

Models, causes, and new hope for neurodegenerative disease

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ABSTRACT

Neurodegeneration is a hallmark of many chronic, incurable disorders, such as Parkinson's disease, that are quickly increasing in incidence. To address these terrible illnesses, new and more effective therapeutic options are urgently needed. Models have shown to be a significant tool in helping researchers shed insight on the processes behind neurodegenerative illnesses, and these developments have already begun to give intriguing treatment possibilities. A special collection of articles focused on neurodegenerative

illnesses is offered in this themed issue of Disease Models & Mechanisms. The collection comprises original research papers that disclose possible biomarkers or treatment targets while also providing fresh insights into the intricate biology of such diseases. Some of the papers provide a novel disease model that allows for more in-depth investigation of important pathways. In addition, we give a series of reviews highlighting some of the most recent translational advancements in neurodegenerative disease research. We summarize the papers in this collection in this Editorial, underlining the influence that model-based investigations have had in this interesting field of study.

Key Words: Neurodegenerative diseases; Glial cells; Parkinson's disease

INTRODUCTION

Neurodegenerative disorders pose a significant hazard to human health. These age-related illnesses are becoming more common, owing in part to a rise in the older population in recent years. Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and spinocerebellar ataxias are examples of neurodegenerative disorders. The etiology of these diseases varies, with some causing memory and cognitive problems and others impacting a person's capacity to move, talk, and breathe. Effective therapies are badly required, but they will only be available if we have a thorough grasp of the origins and processes of each illness.

One strategy to understand how a disease works is to create a model system that mimics the illness's key features. For many years, powerful experimental model species such as the mouse, fruit fly, nematode worm, and even baker's yeast have been employed to research neurodegenerative illnesses, providing critical insights into disease processes.

The capacity to create Induced-Pluripotent Stem Cells (iPSCs) from differentiated human cells has lately enabled the generation of patient-specific cell lines in a tissue culture dish, resulting in human models of human illness. [1] Recently, technical advances have enabled these cells to be cultivated in three dimensions, producing organoids that mimic numerous human tissues, including the brain. Cell-cell interactions and complex cytoarchitecture may be represented and investigated in more depth and more physiological situations in these three-dimensional brain organoid systems than in classic tissue culture models with isolated cells [1]. Furthermore, mounting data reveals that many neurodegenerative disorders are more than just the result of dying neurons. Non-neuronal cells in the brain, such as glial cells, which are even more plentiful than neurons in the brain and central nervous system, play important roles in disease progression. Incorporating these neuroglial interactions into 3D brain organoid models will aid in the understanding of cell non-autonomous disease processes. We hope that these 3D brain organoid systems will be a valuable addition to the experimental arsenal of disease modelers. With remarkable developments in genome sequencing technology, it is now feasible to scan individual patients' genomes to determine the origins of both uncommon and common genetic illnesses.

The invention of a treatment for spinal muscular atrophy is one Inspiring Success Story. SMA, the most prevalent genetic murderer of neonates, is a neuromuscular illness caused by loss-of-function mutations in the SMN1 gene. Pioneering research into the disease's molecular mechanisms and the development of animals laid the groundwork for recent

clinical trials testing Antisense Oligonucleotides (ASOs) as a therapeutic strategy to correct a splicing defect and restore functional SMN protein. Animal model studies indicated that this therapy technique might be effective, and two recent clinical trials in children with SMA proved that the strategy is effective [2]. This medicine was authorized by the US Food and Drug Administration at the end of 2016, making it the first disease-modifying treatment for SMA. A tremendous and game-changing victory for model systems, as well as for patients and their families. These astounding findings bode well for ASO medicines being developed for testing in a variety of other neurodegenerative illnesses, including Huntington's disease and Amyotrophic Lateral Sclerosis (ALS). We now have new hope and a clear road ahead for successful neurodegenerative disease medicines. It is a very exciting and promising moment to be a researcher in this field. Our objective in putting together this Special Disease Models & Mechanisms (DMM) collection, 'Neurodegeneration: From Models to Mechanisms to Therapies,' is to communicate the sense of excitement and promise in the area of neurodegenerative disease research while also acknowledging the challenges ahead. To kick off the collection, we include a variety of fresh reviews and research papers in this issue that highlight the translational significance of studies using neurodegenerative disease model systems. In addition, the collection includes some of DMM's most popular neurodegeneration-related research and review articles from recent years. We begin this issue's emphasis on neurodegeneration with an exclusive interview with Huda Zoghbi, a professor in Baylor College of Medicine's Departments of Pediatrics, Molecular and Human Genetics, Neurology, and Neuroscience. Huda is famous for her contributions to the understanding of the genetic causes and molecular processes underlying spinocerebellar ataxia and Rett syndrome, including her efforts to clarify the genetic origins and molecular mechanisms underpinning spinocerebellar ataxia and Rett syndrome. These discoveries have also given light on the complicated processes at work in neurodegenerative disorders. Huda explains her path from the clinic to the bench in this interview, stressing the experiences, mentors, and partnerships that shaped her research interests. Huda, one of the founding editors of DMM, has long advocated for the use of model systems in human illness research, and her interview highlights the value of animal models for studying brain diseases in particular.

