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Molecular basis of ALS and FTD: implications for translational studies

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are neurodegenerative disorders, related by signs of deteriorating motor and cognitive functions, and short survival. The cause is unknown and no effective treatment currently exists. For ALS, there is only a drug Riluzole and a promising substance arimoclomol. The overlap between ALS and FTD occurs at clinical, genetic, and pathological levels. The majority of ALS cases are sporadic (SALS) and a subset of patients has an inherited form of the disease, familial ALS (FALS), with a common SOD1 mutation, also present in SALS. A few of the mutant genes identified in FALS have also been found in SALS. Recently, hexanucleotide repeat expansions in C9ORF72 gene were found to comprise the largest fraction of ALS- and FTD-causing mutations known to date. TAR DNA-binding protein 43 (TDP-43), encoded by the *TARDBP* gene, has been identified as the pathological protein of FALS, SALS and, less frequently, FTD. The less frequent TDP-43 pathology in other forms of familial FTD has been linked to a range of mutations in GRN, FUS/TLS, rarely VCP, and other genes. TDP-43 and FUS/TLS have striking structural and functional similarities, most likely implicating altered RNA processing as a major event in ALS pathogenesis. The clinical overlap of the symptoms of FTD and ALS is complemented by overlapping neuropathology, with intracellular inclusions composed of microtubule-associated protein tau, TDP-43 and less frequently FUS, or unknown ubiquitinated proteins. Furthermore, new therapeutic approaches continue to emerge, by targeting SOD1, TDP-43 or GRN proteins. This review addresses new advances that are being made in our understanding of the molecular mechanisms of both diseases, which may eventually translate into new treatment options.

KEY WORDS: *dementia; FTLD; FUS/TLS; genetics; motor neuron disease; TDP-43; C9ORF72 nucleotide repeat expansions; TARDBP*

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are related neurodegenerative disorders, which are characterised by decline in motor and cognitive functions, and short survival. ALS is clinically characterised by signs of upper and lower motor neuron degeneration and its progressive spread of signs within a region or to other regions in a time frame, as defined by the revised El Escorial criteria (1). Both diseases have fatal outcome within a few years' time (1). The cause is unknown and no effective treatment currently exists. There is a drug Riluzole, which slightly prolongs survival in patients with ALS (2), and a Phase II/III randomised, placebo-controlled trials of arimoclomol (BRX-345) in familial ALS with SOD-1 mutation (NCT00706147; www.clinicaltrials.gov). The substance arimoclomol may reduce the levels of protein aggregates in motor nerves, a possible cause of ALS, by boosting expression of chaperons Hsp 70 and Hsp 90 which help newly synthesised proteins properly fold (3).

In FTD, which usually clinically presents either behavioural abnormalities or language dysfunction, a considerable number of patients also develop muscle weakness and wasting that is typical for ALS (4, 5) or, vice versa, ALS patients develop impaired executive dysfunction and memory decline (6, 7). The presence of frontotemporal impairment in ALS predicts a shorter survival time (8) and behavioural and functional impairment may decline independently of motor function (9, 10).

The incidence of the ALS disease in Europe is 2.16 per 100,000 (11), while for FTD the incidence is 3.5 per 100,000 (12). Here we present a current understanding of molecular causes of ALS and FTD, in order to understand better pathogenetic mechanisms of both diseases as new design for clinical trials emerges in patients with ALS and FTD.

Genetics

A growing number of ALS-causing genes have been identified recently. These are now under investigation as this could shed some light on the aetiology of the disease. In general, four major ALS-associated genes are superoxide dismutase 1 (*SOD1*), TAR DNA-binding protein (*TARDBP*), fusion in malignant liposarcoma (*FUS*), and the most common chromosome 9 open reading frame 72 (*C9orf72*). Mutations in the tubulin TUBA4A gene have also been

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identified recently to be associated with ALS but also with FTD or mild cognitive impairment (13).

