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Transgenics, toxicity and therapeutics in rodent models of mutant SOD1-mediated familial ALS

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Abstract

Gain-of-function mutations in the Cu,Zn-superoxide dismutase (SOD1) gene are implicated in progressive motor neuron death and paralysis in one form of inherited amyotrophic lateral sclerosis (ALS). At present, transgenic expression of 12 human SOD1 mutations driven by the endogenous promoter is disease-causative and uniformly lethal in mice and rats, despite tremendous biochemical and biophysical variation between the mutants tested. This contrasts with the subclinical motor neuron disease phenotypes of wild-type SOD1 transgenic and knockout mice. Molecular mechanisms such as glutamate-induced excitotoxicity, axonal transport blockade, mitochondrial dysfunction, neuroinflammation and apoptosis triggered by mutant SOD1 catalysed oxidative reactions and/or protein misfolding are proposed to drive ALS pathogenesis. Around 100 genetic cross-breeding experiments with transgenic mutant SOD1 mice have been performed to verify these mechanisms *in vivo*. Furthermore, mounting evidence from mice with cell restrictive, repressible or chimeric expression of mutant SOD1 transgenes and bone marrow transplants supports non-neuronal origins of neuroprotection in ALS. Transgenic mutant SOD1 rodents have also provided the benchmark preclinical tool for evaluation of over 150 potential therapeutic anti-oxidant, anti-aggregation, anti-glutamatergic, anti-inflammatory, anti-apoptotic and neurotrophic pharmacological agents. Recent promising findings from gene and antisense therapies, cell replacement and combinatorial drug approaches in transgenic mutant SOD1 rodents are also emerging, but await successful translation in patients. This review summarises the wealth of known genetic and therapeutic modifiers in rodent models with SOD1 mutations and discusses these in the wider context of ALS pathoetiology and treatment.

Keywords: Amyotrophic lateral sclerosis; Motor neuron disease; Superoxide dismutase 1; Toxicity; Therapeutics; Transgenic models

Contents

Abbreviations: ALS, amyotrophic lateral sclerosis; BMT, bone marrow transplant; CCS, copper chaperone for SOD1; CNR1, cannabinoid receptor 1; CNS, central nervous system; COX1, cyclooxygenase 1; Cdk5, cyclin-dependent kinase 5; DS, Down syndrome; EAAT2, excitatory amino acid transporter 2; FALS, familial ALS; GDNF, glial cell-derived neurotrophic factor; GluR2, ionotropic glutamate receptor 2; HDAC, histone deacetylase; Hsp70, heat shock protein 70; IGF-1, insulin-like growth factor; iNOS, inducible nitric oxide synthase; MCK, muscle creatine kinase; MMP9, matrix metalloproteinase 9; MT, metallothionein; NFL, neurofilament light chain; NFM, neurofilament medium chain; NFH, neurofilament heavy chain; $p75^{NTR}$, p75 neurotrophin receptor; PDTC, pyrrolidine dithiocarbamate; SALS, sporadic ALS; shRNA, short hairpin RNA; SOD1, superoxide dismutase 1; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis; Wld^S, Wallerian degeneration slow; WT, wild-type.

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1. Introduction

Almost 140 years have elapsed since the commonest adult-onset motor neuron disease (MND) was termed amyotrophic lateral sclerosis (Charcot and Joffroy, 1869). Widely recognised as Lou Gehrig's disease in America, Charcot's disease in Europe and MND in the UK and Australia, ALS is a progressive and terminal neurodegenerative disorder characterised by paralysis of motor function due to a combination of voluntary muscle weakness, atrophy and spasticity. The disease derives its name from the combined degeneration of upper and lower motor neurons projecting from the spinal cord, brainstem and cortex (Rowland and Shneider, 2001). ALS primarily targets the large caliber alpha motor neurons of 35–100 μm diameter in the spinal anterior horns (Ravits et al., 2007a). Clinically, lower motor neuron loss usually appears focal and asymmetric in onset and radiates through contiguous anatomical segments especially evident in caudal spinal cord (Ravits et al., 2007b). ALS is strongly associated with middle to late age with a slight male-to-female bias of 1.3 and current estimates suggest a worldwide incidence of 2 per 100,000 and prevalence of 4 per 100,000, in keeping with the average short-term survival of 3–5 years (Hirtz et al., 2007). At present, there exists no prophylactic or curative treatment for ALS and the single prescribed anti-glutamatergic drug Rilutek (riluzole) may have a marginal and unsatisfactory effect in extending life by a few months (Bensimon et al., 1994). Thus, the need for significant disease-modifying therapies is paramount.

The majority of ALS cases are of unknown aetiology and classed as sporadic (SALS). A genetic contribution possibly underlies SALS as a number of susceptibility or modifier genes have been identified by association studies including angiogenin, apolipoprotein E, apurinic endonuclease, neurofilament heavy chain (NFH), peripherin, survival motor neuron and vascular endothelial growth factor (VEGF) as discussed elsewhere (Simpson and Al-Chalabi, 2006). However, the majority of association studies in ALS have not been replicated across all populations, suggesting that population specific oligogenetic susceptibility may operate or that these apparent associations are false positives. The 10% remaining cases are familial (FALS) and 6 disease-causative genes from 11 loci have been identified by linkage analysis and positional cloning as reviewed recently (Gros-Louis et al., 2006). Mutations in Cu,Zn-superoxide dismutase (SOD1) occur in autosomal dominant adult-onset ALS (ALS1) and account for 2–3% of ALS cases overall when considering familial disease (Rosen et al., 1993). It is also noteworthy that SOD1 mutations are reported in up to 7% of SALS cases (Andersen, 2006), though this is in the setting of a specialist ALS clinic population. Autosomal recessive juvenile-onset ALS (ALS2) is caused by loss-of-function mutations in the Rab5 guanine nucleotide exchange factor protein ALS2 or alsin (Hadano et al., 2001; Yang et al., 2001), while autosomal