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Mini review

ALS-related misfolded protein management in motor neurons and muscle cells

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ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is the most common form of adult-onset motor neuron disease. It is now considered a multi-factorial and multi-systemic disorder in which alterations of the crosstalk between neuronal and non-neuronal cell types might influence the course of the disease. In this review, we will provide evidence that dysfunctions of affected muscle cells are not only a marginal consequence of denervation associated to motor neurons loss, but a direct consequence of cell muscle toxicity of mutant SOD1. In muscle, the misfolded state of mutant SOD1 protein, unlike in motor neurons, does not appear to have direct effects on protein aggregation and mitochondrial functionality. Muscle cells are, in fact, more capable than motor neurons to handle misfolded proteins, suggesting that mutant SOD1 toxicity in muscle is not mediated by classical mechanisms of intracellular misfolded proteins accumulation. Several recent works indicate that a higher activation of molecular chaperones and degradative systems is present in muscle cells, which for this reason are possibly able to better manage misfolded mutant SOD1. However, several alterations in gene expression and regenerative potential of skeletal muscles have also been reported as a consequence of the expression of mutant SOD1 in muscle. Whether these changes in muscle cells are causative of ALS or a consequence of motor neuron alterations is not yet clear, but their elucidation is very important, since the understanding of the mechanisms involved in mutant SOD1 toxicity in muscle may facilitate the design of treatments directed toward this specific tissue to treat ALS or at least to delay disease progression.

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1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is the most common adult-onset motor neuron disease. The incidence of ALS is 2 individuals per 100,000 while the prevalence is around 6 per 100,000 of the total population. Most people developing ALS are between the ages of 40 and 70, with an average age of 55 at the time of diagnosis. ALS is 20% more common in men than in women. However, with increasing age, the incidence of ALS becomes similar in the two sexes. The hallmark of the disease is the selective death of upper and, above all, lower motor neurons. This results in progressive paralysis, impaired voluntary muscle functionality with atrophy and disability. It spares cognitive ability, sensation, and autonomic nervous functions, and only in a few cases do patients also develop frontotemporal dementia (FTD). Over 140 years after the first description of ALS by Jean-Martin Charcot, the exact cause of the disease has not been clearly delineated. This disorder is lethal, and death occurs for respiratory failure 3–5 years after the symptom's appearance, with great individual variation in the pathology progression rate. Most of the ALS cases occur in sporadic (sALS) forms, while about 10–15% of the cases are familial (fALS) forms, clinically indistinguishable from sALS (Bendotti et al., 2012). Several genes have been linked to fALS. There is strong evidence supporting a pathogenic role for superoxide dismutase 1 (SOD1), transactive response (TAR) DNA Binding Protein (TDP-43), fused in sarcoma/translocated in liposarcoma (FUS/TLS) and C9orf72 genes (Robberecht and Philips, 2013). Other genes possibly implicated in fALS include angiogenin, ataxin-2, optineurin, profilin 1, ubiquilin-2, valosin containing protein (VCP) and VAMP-associated protein type B (VAPB) genes (Robberecht and Philips, 2013). Most of the mutations reported in these genes are point mutations, which are thought to destabilize protein conformation leading to misfolding (Bendotti et al., 2012). The resulting misfolded proteins may then aberrantly accumulate, or may affect

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several cellular functions, e.g. inducing axonal transport alterations, mitochondrial and/or proteasome dysfunctions (Cozzolino et al., 2008; Pasinelli and Brown, 2006). Even the recently identified ALS-associated gene C9orf72 may activate similar pathways (Al-Sarraj et al., 2011; DeJesus-Hernandez et al., 2011; Renton et al., 2011).

2. Protein misfolding and aggregation in ALS

ALS is often considered a proteinopathy, since the generation of misfolded or abnormal proteins with the propensity to aggregate and to accumulate in the cells is a hallmark of both sALS and fALS forms. The first mutated gene identified in fALS two decades ago is that coding for SOD1, a free radical scavenger enzyme present in almost all cells (Rosen et al., 1993). SOD1 mutations account for 20% of fALS forms. Transgenic mice expressing mutant forms of SOD1 develop a motor neuron disease resembling the human ALS. The mutant SOD1 motoneuronal toxic action is not linked to a loss of its dismutase activity, but rather to a gain of a toxic function (Sau et al., 2007). A great number of evidence indicates mutant SOD1 propensity to misfold and aggregate as the primary toxic gain of function. Several other ALS-linked mutated proteins are associated with an abnormal protein folding and the formation of intracellular aggregates (Bendotti et al., 2012).

TDP-43 is ubiquitously expressed in a variety of human tissues, including brain and spinal cord (Wang et al., 2008b; Zhang et al., 2007). TDP-43 contains two RNA-recognition motifs, nuclear localization (NLS) and export (NES) signal motifs (Buratti and Baralle, 2008). It functions as a transcriptional repressor or activator, and participates in mRNA splicing and/or nucleocytoplasmic transport of RNA. Even if TDP43 is mainly expressed in the nucleus (Ayala et al., 2005), in motor neurons a fraction of TDP-43 also localizes in the cytoplasm, where it is probably involved in the promotion of dendritic branching (Wang et al., 2008a). The analysis of brain and spinal cord tissue of ALS patients has demonstrated that besides the full-length protein (43 kDa), a smaller isoform of 28 kDa is also detectable. This protein isoform lacks the C-terminal portion and seems to be associated with ALS pathology (Neumann et al., 2006). Different screening in ALS patients have described a total of 47 missense variants in ALS cases (see for review Lattante et al., 2013). Taking into account the ALS patients screened since 2008 (over 3000), the current prevalence of these mutations is about 3% of fALS and 1.5% of sALS cases (Lattante et al., 2013). TDP-43 is a major component of ubiquitinated protein aggregates found in the cytoplasm and nucleus of both neurons and glial cells in many patients with sALS or frontotemporal dementia. In ALS, TDP-43 is partially excluded from the nuclei of neurons containing cytoplasmic aggregates supporting the hypothesis that ALS pathogenesis may be driven by TDP-43 loss of function in the nucleus (Neumann et al., 2006; Van Deerlin et al., 2008). Whether aggregation of TDP-43 is a primary event in ALS pathogenesis or whether it is a by-product of the disease process remains unclear.