In 2011, the discovery of the hexanucleotide repeat expansion in *C9orf72* gene, as the most frequent genetic cause of ALS and FTD (14, 15), was a breakthrough: it was the first pathogenic mechanism identified to be a genetic link between familial FTD and dominant ALS. In particular, an expanded G_4C_2 repeat in C9orf72, the most common known genetic cause of both diseases, is pathogenic at greater than 30 repeats (16), with most patients having expansions >500 repeats, which is associated with C9ALS/FTD. The characteristic pathological findings in both ALS and FTD are of dipeptide repeat (DPR) proteins. Possible molecular mechanisms of neurodegeneration include loss or gain of the C9orf72 protein function (10, 17). Loss of protein function reflects reduced levels of C9orf72 in patients' brain and functional work revealing a role of C9orf72 protein in endocyclic and autophagic pathways (17). On contrary, the gain of function is supported by the presence of both repeat RNA and protein aggregates in patients' brain. Repeat RNA aggregates, or RNA foci, have been shown to sequester proteins involved in RNA splicing, editing, nuclear export, and nuclear function. An alternative-RNA-mediated mechanism to RNA binding protein is associated with non-TGA (RAN) translation that produces aberrant peptides or dipeptide polymers that form inclusions in patient tissue (18). In combating gain-of-function toxicity, oligonucleotides targeting C9orf72 showed success (19).

Other three major ALS-associated genes, *SOD1*, located on chromosome 21, which encodes the Cu/Zn superoxide dismutase-1(20), TARDBP, and fusion in malignant liposarcoma/translocated in liposarcoma (*FUS/TLS*) have been identified with a growing number of ALS-causing genes. These genes are now under investigation as providing promise for increased understanding of further aetiology of the disease (21). Other genes, such as, angiogenin (*ANG*), the vesicle-associated membrane protein-associated protein B (*VAPB*), senataxin (*SETX)*, and dynactin gene have been also identified in ALS patients. Mutations in the *FUS/TLS* gene, located on chromosome 16, have been identified as a causal gene for ~4 % of FALS (~0.4 % of all ALS) (22, 23) and FTLD (24). As with TDP-43, FUS is a predominantly nuclear protein that is expressed at low levels in the cytoplasm (25). Although the phenotype associated with FUS mutation is variable, most patients predominantly demonstrate loss of lower motor neurons and short disease survival. Mutations in the *SOD1* gene, located on chromosome 21 have been discovered in 1993 (20). Since than more than 120 different SOD1 mutations have been claimed responsible for 20 % of FALS cases (21). In 2008, Gitcho and colleagues (26) and Sreedharan and colleagues (27) independently reported pathogenic mutations in the *TARDBP* gene located on chromosome 1 encoding TAR DNA-binding protein 43 (TDP-43), which cause several neurodegenerative diseases such as FALS, sporadic ALS, and FTLD. Their findings support a direct role of *TARDBP* mutations in neurodegeneration. TDP-43 is a 414-amino acid ubiquitously expressed nuclear protein, which contains two highly conserved RNA-recognition motifs (RRM1 and RRM2), a nuclear localisation signal at the N-terminus, and a glycin-rich region mediating protein-protein interactions at the C-terminus (25). Pathological C-terminal TDP-43 fragments of 25 kDa are ubiquitinated, hyperphosphorylated and accumulated as cellular inclusions in neurons and glial cells (28). To define the link between mutations in TDP-43 and the spectrum of relevant diseases, the TDP-43 mutant transgenic mice models with clinical features of ALS and FTD have been developed, however, with controversial results (29, 30). Although it is impossible to model accurately a clinical feature of human neurodegenerative diseases in mice, mouse models are able to recapitulate the key histopathological and biochemical features of both ALS and FTD, however not being very successful (31). The identification of SOD-1 mutations in FALS and MAPT mutations in FTDP-17 (20) induced the generation of TARDBP mutations in a variety of transgenic mouse models of either wild-type or mutant TDP-43 (32). However, none of these models is perfect. Mutations in GRN also result in TDP-43 neuropathology in humans, but knockout mice show little pathologically phosphorylated TDP-43 (33), thus not being able to elucidate the way GRN mutations leads to TDP-43 pathology in humans. Recently, the first (34) repeat-expansion mouse model and knockout mice was reported (35), but without a phenotypic description. The high prevalence of C9orf72 mutations in familial FTD-ALS suggests that accurate mouse models of this mutation are likely to contribute to drug development process.

