Acta Neuropathologica (2019) 138:677–680
https://doi.org/10.1007/s00401-019-02079-9

EDITORIAL

On the journey to uncover the causes of selective cellular and regional vulnerability in neurodegeneration

Zane Jaunmuktane[1,2] · **Sebastian Brandner**[1,3]

Received: 15 September 2019 / Accepted: 16 September 2019 / Published online: 24 September 2019

This cluster on cellular and regional vulnerability in neurodegeneration brings together reviews of the known pathomechanisms that influence pathological and clinical patterns of the four major proteinopathies—α-synucleinopathies, tauopathies, Alzheimer's disease (AD) and TDP43 proteinopathies.

The affected cell types and the patterns of misfolded protein aggregates differentiate and define disease entities. In tauopathies, progressive supranuclear palsy (PSP) is characterised by tufted astrocytes, and corticobasal degeneration (CBD) by astrocytic plaques. In α-synucleinopathies, Parkinson's disease and Dementia with Lewy Bodies (DLB) inclusions differ from those in multiple system atrophy (MSA). In frontotemporal lobar degeneration with TDP43 pathology, five distinct types (FTLD-TDP, types A–E) are known. Since the seminal reports on Alzheimer's and Parkinson's disease more than 100 years ago, it has become apparent that most of neurodegenerative diseases can present with a number of distinct clinical symptoms, making accurate diagnosis particularly challenging. For example AD, first described by Alois Alzheimer at the beginning of the twentieth century, can present with visual impairment, corresponding to the clinical syndrome of posterior cortical atrophy, as corticobasal syndrome (CBS), or with behavioural changes and language impairment in the spectrum of frontotemporal dementia (FTD), in addition to the typical amnestic phenotype [1]. In addition to the classical syndrome of PSP, described by John Steele, J Clifford Richardson and Jerzy Olszewski in 1963, seven further clinical syndromes have since been recognised [2]. Whilst MSA most typically presents as movement disorder, several other manifestations, such as CBS, behavioural variant FTD, and non-fluent variant of primary progressive aphasia, have recently been described [3].

Experimental evidence suggests that the pathologies, i.e., affected cell types and appearances of the pathological inclusions, are probably caused by different conformational strains of misfolded proteins [4]. The molecular basis for the formation of different strains and their predilection for certain cell types (also termed selective cellular vulnerability), is not well understood. Amongst many research efforts into the patho-mechanisms of strain formation, it remains to be established how many different strains a single misfolded protein can form within an individual. To this end, we hypothesise that new strains may evolve in the course of a therapy suppressing propagation of one specific strain, perhaps in analogy to clonal evolution and heterogeneity of mutations in cancer. It also remains to be determined whether distinct clinical phenotypes are caused by different sub-strains or by a single strain that has been modified by environmental and genetic factors, subsequently changing topographical distribution and consequently causing a diversity of clinical phenotypes.

Similar as for the underlying reasons for selective cellular vulnerability, it has proven to be a difficult task in determining the basis for differential regional vulnerability, associated with distinct phenotypes. Understanding the pathobiology of selective cellular and regional vulnerability may help accelerating the development of targeted personalised therapies, but we will not know this with certainty until effective disease modifying treatments have been developed.

✉ Zane Jaunmuktane
z.jaunmuktane@ucl.ac.uk

✉ Sebastian Brandner
s.brandner@ucl.ac.uk

[1] Division of Neuropathology, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, Queen Square, London WC1N 3BG, UK

[2] Department of Clinical and Movement Neurosciences and Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology, 1 Wakefield street, London WC1N 1PJ, UK

[3] Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, UK

In prion disease it is established that different strains are associated with varied clinical phenotypes, and that genetics has an important role in phenotypic diversity and regional vulnerability. For example, inherited prion disease caused by the D178N mutation in the *PRNP* gene segregates into two distinct clinical phenotypes with different patterns of regional atrophy and abnormal prion protein deposition, depending on the polymorphism in codon 129 on the same allele: fatal familial insomnia with the thalamic pathology develops in patients with D178N-129M, and a CJD phenotype in patients with D178N-129V [5].

Similar to prion diseases, there is emerging evidence that genetic factors may influence phenotypic diversity also of other neurodegenerative diseases. However, no known genetic correlates as straightforward as the D178N mutation in prion disease are known for any other neurodegenerative disease. In the contrary, it is well known that patients with the same *MAPT* mutation have a remarkable phenotypic variability and the factors underlying this diversity remain to be determined [6]. Furthermore, a single genetic alteration, the A152T mutation in the *MAPT* gene, may, in fact, confer risk to different diseases associated with distinct misfolded proteins, such as AD, CBD, PSP and Lewy body diseases [7].

