

# Neurodegenerative disease: models, mechanisms, and a new hope

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## ABSTRACT

Neurodegeneration is a feature of many debilitating, incurable diseases that are rapidly rising in prevalence, such as Parkinson's disease. There is an urgent need to develop new and more effective therapeutic strategies to combat these devastating diseases. Models – from cell-based systems, to unicellular organisms, to complex animals – have proven to be a useful tool to help the research community shed light on the mechanisms underlying neurodegenerative diseases, and these advances have now begun to provide promising therapeutic avenues. In this themed issue of *Disease Models & Mechanisms*, a special collection of articles focused on neurodegenerative diseases is introduced. The collection includes original research articles that provide new insights into the complex pathophysiology of such diseases, revealing candidate biomarkers or therapeutic targets. Some of the articles describe a new disease model that enables deeper exploration of key mechanisms. We also present a series of reviews that highlight some of the recent translational advances made in studies of neurodegenerative diseases. In this Editorial, we summarize the articles featured in this collection, emphasizing the impact that model-based studies have made in this exciting area of research.

## Introduction

Neurodegenerative diseases represent a major threat to human health. These age-dependent disorders are becoming increasingly prevalent, in part because the elderly population has increased in recent years (Heemels, 2016). Examples of neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia and the spinocerebellar ataxias. These diseases are diverse in their pathophysiology – with some causing memory and cognitive impairments and others affecting a person's ability to move, speak and breathe (Abeliovich and Gitler, 2016; Canter et al., 2016; Taylor et al., 2016; Wyss-Coray, 2016). Effective treatments are desperately needed but will only come with a deep understanding of the causes and mechanisms of each disease.

One way to learn about how a disease works is to develop a model system that recapitulates the hallmark characteristics of the disease. Powerful experimental model organisms such as the

mouse, fruit fly, nematode worm, and even baker's yeast have been used for many years to study neurodegenerative diseases and have provided key insights into disease mechanisms (Link, 1995; Krobisch and Lindquist, 2000; Boillee et al., 2006; Bruijn et al., 1998; Yamamoto et al., 2000; Auluck et al., 2002; Outeiro and Lindquist, 2003; Cooper et al., 2006; Gitler et al., 2008, 2009; Elden et al., 2010; Couthouis et al., 2011; Armakola et al., 2012; Jovičić et al., 2015; Becker et al., 2017).

The more recently acquired ability to generate induced-pluripotent stem cells (iPSCs) from differentiated human cells has made it possible to generate patient-specific cell lines in a tissue culture dish – generating human models of human disease (Han et al., 2011). Recently, there have been technological innovations that allow for these cells to be cultured in three dimensions, to produce organoids that represent various human tissues, even the brain (Marton and Paşca, 2016; Paşca et al., 2015). These three-dimensional brain organoid systems permit cell-cell interactions and complex cyto-architecture to be modeled and studied in greater detail and in more physiological contexts than traditional tissue culture models with isolated cells. Furthermore, accruing evidence suggests that many neurodegenerative diseases are not merely diseases of dying neurons. Non-neuronal cells in the brain, such as glial cells, which are even more abundant in the brain and the central nervous system than neurons, play major roles in disease progression (Ilieva et al., 2009). Incorporating these neuron-glial interactions into such 3D brain organoid models will empower the elucidation of cell non-autonomous disease mechanisms. We anticipate that these 3D brain organoid systems will be a powerful addition to the disease modeler's experimental arsenal. Remarkable advances in genome sequencing technology have made it possible to read genomes of individual patients to discover causes of both rare and common genetic diseases. But which sequence variants are damaging to gene function and which are benign? Model organisms will also be powerful tools to test the effects of candidate gene variants discovered by human genome sequencing.

One highly inspirational success story is the development of a therapy for spinal muscular atrophy (SMA). SMA – a neuromuscular disease caused by loss-of-function mutations in the *SMN1* gene – is the most common genetic killer of babies. Pioneering studies of the molecular mechanisms of the disease and the development of animal models (Hua et al., 2010, 2011) laid the foundation for the recent clinical trials testing antisense oligonucleotides (ASOs) as a therapeutic strategy to correct a splicing defect and restore functional SMN protein. Studies in animal model systems revealed that this therapeutic strategy could work (Hua et al., 2010, 2011) and two recent clinical trials in children with SMA demonstrated that the strategy does work. In a spectacular advance, infants that received the ASO drug showed substantial improvement in motor function compared with children who did not receive the drug (Finkel et al., 2016). At the end of 2016, the United States Food and Drug Administration approved

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this therapy, making it the first disease-modifying treatment for SMA. A remarkable and game-changing win for model systems and especially for patients and their families. These stunning results augur well for ASO drugs that are being developed for testing in several other neurodegenerative diseases, including Huntington's disease and amyotrophic lateral sclerosis (ALS). We now have a new hope and a clear path forward for effective therapies for neurodegenerative diseases. It truly is an inspiring and hopeful time to be a researcher in this field.