Neuropathology of ALS and FTLD

The clinical overlap of symptoms of ALS and FTD is complemented by overlapping neuropathology, such as the deposition of TDP-43 and FUS in patients with both diseases.

The neuropathology of ALS is characterised by the abnormal accumulation of insoluble proteins in the cytoplasm of degenerating motor neurons (28, 36). Until recently, the specific biochemical composition of these neuronal cytoplasmic inclusions (NCIs) was rather unknown, except that the abnormal protein was ubiquitinated. These ubiquitin-immunoreactive (ub-ir) NCIs are most common in lower motor neurons and most often appear as either filamentous skeins or compact round bodies (36).

ALS is accompanied by a wide range of neuropathological features in which both cortical (upper motor neuron) and either brainstem motor neurons or anterior horn cells (lower motor neuron) are involved with the signature lesion: abnormal accumulation of aggregated proteins in cytoplasm of degenerating motor neurons (37). Until recently, limited knowledge about the specific biochemical composition of these neuronal cytoplasmic inclusions existed, except that

the abnormal protein was ubiquitinated. Neuroimmuno pathologic studies of TDP-43 place most sporadic and familial cases of ALS within a spectrum of disorders which include ALS, FTLD, and cases within clinical and neuropathologic features of both ALS and FTLD (38). In pathological conditions, TDP-43 is abnormally accumulated from the nucleus of neurons and glia cells to the NCIs. Biochemical analysis of NCIs indicates that pathologic TDP-43 is ubiquitinated, hyperphosphrylated, and accumulated as abnormal C-terminally truncated form of 25 kDa (28). The neuropathology associated with most FTLD is heterogeneous, characterised by the abnormal accumulation of TDP-43, tau protein or granulin (GRN). More than half of all cases of FTLD have cytoplasmic TDP-43 aggregates; however, it is not clear weather aggregation of TDP-43 is a primary event in ALS pathogenesis or whether it is a by-product of the disease process. Phosphorylated 43kDa TAR DNA-binding protein (pTDP-43) intraneuronal inclusions in ALS are characterised by lesions in the a granular motor cortex, brainstem motor nuclei or cranial nerves V, VII, and X-XII, and spinal cord alpha-motoneurons. In cases with C9orf72 displayed, a greater regional burden of lesions, indicating a more fulminant dissemination of pTDP-43 pathology is present (39). In these cases a cerebellar neuronal cytoplasmic inclusions, ubiquitin positive and TDP-43 negative, are labelled with an anti-polypeptide repeat antibodies (40), Figure 1 and 2.

Innovative perspectives and conclusion

ALS and FTD are both progressive neurodegenerative diseases relatively frequent without a known cause, except for SOD-1. The only drug licensed for symptomatic ALS treatment today is Riluzole and an investigational drug arimoclomol is currently in clinical trials. Major discoveries, however, have been made in the recent past in the genetics, biochemistry, and neuropathology of ALS and FTLD. The hexanucleotide C9orf72 expansion is the most common genetic cause of ALS and FTD, also associated with familial FTD with TDP-43 inclusions. Recently identified C9orf72, TARDBP, and FUS/TLS mutations define a novel class of neurodegenerative diseases called TDP-43-, FUS-proteinopathies. The most frequent C9orf72 hexanucleotide repeat expansions, in which misfolded proteins are novel targets for the development of new diagnostic tests and therapeutics in this spectrum of diseases. Molecular mechanisms that underlie C9orf72-associated ALS and FTD neurodegeneration include loss- or gain of function of the C9orf72 protein. Together with gene (and stem cell) therapies the new discoveries are giving rise to an efficient ALS treatment.

Disclosure

The author declares no competing conflict of interest.