Following that, Edward Lee and colleagues offer a 'At a Glance' summary of RNA metabolism in neurodegenerative illnesses in the review portion of this issue. In recent years, aberrant RNA processing has emerged as a critical contributing component in various neurodegenerative illnesses, mostly as a result of research employing model systems. This paper and accompanying poster show how RNA metabolism dysfunction might contribute to neurodegenerative pathogenesis, as well as highlight possible

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treatment strategies to target these processes. Julie Valastyan and Susan Lindquist's previous DMM 'At a Glance' presentation gives a summary of protein-level pathways that have long been implicated in neurodegenerative and associated illnesses.

The significance of calcium signaling in Parkinson's disease is the subject of another of the new reviews in this issue [3]. Parkinson's disease has been the subject of a lot of model-based research in recent years since it's such a big worldwide health concern, and many of these studies have found that calcium homeostasis disturbance is a crucial pathogenic hallmark. The existing evidence supporting dysregulation of calcium-dependent pathways in this condition, as well as the potential for these results to drive therapeutic development, are discussed in this review by Gabriela Caraveo and colleagues.

Wim Robberecht and colleagues conclude the review part with a detailed description of model systems used to research ALS, ranging from cell-based systems through fruit flies to rodents [4]. Many of the genes and processes involved have been revealed thanks to the varied variety of models available to investigate this dreadful illness – as evidenced by the many ALS-related research papers also published in this issue. The ALS research community is now ready to take these discoveries to the clinic. In a 2014 DMM review, the significance of zebrafish models in particular on increasing our understanding of the pathogenic pathways underlying ALS and similar motor neuron illnesses was emphasized.

This Special Collection includes original research papers that contribute to our understanding of neurodegenerative disease processes in addition to review articles. These publications cover a wide range of ailments, including Parkinson's disease and Alzheimer's disease, as well as unusual neurological conditions. Some work on animal models of human gene abnormalities, while others work on biomarkers to track disease development. They explain how different model systems may be utilized to investigate the processes of neurodegeneration in each scenario. The important results and translational implications of a sample of the new research papers featured in this issue are summarized below.

Javier Fernández-Ruiz and colleagues expand previously reported data from a mouse model of familial ALS to a canine model of the disease in the first of 10 new research articles. Dogs can acquire degenerative myelopathy, a form of neurodegenerative condition caused by mutations in the same gene that is usually mutated in human ALS: Superoxide Dismutase 1. (SOD1). The scientists tested for comparable effects in the dog model after discovering

that Cannabinoid Receptor Type-2 (CB2) expression is elevated in human ALS and a mouse model of ALS induced by SOD1 mutations. They discovered that CB2 receptor expression is elevated in the spinal cord of dogs suffering from degenerative myelopathy, which is consistent with earlier findings. These findings support the possible neuroprotective impact of CB2 receptor modulation in ALS, as well as the utilization of canine degenerative myelopathy as a useful model for studying the disease's etiology. The dog model is the first spontaneous animal model of ALS, and it has significant benefits over transgenic overexpression models.

Paulo Ferreira and colleagues also add to the interesting new hypothesis that defects in nucleocytoplasmic transport might underpin neurodegenerative disorders in this issue. The authors inactivated RANBP2, a regulator of the Ran GTPase cycle, which is known to power nuclear import, in mice using a conditional knockout technique. The selective loss of RANBP2 function in motor neurons resulted in ALS-like symptoms such as progressive neuron loss, weakening, and death. Nucleocytoplasmic transport and proteostasis of substrates required in motor neuron homeostasis were altered at the cellular level, indicating the role of the Ran GTPase cycle in ALS pathogenesis.

Appetite loss and weight loss are frequent symptoms of neurodegenerative disorders such as ALS. Sabine Cordes and colleagues employ mouse genetics to investigate the molecular basis for hunger regulation, focusing on the role of the Tyrosine Receptor Kinase 3 (Tyro3) gene in controlling the brain circuitry that drives appetite. They show that Tyro3 can operate as a modulator for the mouse anorexia mutation. In addition to shedding insight on the neuropathological underpinnings of anorexia, the researchers' results may aid in the development of therapies to prevent or reduce weight loss associated with neurodegenerative illnesses.

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