Our goal in compiling this special Disease Models & Mechanisms (DMM) collection, 'Neurodegeneration: From Models to Mechanisms to Therapies', is to convey the sense of excitement and hope in the neurodegenerative disease research field as well as to acknowledge the challenges ahead. To launch the collection, we present, in this issue, a number of new reviews and research articles that demonstrate the translational impact of studies involving neurodegenerative disease model systems. The collection also includes some of DMM's most-read neurodegeneration-focused research and review content from recent years. Below, we summarize the collection so far and provide a preview of what's to come in upcoming issues of the journal.

### Reviews: trends in neurodegeneration research

We begin this neurodegeneration-focused issue with an exclusive interview with Huda Zoghbi, a professor in the Departments of Pediatrics, Molecular and Human Genetics, Neurology and Neuroscience at Baylor College of Medicine. Huda is renowned for her many groundbreaking discoveries in neurological disease research, not least her contributions to elucidating the genetic causes and molecular mechanisms underlying spinocerebellar ataxia and Rett syndrome. These insights have also shed light on the complex mechanisms at play in common neurodegenerative diseases. In this interview, Huda describes her journey from the clinic to the bench, highlighting the experiences, mentors and collaborations that helped to shape her research interests (Zoghbi, 2017). One of the founding editors of DMM, Huda has always been an advocate of the use of model systems in human disease research, and her interview particularly emphasizes the power of animal models for exploring brain disorders. Previous DMM 'A Model for Life' interviewees whose research is also focused on neurodegenerative diseases include David Rubinsztein and Rick Morimoto (all interviews can be found at: [http://dmm.biologists.org/content/by/section/A\\_MODEL\\_FOR\\_LIFE](http://dmm.biologists.org/content/by/section/A_MODEL_FOR_LIFE)).

Next, in the review section of this issue, Edward Lee and colleagues present an 'At a Glance' overview of RNA metabolism in neurodegenerative diseases (Liu et al., 2017). In recent years, altered RNA processing has emerged – largely through studies involving model systems – as a key contributing factor in several neurodegenerative diseases. This article and its accompanying poster illustrate how impaired RNA metabolism can underlie the pathophysiology of neurodegeneration, as well as discussing potential therapeutic interventions to target these processes. An earlier DMM 'At a Glance' poster, by Julie Valastyan and Susan Lindquist, provides a snapshot of protein-level mechanisms that have long been implicated in neurodegenerative and related disorders (Valastyan and Lindquist, 2014).

Another of the new reviews published in this issue focuses in on the role of calcium signaling in Parkinson's disease. As a major global health problem, Parkinson's disease has been the focus of a high proportion of model-based research in recent years, and many such studies have indicated that disruption of calcium homeostasis is a key pathological feature. This review, written by Gabriela Caraveo and

colleagues, discusses the current evidence for dysregulation of calcium-dependent pathways in this disease and potential for these findings to guide drug development (Zaichick et al., 2017).

Rounding up the review section, Wim Robberecht and colleagues provide a comprehensive discussion of model systems used to study ALS, from cell-based systems to fruit flies to rodents (Van Damme et al., 2017). Thanks to the diverse range of models available to study this devastating disease – emphasized by the many ALS-related research papers also published in this issue (see below) – many of the genes and pathways involved have been unveiled. The ALS research community is now poised to translate these findings to the clinic. A related DMM review published in 2014 highlighted the impact that zebrafish models in particular have made in improving our understanding of the pathogenic mechanisms underpinning ALS and related motor neuron disorders (Patten et al., 2014).

### New research: models, mechanisms and more

In addition to the review content, this Special Collection showcases original research articles that impact our understanding of neurodegenerative disease mechanisms. These papers span different diseases, from common ones such as Parkinson's disease and Alzheimer's disease to rare neurological disorders. Some focus on modeling human gene defects in animals, whereas others develop biomarkers to track disease progression. In each case, they show how diverse model systems can be powerfully used to explore the mechanisms of neurodegeneration. Below, we highlight the key findings and translational implications of a subset of the new research papers published in this issue.

