investigate NDs, emphasizing the need for diverse approaches to better understand the mechanisms of protein aggregation and to identify reliable biomarkers for a more precise and early, biologically driven diagnosis.

Author Contributions

MBB, AC, GG and FM contributed to the editorial preparation, conceptualization and interpretation. All authors critically reviewed the editorial and approved its final version. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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