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Review

Sporadic and hereditary amyotrophic lateral sclerosis (ALS)☆

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ABSTRACT

Genetic discoveries in ALS have a significant impact on deciphering molecular mechanisms of motor neuron degeneration. The identification of SOD1 as the first genetic cause of ALS led to the engineering of the SOD1 mouse, the backbone of ALS research, and set the stage for future genetic breakthroughs. In addition, careful analysis of ALS pathology added valuable pieces to the ALS puzzle. From this joint effort, major pathogenic pathways emerged. Whereas the study of TDP43, FUS and C9ORF72 pointed to the possible involvement of RNA biology in motor neuron survival, recent work on P62 and UBQLN2 refocused research on protein degradation pathways. Despite all these efforts, the etiology of most cases of sporadic ALS remains elusive. Newly acquired genomic tools now allow the identification of genetic and epigenetic factors that can either increase ALS risk or modulate disease phenotype. These developments will certainly allow for better disease modeling to identify novel therapeutic targets for ALS. This article is part of a Special Issue entitled: Neuromuscular Diseases: Pathology and Molecular Pathogenesis.

1. Introduction

Amyotrophic lateral sclerosis is an adult onset, fatal neurodegenerative disorder involving the large motor neurons of the brain and the spinal cord. It is clinically characterized by progressive paralysis and eventual death from respiratory failure within three to five years. ALS is in the main a sporadic disease but about 10% of ALS cases are familial. SOD1 was the first gene to be discovered about two decades ago, but in the last fifteen years, a number of new ALS causing genes have been discovered (Table 1). These genes can play an important role in our understanding of the pathogenesis of familial and sporadic ALS.

2. Clinical features and diagnosis

Progressive pure motor weakness starting focally is the most distinctive clinical feature of ALS. The disease starts with limb weakness in about two-thirds of patients, often preceded by cramps, and with bulbar weakness causing dysarthria and dysphagia in the remaining one-third. In rare instances, cognitive impairment, behavioral disturbances or early respiratory failure can be the initial manifestation of ALS. The characteristic combination of upper and lower motor neuron dysfunction is usually evident on neurological examination with the presence of weakness, atrophy and fasciculations together with hyper-reflexia and increased tone in the same motor segment and not infrequently an extensor response to plantar stimulation. Sensory findings are minimal or absent. Relentless, the disease contiguously spreads to other body parts and eventually to respiratory muscles leading to death from respiratory failure within 30 months on average [1]

The diagnosis of ALS is clinical, based on the history and physical examination showing progressive upper and lower motor neuron dysfunction. It is usually supported by electrophysiological studies and neuroimaging and laboratory tests to exclude mimickers. The El Escorial criteria have been developed to standardize the diagnosis for clinical research [2].

Familial ALS is more easily identified when there is a positive family history; however, familial ALS may present as sporadic disease on account of incomplete penetrance or incomplete family history. In the absence of family history, an early age of onset, atypical rapid or slow disease progression, pure lower motor neuron presentation or the presence of dementia may alert to a familial etiology.

3. Update in the pathogenesis of familial ALS

The initial paradigm shift in approaching ALS pathogenesis, although recently recognized [3], occurred about 30 years ago when the tools of molecular genetics were applied to ALS. This effort led to the identification of the first ALS gene: superoxide dismutase 1 (SOD1), which accounts for 20% of familial ALS cases [4–7], and turned the attention to hereditary ALS as a means to investigate motor neuron degeneration.

SOD1 catalyzes the dismutation of superoxide radicals and protects the cell against reactive oxygen species. More than 160 mutations in SOD1 have been reported. Almost all are dominant missense mutations

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Table 1
Causative ALS genes.

Gene symbol	Locus	Function	Phenotype
SOD1	21q22	Superoxide metabolism	AD-ALS/ALS1
TARDBP	1p36	RNA metabolism	AD-ALS/ALS10, ALS-FTD
FUS	16p11	RNA metabolism	AD-ALS/ALS6, ALS-FTD
OPTN	10p13	Many functions including membrane and vesicular trafficking	AD & AR-ALS/ALS12
VCP	9p13	Ubiquitinated protein trafficking Autophagosme maturation	AD-ALS/ALS14, ALS-FTD, IBMPFD
SQSTM1	5q35	Protein degradation	AD-ALS, ALS-FTD, Paget's disease of bone
UBQLN2	Xp11	Protein degradation	X-linked adult and juvenile ALS/ALS15, ALS-Dementia
C9ORF72	9p21	Unknown	AD & sporadic-ALS/ALS-FTD
PFN1	17p13	Actin polymerization	AD-ALS