It is debated what predisposes to distinct neuropathological and clinical phenotypes—self-amplifying templated seeding of like proteins with subsequent transcellular propagation of the misfolded forms, or genetic and epigenetic, environmentally influenced cellular and regional variation between individuals. Multiple lines of evidence indicate a synergistic role of transcellular propagation of self-amplifying proteopathic seeds and (epi-) genetically determined, environmentally influenced cellular and regional susceptibility or resistance. There is indeed increasing evidence that genome-wide alterations [8], gene expression patterns [9], epigenome-wide DNA methylation profiles [10] as well as sex-specific biological differences [11, 12] influence selective vulnerability, and resistance to noxious proteopathic seeds. A proposed model of the network of genetic and environmental factors and its impact on the clinical-pathological phenotype is shown in Fig. 1.

In this cluster we present reviews covering the four most prominent proteinopathies. The review of Alegre-Abarrategui et al. covers selective vulnerability in α-synucleinopathies, giving a detailed insight into endogenous physiological and pathological forms of this protein, and how metabolic burden, genetic signatures and epigenetic modifications render certain cell types, regions and anatomical connections vulnerable to degeneration and how these parameters influence structural differences of its pathological form. Somatic mutations in neurones are increasingly recognised to occur during ageing and cause neurodegeneration [13]. In this review the authors draw attention to the role of mosaicism in α-synucleinopathies at the level of nuclear and mitochondrial genome level. The authors also discuss structurally, biophysically and biochemically distinct α-synuclein confirmations associated with distinct

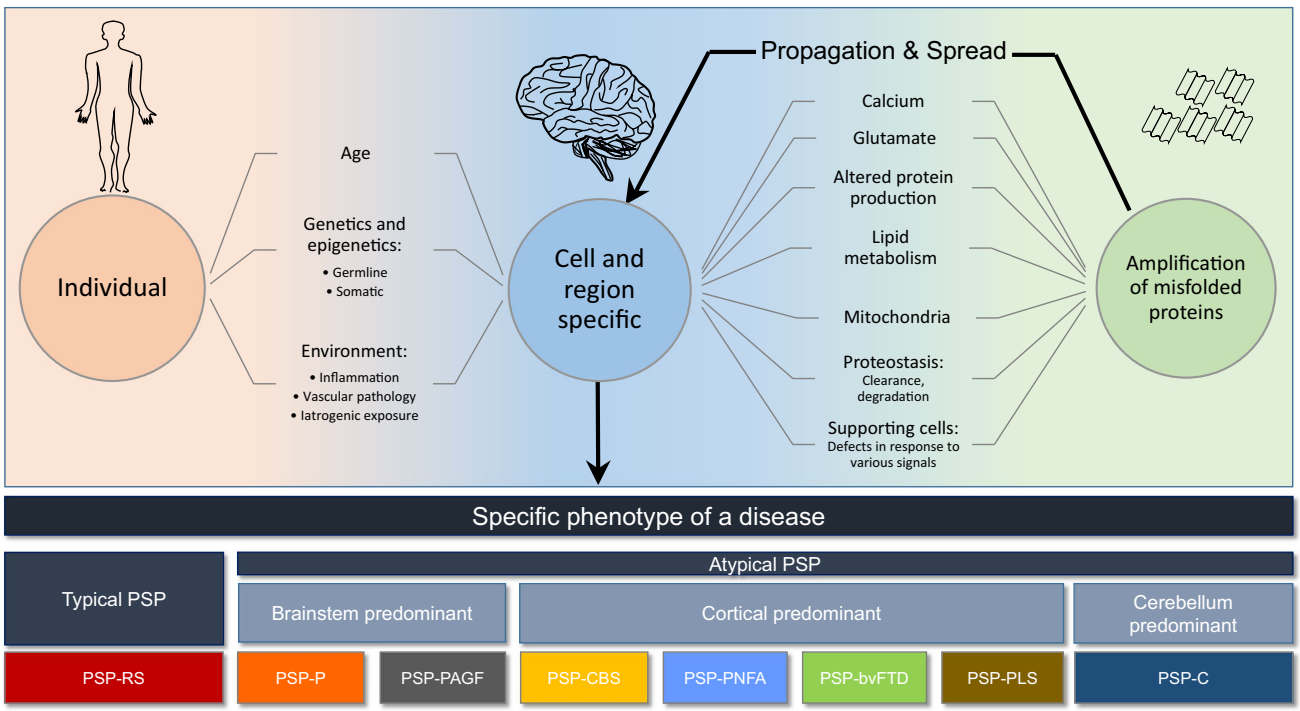

Fig. 1 Summary of the factors underpinning phenotypic diversity in neurodegeneration