In the first of ten new research papers, Javier Fernández-Ruiz and colleagues extend previously published observations from a mouse model of familial ALS to a canine model of the disease (Fernández-Trapero et al., 2017). Dogs can develop a type of neurodegenerative disorder called degenerative myelopathy, which can be caused by mutations in the same gene that is frequently mutated in human ALS: superoxide dismutase 1 (*SOD1*). The observation that cannabinoid receptor type-2 (CB<sub>2</sub>) expression is upregulated in human ALS and in a mouse model of ALS caused by *SOD1* mutations led the authors to test for similar effects in the dog model. Consistent with previous results, they found that CB<sub>2</sub> receptor expression is upregulated in the spinal cord of dogs affected by degenerative myelopathy (Fernández-Trapero et al., 2017). These results lend weight to the putative neuroprotective effect of CB<sub>2</sub> receptor modulation in ALS, and further support the use of canine degenerative myelopathy as a relevant model to study the pathophysiology of this disease. The dog model represents the first spontaneous animal model of ALS, offering several advantages over models that rely on transgenic overexpression.

Also in this issue, Paulo Ferreira and colleagues contribute to the exciting new concept that impairments in nucleocytoplasmic transport can underlie neurodegenerative diseases (Cho et al., 2017). Using a conditional knockout approach in mice, the authors inactivated RANBP2, a regulator of the Ran GTPase cycle, which is known to power nuclear import. Selective loss of RANBP2 function from motor neurons led to ALS-like symptoms, including progressive neuron loss, weakness, and fatal paralysis. At the cellular level, nucleocytoplasmic transport and proteostasis of substrates involved in motor neuron homeostasis were disrupted, supporting the involvement of the Ran GTPase cycle in ALS pathophysiology. The new conditional mouse model generated here can be used for further mechanistic exploration (Cho et al., 2017).

Loss of appetite and weight loss are common features of neurodegenerative diseases such as ALS. In another new paper,

Sabine Cordes and colleagues use mouse genetics to explore the molecular basis for regulating appetite and focus their studies on a role of the tyrosine receptor kinase 3 (*Tyro3*) gene in regulating the neural circuitry that governs appetite (Kim et al., 2017). They provide evidence that *Tyro3* can act as a modifier for the *anorexia* mutation in mouse. In addition to shedding light on the neuropathological basis of anorexia, their findings could help suggest strategies to prevent or slow weight loss that accompanies neurodegenerative disorders.

The neuromuscular junction is a remarkable structure that is particularly vulnerable to neurodegenerative disease. However, it possesses powerful ways to resist injury and to regenerate. In their new DMM paper, Michela Rigoni and colleagues use an *in vitro* cellular model of the degenerative disease Miller Fisher syndrome to define the Schwann cell and neuron signaling events, components and cross-talk required to promote nerve regeneration in the face of peripheral neuropathies (Rodella et al., 2017).

The peripheral nervous system (PNS) is also a target of neurodegenerative disease. A group of disorders called hereditary sensory and autonomic neuropathies (HSANs) are caused by PNS dysfunction. One such disorder, familial dysautonomia, is caused by mutation of the *IKBKAP* gene. Reported in this issue, Frances Lefcort and colleagues generate the first mouse model to study the consequence of loss of *IKBKAP* specifically in neurons (Chaverra et al., 2017). The mutant mice develop both autonomic and non-autonomic neuronal deficits, suggesting a role for *IKBKAP* beyond the PNS, to CNS development and function.

Parkinson's disease (PD) is one of the most common age-related neurodegenerative disorders worldwide. The ability to predict and detect the disease presymptomatically on the basis of biomarkers is likely to give therapies the best chance of working. Non-invasive biomarkers, such as blood or imaging-based markers are ideal, because they can be analyzed longitudinally and could even be used to track the efficacy of a proposed treatment. In one of two new PD-focused studies in this issue, Georg Auburger and colleagues analyzed the blood samples of a large Turkish family affected by a PD-causing duplication of the  $\alpha$ -synuclein gene (*SNCA*) (Lahut et al., 2017). They detected significant downregulation of complexin-1 (*CPLX1*) mRNA in the blood of presymptomatic heterozygotes at risk of PD based on prodromal features, and performed functional studies to provide insight into the role of *CPLX1* in PD. Their study provides a new blood biomarker with the potential to be used in early screens for PD risk.