and account for 20% of familial ALS and for 2%–3% of apparently sporadic cases (www.alsod.org). The A4V mutation is the most common mutation in North America, followed by the I113T mutations [8]. Our current understanding of the pathogenic role of mutant SOD1 comes primarily from the study of transgenic rodents overexpressing mutant SOD1 and in particular from the G93A mouse model [9] as it recapitulates many features of the human SOD1 type disease. Although the exact toxic mechanism of SOD1 mutations is not completely elucidated, the mutant protein is misfolded and gains many toxic functions that can cause endoplasmic reticulum (ER) stress and include: overloading the unfolded protein response, mitochondrial dysfunction and disruption of axonal transport. Mutant SOD1 forms aggregates through an oxidation-mediated mechanism and recruit wild-type SOD1 by crosslinking of intermolecular disulifide bonds [10]. Inclusions containing these aggregates are found in the lower motor neuron and are a prominent pathological feature of human familial ALS due to SOD1 mutations and in the SOD1 mouse models [11–13]. Demetalled and unfolded apoform of SOD1 enters the intermembrane space of the mitochondria, where it is refolded by the chaperone of superoxide dismutase (CCS), copper and zinc ions are acquired and intermolecular disulphide bonds form between cysteine 57 and cysteine 146 [10,14]. In the SOD1 mouse models (G93A, L126X and A4V), the apoprotein forms intermolecular covalent bonds in the intermembrane space of the mitochondria, heralding the onset of symptoms. This is particularly notable because the A4V mice never becomes symptomatic until crossbred with mice overexpressing wild-type SOD1, and the onset of symptoms coincides with the formation of insoluble aggregates consisting of apo SOD1 with intermolecular covalent bond formation [10,14]. Not only mutant SOD1 but wild-type SOD1 has also been proposed to undergo post-translational modifications that can cause misfolding [15]. Using conformation-specific antibodies, misfolded wild-type SOD1 has been reported in the spinal cord of sporadic ALS patients and in non-SOD1 familial ALS but not in controls, implicating wild-type SOD1 aggregation in the pathogenesis of sporadic ALS [16,17]. Following the discovery of SOD1-familial ALS, several other genes causing ALS or ALS-like syndromes were unraveled (Table 2), starting with the gene for ALS2 coding the protein ALSIN that was discovered in 2001 [18]. A major step forward was the discovery of TAR DNA-binding protein (TDP-43/TADBP) in 2006 as a major component of ubiquitinated inclusions in ALS and subsequently in other neurodegenerative diseases [19]. ALS families were then screened and mutations in TARDBP were also found to cause familial ALS [20]. This important discovery provided a direct pathogenic link between TDP43 and sporadic ALS similar to the role of β-amyloid precursor protein in Alzheimer's disease and α-synuclein in Parkinson's disease [20]. TDP43 is a DNA/RNA binding protein involved in many cellular functions such as transcription and splicing regulation, mRNA stability and microRNA processing [21,22]. TDP43 is primarily a nuclear protein, but after acute neuronal injury, TDP43 translocates to the cytoplasm and forms stress granules that dissolve after recovery, suggesting that TDP43 shuttles between the nucleus and cytoplasm as a response to injury [23]. In the cortex of ALS and FTD patients, TDP43 is phosphorylated, ubiquitinated and cleaved, forming 20–25 kDa C-terminal insoluble fragments that aggregates in the cytoplasm with loss of the normal TDP43 nuclear staining in a sizable minority of neurons [19]. Over the years, several cell and transgenic animal models of TDP43 have been developed from yeast, zebra fish, drosophila, mice and rats. Although these animal models do not exactly replicate an ALS-like phenotype, most suggested that either the loss of nuclear or cytoplasmic TDP43 function or the gain of new toxic function through the sequestration of essential proteins in the aggregates plays an important role in neuronal degeneration. Recently, TDP43 was also found to play a role in the axonal transport of certain target mRNAs into distal neuronal compartments. ALS-causing mutations in TDP43 impaired axonal trafficking of these target mRNA in Drosophila, in mouse cortical neurons and in ALS patients' motor neurons derived from induced pluripotent stem cells, implicating the loss of this new cytoplasmic function in the pathogenesis of ALS [24].

Table 2
Other genes causing ALS or ALS-like syndromes.

Gene	Locus	Function	Phenotype
ALSIN	2q33	Vesicle trafficking	AR-Juvenile ALS/ALS2/PLS, infantile onset spastic paraplegia
SETX	9q34	RNA/DNA helicase	AD-juvenile ALS/ALS4 AR-ataxia with oculomotor apraxia
VAPB	20q13	Vesicle trafficking	AD-ALS/ALS8, AD-distal SMA
DCTN1	2p13	Axonal transport	AD-ALS, PMA
ANG	14q11	Hypoxia responsive ribonuclease	AD-ALS/ALS9
CHMP2B	3p11	Vesicle trafficking	AD-ALS, ALS-FTD
FIG4	6q21	Vesicle trafficking	AD-ALS/ALS11, PLS, CMT4J
DAO	12q24.11	Unknown	AD-ALS
ATXN2	12q24.12	Unknown	AD-ALS/ALS13, SCA2
hnRNPA2B1	7p15	RNA metabolism	AD-ALS, multisystem proteinopathy
hnRNPA2A1	12q13	RNA metabolism	AD-ALS, multisystem proteinopathy

Shortly after the discovery of TDP43 mutations causing familial ALS, mutations in fused in sarcoma/translocated in liposarcoma (FUS/TLS), another RNA binding protein, were identified as causing about 4% of familial ALS and rare sporadic ALS cases [25,26]. Like TDP43, FUS/TLS is a nuclear protein with many RNA regulation and processing functions. FUS immunoreactive inclusions are also found in sporadic ALS, in non-SOD1 familial ALS and in ALS/dementia tissue [27].

It is presently not clear whether the role that TDP43 and FUS play in motor neuron degeneration is through common or divergent pathways. Prior genome-wide deletion and overexpression screens in yeast failed to show significant overlap in genetic modifiers of TDP43 and FUS toxicity [28]. However, FUS was recently found to bind thousands of human and mouse brain mRNAs, some shared with TDP43 [29]. The depletion of FUS/TLS and TDP43 in human neurons, differentiated from pluripotent stem cells, resulted in the down-regulation of long intron containing TDP43 or FUS targets, some with important neuronal functions, suggesting a common pathway for FUS and TDP43 in motor neuron death [29]. In addition, using computational algorithms to

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