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Als and Ftd: Insights into the disease mechanisms and therapeutic targets

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are neurodegenerative disorders, related by signs of deteriorating motor and cognitive functions, and short survival. The causes are still largely unknown and no effective treatment currently exists. It has been shown that FTLD may coexist with ALS. The overlap between ALS and frontotemporal dementia (FTD), the clinical syndrome associated with FTLD, occurs at clinical, genetic, and pathological levels. The hallmark proteins of the pathognomonic inclusions are SOD-1, TDP-43 or FUS, rarely the disease is caused by mutations in the respective genes. Frontotemporal lobar degenerations (FTLD) is genetically, neuropathologically and clinically heterogeneous and may present with behavioural, language and occasionally motor disorder, respectively. Almost all cases of ALS, as well as tau-negative FTLD share a common neuropathology, neuronal and glial inclusion bodies containing abnormal TDP-43 protein, collectively called TDP-43 proteinopathy. Recent discoveries in genetics (e.g. C9orf72 hexanucleotide expansion) and the subsequent neuropathological characterization have revealed remarkable overlap between ALS and FTLD-TDP indicating common pathways in pathogenesis. For ALS, an anti-glutamate agent *riluzole* may be offered to slow disease progression (Level A), and a promising molecule, *arimoclomol*, is currently in clinical trials. Other compounds, however, are being trailed and some have shown encouraging results. As new therapeutic approaches continue to emerge by targeting SOD1, TDP-43, or GRN, we present some advances that are being made in our understanding of the molecular mechanisms of these diseases, which together with gene and stem cell therapies may translate into new treatment options.

1. Introduction

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are related clinical phenotypes, which are characterized by decline in motor and cognitive functions, and short survival. ALS is the most common adult-onset motor neuron disease, characterized by the progressive, irreversible motor neuron loss leading to denervation atrophy of muscles and death by respiratory failure (Brookset al., 2000). Both diseases are invariably fatal after only a few years (Brooks et al., 2000). The causes of the more frequent sporadic forms remain unknown and no effective treatment currently exists. However, an anti-glutamate agent *Riluzole* has shown modest benefit and is the only drug, so far, to receive US Food and Drug Administration (FDA) approval for treatment of ALS (Miller et al., 1999). Also a Phase II/III randomised, placebo-controlled trial of arimoclomol (BRX-345) in familial ALS with SOD-1 mutation is underway (NCT00706147; www.ClinicalTrials.gov).

Arimoclomol, is a hydroxylamine derivative, a group of compounds which have unique properties as co-inducers of heat shock protein expression, but only under conditions of cellular stress which is involved in the ethiopathogenesis of multiple neurodegenerative diseases including ALS (Kalmar et al., 2014). Treatment with arimoclomol has been reported to improve survival and muscle function in different mouse models of motor neuron disease including ALS and in mutant superoxide dismutase 1 (SOD1) mice.

The small molecule arimoclomol may reduce the levels of protein aggregates in motor nerves, a possible cause of ALS, by boosting expression of the heat shock proteins Hsp 70 and Hsp 90 which help newly synthesised proteins to properly fold (www.alstdi.org; (Scotter et al., 2015). Other compounds, including ceftriaxone and dexpramipexole, have been promoted and show encouraging results at phase II clinical trials.

Ceftriaxone, belongs to a third generation of cafalosporine antibiotics, which can penetrate the blood brain barrier (BBB) and enter the CNS. In addition to bactericidal action, ceftriaxone has been found in various animal models to exert neuroprotective action caused by increased expression of the astrocytic glutamate transporter, EAAT2 in humans and GLT1 glutamate transporter in rodents. Glutamate transporter EAAT2 increases the clearance of synaptic glutamate and protects neurons from glutamate-mediated excitotoxicity which is thought to be a factor in their pathogenesis of ALS (Jagadapillai et al., 2014). In

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ALS animal models, as well as in human post-mortem tissue, decreased expression of glutamate transporter EAAT2 has been demonstrated.

Dexpramipexole is the enantiomer of pramipexole that is significantly less effective dopamine receptor agonist but shows better neuroprotective action. Dexpramipexole has been shown to inhibit the opening of the mitochondrial permeability transition pore (PTP), improving mitochondrial function and conferring significant protection to neurons exposed to free radicals under cellular stress (Vieira et al., 2014).

Unfortunately, neither of these compounds showed efficacy at stage III clinical trials (Cudkowicz et al., 2014, 2013), most likely due to already well-established disease. Stem cell therapies are emerging as potential disease modulating therapies in autoimmune diseases e.g. rheumatoid arthritis, multiple sclerosis, and lupus (Mazzini et al., 2010). Preclinical studies have shown that neurotrophic growth factors (NTFs) extend the survival of motor neurons in ALS. Recently, an Israeli research group developed a culture-based method for inducing mesenchymal stem cells (MSCs) to secrete neurotrophic growth factors (NTFs). These MSC-NTF cells have been shown to be protective in animal models of neurodegenerative diseases. They successfully administered autologous MSC-NTF cells, derived from bone marrow samples given by participants (26 ALS patients) in the trial, via intrathecal (i.t) or intramuscular (i.m.) administration which proved to be safe and provided indications of possible clinical benefits. These experiments are to be tested in upcoming clinical trials (Petrou et al., 2016). This study showed that implanting stem cells that produce neurotrophic factors (MSC-NTF) into either muscle or the intrathecal space, or both, were shown to be safe and associated with only mild adverse effects, principally headache and fever. This is the first study in which stem cells that have been modified to secrete neurotrophic factors have been implemented in patients with ALS. These results, however, should be treated with caution, since the study included relatively small group of patients and the trial did not include a placebo comparator.

