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Review

Translating biological findings into new treatment strategies for amyotrophic lateral sclerosis (ALS)

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is characterized by the selective death of motor neurons in the motor cortex, brainstem and spinal cord. It is a neurodegenerative disorder with high genetic and phenotypic variability. In most patients, the cause of the disease is unknown. Until now, no treatment strategy has been discovered with the exception of riluzole which has a moderate effect on the disease process. While developing a new causal therapy targeting a specific disease-causing gene can have a huge effect on the disease process, only a limited number of ALS patients will benefit from such a therapy. Alternatively, pathogenic processes that are common in ALS patients with different etiology can also be targeted. The effect of such a modifying treatment will be smaller, but the target population will be larger as more ALS patients could benefit. In this review, we summarize the evidence for the involvement of different biological processes in the pathogenesis of ALS and will discuss how strategies influencing these processes can be translated into new therapeutic approaches. In order to further improve this translational step, there is an urgent need for a better understanding of the underlying mechanism(s), for new ALS animal models and for rigorous protocols to perform preclinical studies.

Contents

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Introduction

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disorder characterized by selective motor neuron death. Both upper motor neurons in the motor cortex and lower motor neurons in the brainstem and in the ventral horn of the spinal cord are affected. Patients develop a progressive muscle phenotype characterized by spasticity, hyperreflexia, fasciculations, muscle atrophy and paralysis. ALS is usually fatal within 3 to 5 years after the diagnosis (Cudkowicz et al., 1997).

In most cases (~90%), there is no family history of ALS and these patients are classified as sporadic ALS (SALS) patients. However, a clear family history is present in approximately 10% of ALS patients, and these patients suffer from familial ALS (FALS). Although the disease is in almost all cases inherited in an autosomal dominant way, also autosomal recessive and X-linked forms exist. Mutations in more than 10 different genes are known to cause FALS (reviewed in (Renton et al., 2014)). The most common ones are found in the genes encoding superoxide dismutase 1 (SOD1; ~20%), fused in sarcoma (FUS; 1-5%) and TDP-43 (TARDBP; 1%–5%). Recently, a hexanucleotide repeat expansion $(GGGGCC)_n$ in the C9ORF72 gene was identified as the most frequent cause of FALS (~40%) in the Western population (DeJesus-Hernandez et al., 2011; Renton et al., 2011).

Not only genetically, but also clinically, ALS is a heterogeneous disease. The age and site of onset, the rate of progression and the presence and degree of cognitive dysfunction are variable. In some patients, also neurons in the prefrontal and temporal cortex are affected. This leads to cognitive and/or behavioral problems. These can be very subtle, but in about 15% of ALS patients frontotemporal dementia (FTD) is present, the main symptom of frontotemporal lobe degeneration (FTLD). These patients are diagnosed as suffering from ALS-FTLD (Lillo and Hodges, 2009; Ringholz et al., 2005). On the other hand, 15% of FTLD patients show signs of motor neuron degeneration (Burrell et al., 2011; Lomen-Hoerth et al., 2002). This suggests that ALS and FTLD are at the ends of a disease spectrum. This is also reflected by gene mutations that are common to both diseases (e.g. C9ORF72 and VCP) (Al-Chalabi et al., 2012) and by a similar neuropathology (e.g. TDP-43 aggregates). The large variation in disease presentation is even observed in families with the same causal gene mutation. This strongly suggests that there are factors, environmental or genetic in nature, that modify the clinical phenotype of the disease. Genetic modifiers of ALS are those genes that influence the severity of the disease process and these genes could also affect the risk for developing ALS. As a consequence, they are very important as these genetic factors could be responsible for the clinical variability in ALS and could also play an important role in the susceptibility for SALS.

Currently, there is no curative treatment for ALS. In 1995, riluzole was approved by the US Food and Drug Administration (FDA) for the treatment of ALS (Bensimon et al., 1994). Almost two decades later, this drug remains the only approved treatment. Riluzole increases the life span of the patients with an average of 2–3 months (Miller et al., 2007, 2012), an effect that was reproduced in different clinical trials (Bensimon et al., 1994, 2002; Lacomblez et al., 1996; Yanagisawa and Shindo, 1996). As a consequence, the search for new and better treatment strategies for ALS is a top priority. The hope is to find additional treatments that have cumulative effects to riluzole and that can halt the disease process in an early state. The search for these new treatment strategies is facilitated by the availability of good rodent models for ALS. A number of animal models were created that faithfully reproduce the human disease (reviewed in (McGoldrick et al., 2013)). The first generated mouse model overexpresses the human SOD1 gene containing a substitution of glycine to alanine at position 93 ($SOD1^{G93A}$) under the control of the human SOD1 promoter (Gurney et al., 1994). This ubiquitous overexpression of human mutant SOD1 causes a progressive motor phenotype that resembles the human disease and it is considered as the best rodent model so far. Extensive efforts were made to generate other rodent models that recapitulate ALS, using other mutations in the SOD1, TDP-43, or FUS gene. Whereas SOD1 mouse and rat models overexpressing different missense mutations result in an adult-onset and progressive neurodegeneration, most of the TDP-43 and FUS models generated so far show an axonopathy and muscle atrophy but hardly any of them show extensive motor neuron death. As a consequence, rodent mutant SOD1 models are the most frequently used models in translational research as these are the only ones that resemble clinically and pathologically the human situation.

Our expanding knowledge of both the biology of ALS and delivery strategies for drugs in the nervous system has resulted in a number of potential therapeutic strategies. Based on their target, these strategies can be subdivided into two main categories: causal or modifying treatments. While the first type of strategies aims to directly target disease-causing genes in order to avoid their expression and pathogenic effects, the second one targets factors or mechanisms that influence pathological processes related to ALS.

In this review, we will discuss a number of examples to illustrate how strategies influencing different biological processes involved in ALS can be translated into therapeutic approaches. We will summarize the most promising attempts to develop causal treatment strategies, while the main focus of this review is on the efforts to obtain disease-modifying therapies. We will discuss the problems that arise when potential therapeutic strategies are translated into clinical therapies as well as strategies that could improve the success of this translational step.

Causal treatments

Curing neurodegenerative diseases could be extremely difficult as the damage caused by the disease process seems to be irreversible. However, using a number of conditional animal models for different neurodegenerative diseases it was shown that it is possible to reverse the disease phenotype if the expression of the mutant gene causing the disease is halted. The first evidence was published in 2000 by Yamamoto et al. using a mouse model of Huntington's disease using a tetracycline-controlled system (Yamamoto et al., 2000). Turning off the expression of the mutated transgene after disease onset resulted in an almost complete reversal of the disease phenotype as well as in the clearance of the aggregates that are the histopathological hallmark of the disease (Yamamoto et al., 2000). Similar effects were observed in two mouse models for different types of spinocerebellar ataxia, SCA1 and SCA7, in which a reduction of the mutant gene expression in symptomatic mice could halt and even reverse the disease phenotype (Furrer et al., 2013; Zu et al., 2004). In ALS, a partial reversal of the motor phenotype after silencing of the transgene was observed in a TDP-43 overexpressing animal. Cell-type specific overexpression of human mutant TDP-43 in rat, using a tetracycline-controlled system, caused progressive paralysis with loss of motor neurons in the ventral horn of the spinal cord (Huang et al., 2012). Disease progression was halted and functional motor improvement occurred after mutant gene expression was switched off (Huang et al., 2012).

These findings strongly suggest that motor neuron degeneration can be stopped and that symptoms can be reversed if expression of the

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