α-synucleinopathies and the potential diagnostic and therapeutic value of their identification throughout disease progression. The authors also describe the role of known exogenous and environmental factors ranging from neurotoxins, heavy metals, brain trauma and sleep disturbance.

In their review on the cellular and regional vulnerability in frontotemporal tauopathies, Forrest et al. present collective evidence that the diversity of clinical phenotypes of neurodegenerative diseases correlate most with anatomical distribution of the pathology and not necessarily to a specific misfolded protein. They discuss the function of physiological tau and cellular consequences of abnormal tau aggregation. Differentiating features and clinicopathological correlations in FTLD-tau are presented. They highlight the role of genetic diversity in the *MAPT* gene on selective cellular and regional vulnerability and summarise the findings from genome-wide association studies. The authors also discuss the potential role of inflammation on selective cellular and regional vulnerability in tauopathies.

The review of the basis of cellular and regional vulnerability in Alzheimer's disease by Mrdjen et al. dissects the differences between vulnerable and resilient neuronal cell types in AD. The authors highlight regional differences in physiological protein expression and synopsise the studies on the biochemical and structural heterogeneity of amyloid-β and tau conformers with respect to clinical phenotypes. Phenotypic diversity of early and late onset AD is reviewed with emphasis on the genetic predisposition to differential vulnerability, and the role of somatic mosaicism and epigenetic alterations is discussed. The article covers neuroanatomical selectivity (and resistance) in AD, for example, through disturbances in calcium and neurotransmitter homeostasis, maintenance of protein solubility and proteostasis.

The clinical-pathological heterogeneity of TDP43 proteinopathies is covered in the review by Kawakami et al. The authors highlight that also in TDP43 proteinopathies the phenotypic diversity correlates with the neuroanatomical distribution of misfolded TDP43. The authors discuss the structure and function of TDP43 and the molecular alterations observed in pathological aggregated state leading to various pathological and clinical phenotypes. The current limitations of CSF analysis for the diagnosis of TDP43 proteinopathy and the value of imaging studies are discussed, and histological and biochemical evidence supporting the existence of distinct TDP43 strains is summarised. The article also outlines the challenges of mouse models for studying phenotypic and pathological diversity of TDP43 proteinopathies and what we can learn from these models about the formation and spreading of TDP43 pathology.

This cluster presents state-of-the-art evidence, discusses provocative hypotheses, and also underpins the challenges that this field is facing. Still, large gaps remain in the understanding of selective cellular and regional vulnerability in neurodegeneration. All reviews present ideas for future research to better understand the patho-mechanisms underlying selective regional and cellular vulnerability.

The advancing technologies to study diseases at a single-cell level undoubtedly will have a major role in understanding the complexity of the factors driving cellular and regional vulnerability and strain diversity. However, a critical determinant of successful studies, particularly those involving the most advanced single-cell-based technologies, is the availability of high-quality, accurately dissected human post mortem brain samples. The value of research data output always will be determined by the quality of the input material. For the latter to be of the highest quality, it is essential, that any sample used for comparative studies, for example to assess the pathology burden and cellular and regional genetic, epigenetic or structural heterogeneity, is curated with expert clinical neuropathologist oversight.