Immunological therapies originally proved more promising, with a Phase III antibody-Nogo study. The Nogo A is one of the three isoforms of the Nogo protein that acts as a neurite outgrowth inhibitor of the Nogo protein, encoded by the *RTN4* gene (Pernet and Schwab, 2012). However, although the study has been completed (NCT00406016, www.ClinicalTrials.gov), no results have been published. For more on clinical trials, please refer to www.ClinicalTrials.gov.

In FTD, which typically presents with either behavioural abnormalities or language dysfunction, a considerable number of patients also develop muscle weakness and wasting that is typical for ALS (Strong, 2008; Strong et al., 2009) or, vice versa, ALS patients may develop impaired executive dysfunction and memory decline (Lomen-Hoerth et al., 2002; Lomen-Hoerth et al., 2003). The presence of frontotemporal impairment in ALS predicts a shorter survival time (Hodges et al., 2003) and behavioural and functional impairment may decline independently of motor function (De Silva et al., 2015; Rohrer et al., 2015).

With regard to treatments for FTD, a lot of symptomatic treatments have been reported so far. Open-label studies of anticholinesterase medicines have been negative and, in some cases they may even exacerbate behavioural symptoms (Devenney, Vucic, Hodges, and Kiernan, 2015). Similarly, a memantine study showed no effective treatment in a recent randomized placebo controlled trial (Boxer et al., 2012). The selective serotonin reuptake inhibitors and antipsychotic therapies are generally considered helpful in the management of mood and behavioural features in individual patients despite lack of evidence (Devenney et al., 2015). Tauopathy, however, has been a focus for research and the development of potential disease-modifying treatments (Devenney et al., 2015). According to the latest study on tau-transgenic mice, methylene blue substance, a drug in Phase III clinical trials stops decline in its tracks- but only when given at the earliest stages (Hochgrafe et al., 2015). This TRx-237-007 Phase 3 clinical trial conducted in 220 subjects with bvFTD was stopped, as it failed to reach its co-primary endpoints (TauRx Therapeutics Ltd. Sep 2016 conference news; company press release).

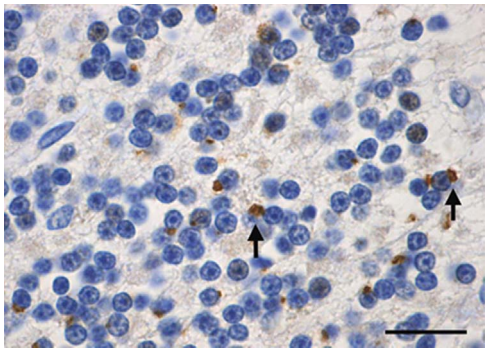

Fig. 1. Pathology in cases of frontotemporal lobar degeneration-motor neuron disease (FTLD-ALS) with *C9orf72* expansion. The figure shows ubiquitin-positive, TDP-43-negative neuronal cytoplasmic inclusions (arrows) in the granule cells of the cerebellum (p62 immunohistochemistry). Scale bars: 20 micrometres. Courtesy of N.J. Cairns, Washington University in St. Louis, USA.

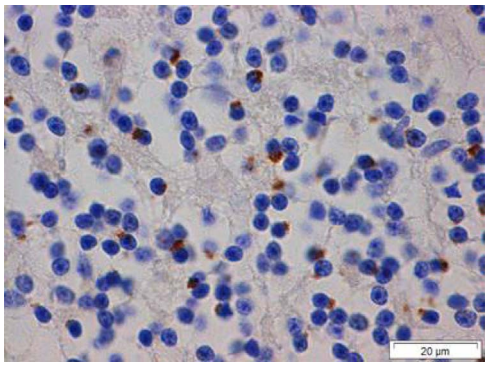

Fig. 2. Pathology in cases of frontotemporal lobar degeneration-motor neuron disease (FTLD-ALS) with *C9orf72* expansion. The figure shows the cerebellar inclusions are labelled with anti-dipeptide repeat antibodies (poly-GA immunohistochemistry). Scale bars: 20 micrometres. Courtesy of N.J. Cairns, Washington University in St. Louis, USA.

The incidence of ALS in Europe is 2.16 per 100,000 (Logroscino et al., 2010), while for FTD the incidence is 3.5 per 100,000 (Mercy et al., 2008). Here we present a current understanding of molecular causes of ALS and FTLD, in order to better understand pathogenetic mechanisms of both diseases as new design for clinical trials emerges in patients with ALS and FTD.

2. Genetics

A growing number of ALS-causing genes have been identified recently. These are now under investigation as these may shed some light on pathogenesis. Four major ALS-associated genes are: superoxide dismutase 1 (*SOD1*), the first genetic cause to be identified, TAR DNA-binding protein (*TARDBP*), fusion in malignant liposarcoma/

translocation in liposarcoma (*FUS/TLS*), and the most common chromosome 9 open reading frame 72 (*C9orf72*).

Identification of disease linked mutations in TDP-43 and FUS/TLS highlight dysfunctions in RNA metabolism as a common pathogenic pathway in both ALS and FTD. TDP-43 and FUS/TLS have similar structures and are involved in several RNA processing steps. TDP-43 binds to more than 6000 RNA targets and acts as a transcriptional repressor through its direct binding to DNA. It is involved in splicing, microRNA biogenesis, RNA transport and translation, and stress granule formation. However, FUS/TLS can bind to a single or double-stranded DNA and RNA. FUS/TLS interacts with RNA polymerase II and promotes or represses the transcription of distinct genes and affects