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Neurodegenerative diseases: special issue of *Laboratory Investigation*

About 5.8 million people in the United States are afflicted with Alzheimer's disease (AD) and related dementias, and with continued increase in the aging population it is estimated that by 2050 this number will rise to nearly 14 million, with an estimated cost of over \$2 trillion to health care systems. The physical and emotional cost to families and caretakers is not measurable. AD remains the sixth leading cause of death in the United States, and about one in three senior citizens will die with some form of dementia. The growing burden of neurodegenerative diseases on patients, their families, and health care providers has also stimulated some exciting new developments in the field. This issue of *Laboratory Investigation* provides a broad view of the field of neurodegenerative diseases, with diverse papers focusing on basic research, clinicopathological correlation, and neuropathological diagnosis.

Neurodegenerative disease proteinopathies: therapies and transmission. In addition to AD, a host of other neurodegenerative disorders and age-associated comorbidities may underlie the signs and symptoms of progressive dementia. Most of these disorders are characterized by abnormal protein metabolism leading to abnormal forms of Aβ-amyloid, α-synuclein, tau, and TDP-43 (transactive response DNA 43 kDa binding protein). In this issue, Castellani and colleagues review the central role of amyloid β (Aβ) accumulation in aging and AD and explore possible reasons for the disappointing results of Aβ-targeted clinical trials. They conclude that therapies targeted at the removal of Aβ alone may be insufficient for disease modification.

A particularly exciting area of research in neurodegenerative diseases is the transmission of pathogenic proteins from cell to cell, most notably α-synuclein and tau, during disease progression. Karpowicz et al. review cell-to-cell transmission of α-synuclein in the diverse clinical syndromes of Parkinson's disease, dementia with Lewy bodies, and multiple-system atrophies. This paper presents evidence suggesting a structural/molecular basis for the clinical

heterogeneity of the synucleinopathies and that certain risk factors for these diseases may potentiate cell–cell transmission. The existence of molecular diversity of pathologic α-synuclein is supported by the findings of Dhillon and colleagues, who used a battery of epitope-specific antibodies to characterize pathologic inclusions in multiple-system atrophy. Strang et al. present a mechanistic view of the tauopathies in which mutations of the *MAPT* gene result in pathogenic forms of tau having transmissible, prion-like properties. Further work in this area may lead to novel therapeutic approaches that target these abnormal transmissible proteins.

In their thought-provoking review, Chornenkyy and colleagues describe how both upstream and downstream pathogenetic factors may influence disease progression in a growing spectrum of tau and TDP-43 proteinopathies. Abnormally phosphorylated forms of tau and TDP-43 sometimes colocalize in AD neurofibrillary tangles and other pathological inclusions in neurodegenerative conditions. Huntley et al. present data suggesting that TDP-43 accumulation can be seen in mitochondria in inclusion body myopathy, a degenerative neuromuscular disease.

Advances in diagnosis. Diagnostic advances in the neurodegenerative diseases are also occurring. Luminex assays developed by Keene and colleagues may provide more quantitative analysis of Aβ and hyperphosphorylated tau in formalin-fixed paraffin-embedded material. Artificial intelligence (AI) is being applied to many clinical and research paradigms. Signaevsky et al. discuss initial studies applying AI to detailed pathological assessment of AD and

other tauopathies. These methods will promote further research on human central nervous system material and increase the value of tissues already available in neurodegenerative disease tissue banks.

Nucleotide repeat disorders are a separate class of genetically determined neurodegenerative disorders. Banez-Coronel and Ranum review the recent identification and pathobiology of repeated-associated non-AUG (RAN) translation products in Huntington's disease, the spinocerebellar ataxias, and myotonic dystrophy. Patients with triple repeat disorders have been reported to also develop "Alzheimer disease-like" changes as they age; the spectrum of tau pathology in Huntington's disease is described by Upadhyay Baskota et al.

Risk factors in neurodegenerative diseases. Cognitive dysfunction has been associated with the sequelae of processes such as trauma and sepsis, as well as after surgery. Schwab et al identified DNA damage in patients diagnosed with mild traumatic brain injury and suggest that DNA damage plays a role in trauma-associated neurodegenerative processes. Experimental findings by Xu et al. show that central cholinergic pathways may be affected in postsurgical cognitive dysfunction. Teylan et al. present a large collaborative clinicopathological study of clinical diagnoses in patients diagnosed with PART (primary age-related tauopathy) vs. Alzheimer's neuropathological changes. The results suggest that clinical criteria for premortem diagnosis of PART may soon be available that will improve management of patients with mild cognitive impairment. Liu and colleagues review clinical and experimental studies on the beneficial effects of exercise in aging and in neurodegenerative diseases.

It is hoped that this issue of *Laboratory Investigation* will stimulate increased awareness of progress in the field and promote continued basic and translational research in the neurodegenerative diseases.

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Immunotherapy induces ferroptosis through IFN- γ

Wang et al. sought to determine whether immunotherapy enhances the activity of CD8⁺ T cells and induces cancer cell death through ferroptosis. They found that interferon gamma (IFN- γ) released from CD8⁺ T cells downregulates the expression of SLC3A2 and SLC7A11, two subunits of the glutamate-cystine antiporter system. This impairs the uptake of cystine by tumor cells, thereby promoting tumor cell lipid peroxidation, a form of cell death termed ferroptosis. Human transcriptomes analyzed before and during nivolumab therapy revealed a correlation between clinical benefit, reduced expression of SLC3A2, and increased IFN- γ by promoting tumor cell lipid peroxidation and sensitizing tumors to ferroptosis. The authors propose that the T-cell-promoted tumor ferroptosis pathway may supplement the more recognized Fas-Fas and perforin-granzyme mediators of cell death, which could yield therapeutic benefit to patients receiving immunotherapy if it can be further modulated.

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New tool for analyzing progression of Alzheimer's disease

Mathys et al. took 80,660 single-nucleus transcriptomes from the prefrontal cortex of 48 individuals with varying degrees of Alzheimer's disease (AD) to better understand the disorder's molecular and cellular basis. The group found that the strongest AD-associated changes appeared early in pathological progression and were highly cell-type-specific. These findings, which could have implications for therapeutic intervention and will require further investigation, indicate the potential importance of tools for early detection and diagnosis. The genes that were upregulated later in development of AD were common across cell types and primarily involved in global stress response. Overall, regulators of myelination, inflammation, and neuron survival prevailed in the analysis, but further analysis will be needed to assess the responsive versus driving nature of the transcriptional alterations to guide research toward a better understanding of AD progression.

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CLSTN3 β -s100b-derived metabolism enhancement

Calsyntenin 3 β (CLSTN3 β) is a mammal-specific membrane protein that promotes the sympathetic innervation of brown and beige adipocytes by binding to S100b, which in turn acts as a neurotrophic factor to stimulate sympathetic axon growth. CLSTN3 β localizes to the endoplasmic reticulum; this interaction enables it to enhance secretion of S100b via direct physical interaction. S100b is a secreted protein with a single peptide that is abundantly expressed in adipocytes. It promotes adipose thermogenesis, which Zeng et al. propose is directly related to its connection with sympathetic innervation of adipose tissue. CLSTN3 β expression restoration isolated to the brown adipocytes was sufficient to rescue the defects of *Clstn3b*-knockout mice. The group suggests that a better understanding of this soluble protein may have therapeutic benefits by promoting thermogenic fat activity in the treatment of obesity and other metabolic disorders.

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