Defining intrinsic cellular defects that characterize a particular disease state can provide mechanistic insight but could also serve as a biomarker to predict disease based on analysis of patient cells. Miguel Weil and colleagues discovered that human mesenchymal stem cells (hMSCs) isolated from the bone marrow of sporadic ALS patients have an altered response to DNA-damaging agents compared with hMSCs from healthy subjects (Wald-Altman et al., 2017). The authors connect this defect to autophagy and show that autophagy regulation is perturbed in ALS-patient cells. These findings reinforce a role for autophagy dysregulation in ALS and also provide a potential cellular biomarker of the disease.

Last but not least, Laura Calzà and colleagues examined the vulnerability of neurons from a transgenic mouse model of Alzheimer's disease (AD) to oxygen-glucose deprivation (an *in vitro* model of hypoxia) (Baldassarro et al., 2017). This is an important question in AD research as vascular dysfunction is a feature of the disease, but the link with amyloid pathology remains unclear. Calzà and co-authors demonstrate that intraneuronal amyloid- $\beta$  ( $A\beta$ ) accumulation in neurons increases vulnerability to cell death upon oxygen-glucose deprivation, and interestingly,

exposure of neurons to astrocyte-conditioned culture media confers protection. These results highlight important cell non-autonomous interactions between neurons and glia in Alzheimer's disease.

### Greatest hits

Beyond the papers featured in this thematic issue, there have been several exciting papers focused on neurodegeneration published in *DMM* in the past year. We cannot highlight all of them because of space limitations, but we would like to mention a couple of standout papers from 2016. First, in a study examining the convoluted issue of mitochondrial dysfunction in PD, Paul Fisher and colleagues reported that patient-derived immortalized lymphoblasts show enhanced respiratory activity compared with control cells (Annesley et al., 2016). The authors propose that this trait could provide a reliable biomarker of the disease.

The second study of note is by Ellen Sidransky and colleagues, and focuses on Gaucher disease. Mutation of *GBA1*, which encodes the lysosomal enzyme glucocerebrosidase, causes Gaucher disease. In one of the most exciting recent developments in the neurodegenerative disease field in the last several years, it has been appreciated that mutations in *GBA1* are also a risk factor for Parkinson's disease. How Gaucher disease connects to Parkinson disease at the molecular and cellular level is an area of intense interest (Abeliovich and Gitler, 2016). Sidransky and her colleagues have generated a mouse neuronal cell model with nearly complete loss of glucocerebrosidase activity, mimicking the situation in Gaucher disease (Westbroek et al., 2016). This model provides the field a powerful tool to study not only Gaucher disease but also to explore potential connections with PD pathophysiology. Keep an eye out for a review by Sidransky and co-authors on iPSC models of lysosomal storage disorders in an upcoming issue of the journal.

### Concluding remarks

We hope you enjoy this issue and the overall collection, which will be added to over the coming months. All articles can be freely accessed via this dedicated page: <http://dmm.biologists.org/collection/neurodegenerative-disorders>. We dedicate this collection to Susan Lindquist, our beloved mentor, friend, and founding editor of *DMM* who sadly passed away in October, 2016. Among several moving tributes (Chernoff, 2017; Serio, 2017; Bevis, 2017; Morimoto, 2016; Hartl, 2016; Shorter and Gitler, 2016; Whitesell and Santagata, 2016; Fuchs, 2016; Khurana et al., 2017), a particularly touching obituary written by Vivian Siegel was published in *DMM* (Siegel, 2017). Sue was a visionary pioneer who was unsurpassed in her ability to harness model systems to explore fundamental biology and elucidate mechanisms of human disease. Her fearlessness led her to champion the humble budding yeast as a simple, yet powerful new model to study the cell biology underpinning neurodegeneration. This pioneering strategy allowed Sue to quickly arrive at mechanism, which could then be rapidly translated to more complex model systems. We suspect that these insights will soon reach the clinic.

This article is part of a special subject collection 'Neurodegeneration: from Models to Mechanisms to Therapies', which was launched in a dedicated issue guest edited by aron Gitler and James Shorter. See related articles in this collection at <http://dmm.biologists.org/collection/neurodegenerative-disorders>.

### Acknowledgements

We would like to thank the authors, reviewers and editors who helped to compile this special issue and ongoing collection. Particular thanks are due to Monica Justice for valuable advice, and to Steven Clapcote for handling many of the research articles published in this issue.



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