Published in final edited form as:

Exp Neurol. 2014 December ; 262(0 0): 73–74. doi:10.1016/j.expneurol.2014.08.020.

Special Issue on amyotrophic lateral sclerosis

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This Special Issue of Experimental Neurology is devoted to advances in amyotrophic lateral sclerosis (ALS) research. ALS is the most common, adult-onset neuromuscular disease and among one of the most common neurodegenerative diseases (Pasinelli and Brown, 2006). Median survival from symptom onset is three to five years and approximately 6000 Americans die each year from the condition (Hirtz et al., 2007). Moreover, cognitive impairment is present in a large percentage of ALS patients, and ALS and frontotemporal dementia (FTD) are now thought to represent a spectrum of disease unified by a neuropathological substrate of TDP-43-positive, ubiquitin-positive neuronal inclusions (Neumann et al., 2006). Current treatment focuses on symptom management and there is a critical unmet need for effective, disease-modifying therapies. Apart from riluzole, which prolongs life by three to six months (Lacomblez et al., 1996), clinical trials in ALS have been disappointing. Driven by genetic discoveries and a greater understanding of the underlying pathogenesis, it is now clear that the clinical syndrome that we know as ALS is not a single entity, but rather represents a heterogeneous group of diseases (Renton et al., 2014). This has inevitably led to the idea that personalized therapeutics targeting the underlying etiologies are needed. This Special Issue on ALS reviews the latest advances in ALS research, and examines strategies that may lead to disease-modifying treatments.

Articles in the Special Issue

ALS and frontotemporal dementia

The relationship between ALS and frontotemporal dementia is now firmly established, but many questions remain. For example, would every single ALS patient develop frontotemporal dementia if they lived long enough, and vice-a-versa? Hardy and Rogaevea (2014) explore this aspect of the disease in a tour de force analysis of genetic evidence assembled worldwide. They dissect out the various pathways contributing to each clinical entity and outline common susceptibilities to disease. They present a nuanced view of how

disruption of autophagy and abnormal RNA metabolism pathways may lead to these linked, but clinically disparate diseases.

Pathogenesis of frontotemporal lobar degeneration and its relationship to ALS

Continuing along this theme, Bennion Callister and Pickering-Brown (2014) review current thinking on the genetic and pathological features of the FTD-ALS spectrum in light of recent discoveries. Notably, they discuss how the discovery of the C9ORF72 hexanucleotide repeat expansion has already greatly affected how these diseases are diagnosed, investigated and perceived, and how C9ORF72 provides a mechanistic link between two clinically distinct disorders, ALS and FTD. Further, this mutation underlies a significant proportion of ALS and FTD cases lacking a family history, representing the first time that a common genetic cause has been identified for the sporadic form of these diseases.

Genetics of ALS

Understanding the genetic architecture of ALS has substantially improved how we think about this disease and the underlying pathobiology. Mutations in several genes have been identified as causative in familial ALS, with SOD1, TDP-43, FUS and the hexanucleotide repeat expansion in C9ORF72 being the most common. In contrast, the genetics of sporadic ALS is less well understood. Whole genome association studies have identified a small number of putative genetic risk factors, but more work needs to be done in this area. Leblond et al. (2014) discuss how whole exome and whole genome sequencing data may help fill this void and shed light on this important area of ALS research.

C9ORF72 and ALS

The discovery of an expanded GGGGCC hexanucleotide repeat in C9ORF72 has been an exciting advance in the ALS field. This repeat expansion is the most frequent cause of both ALS and FTD, effectively unifying these two disparate clinical syndromes. The mechanism by which this mutation leads to neurodegeneration remains unclear, though several hypotheses have already emerged. Heutink et al. (2014) review the current status of C9ORF72 research, and discuss what is known about the pathobiology of this repeat expansion disease.

Glia and ALS

Growing evidence suggests that ALS is a non-cell autonomous disease and that dysfunctional glia play an important role in the death of motor neurons (Neusch et al., 2007). Originally, astrocytes were proposed as a central contributor to disease, but recent data have pointed to equally important contributions from microglia and oligodendrocytes. This review by Philips and Rothstein (2014) provides a timely and detailed overview of the function played by each specific glial subtype in motor neuron degeneration and how this knowledge may lead to the development of therapeutics specifically targeting the glial compartment.

Where does ALS start?

One of the most striking aspects of ALS is the focal onset of clinical symptoms, followed by remarkably fast progression to involve other limbs, bulbar function, and ultimately respiratory muscles. In this review, Ravits (2014) deconstructs the early stages of ALS and outlines the mechanisms underlying this temporo-spatial spread which may be key to understanding the disease as a whole. Cataloging the rapid spread of pathology across the neuroaxis also provides a template to unify seemingly diverse and distinct clinical presentations of ALS.

Stem cells as a potential therapy for ALS

Stem cell therapy for ALS has emerged as a promising treatment approach for ALS, either as motor neuron replacement or as a means of providing support to dying motor neurons. The article by Thomsen et al. (2014) reviews ongoing efforts to move stem cells towards clinical trials. The authors also outline the various challenges that remain before stem cells can be used as therapy in humans, not the least of which are pre-clinical experiments required to ensure safety and minimize risk to patients.

Developing therapies for ALS

In this review, Van Den Bosch and colleagues discuss drug discovery and therapeutic development in ALS (Poppe et al., 2014). Efficient bench-to-bedside translation will rely on improved insight into the pathogenesis of motor neuron degeneration, building improved animal models of the disease, and meticulous pre-clinical studies. These common sense approaches form the fundamental building blocks necessary to build upon our growing knowledge of the disease and provide a roadmap to transform those insights into new therapies that help patients.

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