Distinct clinical phenotypes and variable regional severity of the respective pathology are caused by a combination of factors in each individual (top, left), on a cellular and regional level within the CNS (top, centre) resulting in aggregation of misfolded protein (top, right). In an individual, the determinants can be categorised into age, genetic/epigenetic, and environmental factors. The strongest determinant for the development of a neurodegenerative disease is age. The genetic and epigenetic (sex-specific) alterations can be germline or somatic. The cell and tissue environment can be identified as a local or systemic inflammation (including responses to it, with generation of reactive oxygen species or reactive nitrogen species), vascular pathology and iatrogenic exposure. On the other side of the scheme (right), misfolded protein formation, cell and region-specific propagation and spread involves various different pathways. The pathways span from those involved in calcium and neurotransmitter (glutamate in particular) homeostasis, altered protein production, metabolism of lipids and cholesterol, mitochondrial function, proteostasis (protein degradation or clearance via fluids), supporting cell response to various signals and effects involving direct neuronal and glial (including microglial) cell function. Defects in one or more of these components initiate a self-amplifying cascade of misfolded proteins, which propagate from cell to cell and spread from region to region, depending on the cell- and region-specific (epi-) genetic variations, influenced by local or systemic environment. The bottom of the schematic exemplifies the impact of the three major determinants on a disease and pathology phenotype in the primary tauopathy progressive supranuclear palsy (PSP). Eight distinct clinical presentations can be identified, with identical, variably prominent, hallmark pathology of four-repeat tau-immunoreactive tufted astrocytes, coiled bodies, threads and neuronal (pre-) tangles (selective cellular vulnerability), and varied topographical distribution of the pathology burden (selective

regional vulnerability). The typical PSP phenotype is the Richardson's syndrome (PSP-RS). Atypical PSP includes two brainstem-predominant variants: PSP-P with dominant clinical presentation of parkinsonism, closely resembling Parkinson's disease and PSP-PAGF characterised by primary akinesia with gait freezing. Four PSP clinical phenotypes with most prominent cortical pathology load include corticobasal syndrome (PSP-CBS), primary non-fluent aphasia (PSP-PNFA), behaviour variant PSP (PSP-bvFTD), and primary lateral sclerosis (PSP-PLS). The rarest of all is the PSP variant with predominant cerebellar pathology (PSP-C).

References

1. Elahi FM, Miller BL (2017) A clinicopathological approach to the diagnosis of dementia. Nat Rev Neurol 13(8):457–476
2. Ling H (2016) Clinical approach to progressive supranuclear palsy. J Mov Disord 9(1):3–13
3. Aoki N, Boyer PJ, Lund C, Lin WL, Koga S, Ross OA et al (2015) Atypical multiple system atrophy is a new subtype of frontotemporal lobar degeneration: frontotemporal lobar degeneration associated with alpha-synuclein. Acta Neuropathol 130(1):93–105
4. Soto C, Pritzkow S (2018) Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. Nat Neurosci 21(10):1332–1340
5. Goldfarb LG, Petersen RB, Tabaton M, Brown P, LeBlanc AC, Montagna P et al (1992) Fatal familial insomnia and familial Creutzfeldt-Jakob disease: disease phenotype determined by a DNA polymorphism. Science 258(5083):806–808
6. Ghetti B, Oblak AL, Boeve BF, Johnson KA, Dickerson BC, Goedert M (2015) Invited review: frontotemporal dementia caused by microtubule-associated protein tau gene (MAPT) mutations: a chameleon for neuropathology and neuroimaging. Neuropathol Appl Neurobiol 41(1):24–46
7. Coppola G, Chinnathambi S, Lee JJ, Dombroski BA, Baker MC, Soto-Ortolaza AI et al (2012) Evidence for a role of the rare p.A152T variant in MAPT in increasing the risk for FTD-spectrum and Alzheimer's diseases. Hum Mol Genet 21(15):3500–3512
8. Arneson D, Zhang Y, Yang X, Narayanan M (2018) Shared mechanisms among neurodegenerative diseases: from genetic factors to gene networks. J Genet 97(3):795–806
9. Allen M, Wang X, Serie DJ, Strickland SL, Burgess JD, Koga S et al (2018) Divergent brain gene expression patterns associate with distinct cell-specific tau neuropathology traits in progressive supranuclear palsy. Acta Neuropathol 136(5):709–727
10. Gangisetty O, Cabrera MA, Murugan S (2018) Impact of epigenetics in aging and age related neurodegenerative diseases. Front Biosci (Landmark Ed) 23:1445–1464
11. Deming Y, Dumitrescu L, Barnes LL, Thambisetty M, Kunkle B, Gifford KA et al (2018) Sex-specific genetic predictors of Alzheimer's disease biomarkers. Acta Neuropathol 136(6):857–872
12. Liesinger AM, Graff-Radford NR, Duara R, Carter RE, Hanna Al-Shaikh FS, Koga S et al (2018) Sex and age interact to determine clinicopathologic differences in Alzheimer's disease. Acta Neuropathol 136(6):873–885
13. Leija-Salazar M, Piette C, Proukakis C (2018) Review: somatic mutations in neurodegeneration. Neuropathol Appl Neurobiol 44(3):267–285