The discovery of mutations in another RNA/DNA binding protein, FUS/TLS rapidly followed the identification of TDP-43 mutations in ALS. Till now, fifty mutations have been reported in 4% of fALS and sALS patients (Lanson and Pandey, 2012). FUS is ubiquitously expressed and is mainly nuclear, with lower levels of cytoplasmic accumulation, and it continuously shuttles between nucleus and cytoplasm (Dormann et al., 2010). FUS nuclear staining was occasionally reduced in neurons bearing cytoplasmic inclusions (Neumann et al., 2009; Vance et al., 2009). FUS inclusions are common in both sALS and fALS, but not in cases caused by SOD1 mutations (Lanson and Pandey, 2012). Furthermore, inclusions are not always ubiquitinated. FUS is a multifunctional protein that might be involved in neuronal plasticity and maintenance of dendritic integrity by transporting messenger RNA to dendritic spines for local translation. Regarding the pathogenic mechanism linked to FUS, it seems conceivably both a toxic gain of function, and a loss of function mechanism by depletion of physiological FUS; co-sequestration of other vital factors may be also possible. However, FUS is recruited into stress granules and this interferes with its nuclear import (Dormann et al., 2010).

Through classical linkage studies a new locus for ALS, the 9p21 that results in an expansion of a hexanucleotide GGGGCC (G4C2) repeat in the C9orf72 gene (DeJesus-Hernandez et al., 2011; Gijselinck et al., 2012; Renton et al., 2011), present in about half of fALS and in approximately 6% of sALS worldwide, has been recently discovered; differences have been reported among geographic areas (e.g., up to 15–20% found in Sweden and Finland sALS cases), but it represents the most common genetic cause of sALS (Rademakers and van Blitterswijk, 2013). In the healthy population, the GGGGCC hexanucleotide repeat comprises between 2–23 units, while in affected FTD or ALS patients the GGGGCC is greater than 30 repeats and up to 500 repeats. The C9orf72 gene is highly conserved across multiple species and codes for a predicted protein of the class of guanine nucleotide exchange factor (GEF) for small Rab GTPases (Levine et al., 2013; Zhang et al., 2012). C9orf72 is transcribed into five splice variants, which generate two alternative cytoplasmic protein isoforms (a and b) of unknown functions (Liu et al., 2013), highly expressed in the central nervous system, and several other tissues in the body. While the pathogenic repeat expansion does not affect the sequence of the protein products, there is an inverse correlation between GGGGCC repeat number and C9orf72 transcription/translation into a protein product (Liu et al., 2013). Both gain and loss of function have been postulated as potential molecular mechanisms of C9orf72 toxicity. Loss of function of the zebrafish or *C. elegans* orthologue of C9orf72 is associated with motor neurons degeneration, suggesting that the disease may be associated to a loss-of-function mechanism (Ciura et al., 2013; Therrien et al., 2013). Moreover, GGGGCC-associated alteration of untranslated RNA sequences are conferred by the expansion, thus there is a possible neurotoxicity associated to DNA and RNA G-quadruplexes formation (Haeusler et al., 2014) or to aberrant RNA metabolism and functions (DeJesus-Hernandez et al., 2011). Characteristic intracellular inclusions of misfolded proteins also define C9orf72 pathology (Ash et al., 2013), explained by the fact that despite the GGGGCC repeats in the 5′-UTR of the C9orf72 mRNA, it can be translated by a rare unconventional mechanism of repeat-associated non-ATG-initiated (RAN) translation. RAN translation occurs in both senses on all three possible open reading frames (ORF), generating highly hydrophobic dipeptides (mainly poly-(Gly-Ala), poly-(Gly-Pro), poly-(Gly-Arg), but also poly-(Ala-Pro) and poly-(Pro-Arg) or translated repetitive dipeptide repeat (DPRs)), which accumulate in neurons of FTD or ALS patients (Ash et al., 2013; Cleary and Ranum, 2013; Lashley et al., 2013; Mori et al., 2013a, 2013b).

Recently, it has been reported the possibility of a dual toxicity mechanism linked to a gain of function of both arginine-rich proteins and repeat RNA that contributes to C9orf72-mediated neurodegeneration (Mizielinska and Isaacs, 2014; Mizielinska et al., 2014).

3. Clearance of aberrant protein in ALS

The neurotoxic potential of aggregated proteins is still largely debated (Aguzzi and O'Connor, 2010), but it is commonly accepted that the oligomeric species of misfolded proteins directly exert neurotoxic effects, whereas macroscopic aggregates could exert a protective role by trapping neurotoxic species into a specific subcellular compartment, until their clearance from the cells (Carra et al., 2012). Nevertheless, formation of aggregated structures could actively contribute to their toxic role in different ways, for example inducing axonal transport alterations or mitochondrial and

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