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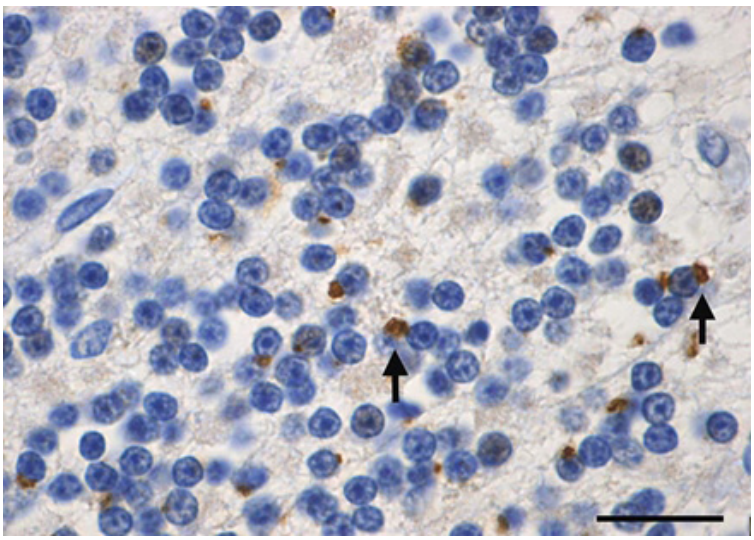

Figure 1 *Pathology in cases of frontotemporal lobar degeneration-motor neuron disease (FTLD-ALS) with C9orf72 expansion. The figure shows ubiquitin-positive, TDP-43-negative neuronal cytoplasmic inclusions (arrows) in the granule cells of the cerebellum (p62 immunohistochemistry). Scale bars: 20 micrometres.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

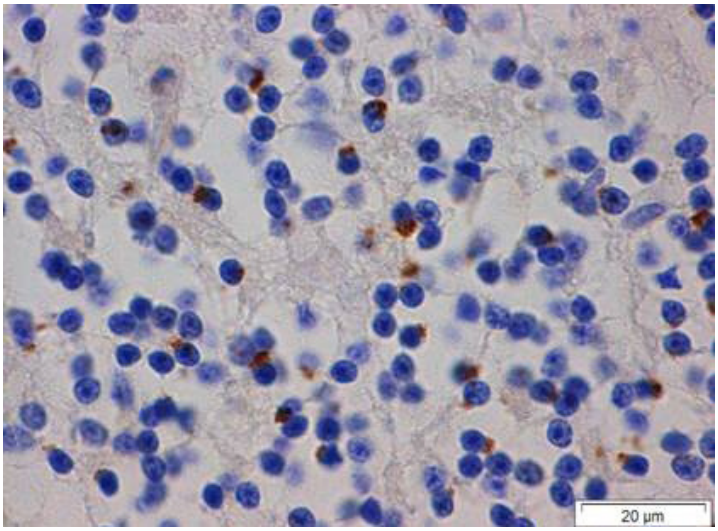

Figure 2 *Pathology in cases of frontotemporal lobar degeneration-motor neuron disease (FTLD-ALS) with C9orf72 expansion. The figure shows the cerebellar inclusions are labelled with anti-dipeptide repeat antibodies (poly-GA immunohistochemistry). Scale bars: 20 micrometres. Courtesy of NJ Cairns, Washington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

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Molekularna osnova ALS-a i FTD-a: implikacije za translacijska istraživanja

Amiotrofična lateralna skleroza (ALS) i frontotemporalna demencija (FTD) neurodegenerativni su poremećaji koji su povezani znakovima pogoršanja motoričkih i kognitivnih funkcija i kratkim vremenom preživljavanja. Uzrok je nepoznat i trenutačno ne postoji učinkovita terapija, tek lijek Riluzol i obećavajuća nova tvar arimoclomol za liječenje ALS-a. Preklapanje između ALS-a i FTD-a odvija se na kliničkoj, genetičkoj i patološkoj razini. Većina slučajeva ALS-a je sporadična (SALS), a podskupina bolesnika ima naslijeđeni oblik bolesti, obiteljski ALS (FALS), sa zajedničkom mutacijom SOD1, koja je prisutna i kod SALS-a. Nekoliko mutiranih gena koji su utvrđeni u FALS-u, pronađeni su i u SALS-u. Nedavno je utvrđeno da ponavljajući sljedovi heksanukleotida u genu C9orf72 sadrže najveću frakciju mutacija koje uzrokuju ALS i FTD, koja je poznata do danas. TAR DNA-povezujući protein 43 (TDP-43), koji kodira gen TARDBP, identificiran je kao patološki protein FALS-a, SALS-a i rjeđe FTD-a. Rjeđa TDP-43 patologija u drugim oblicima obiteljskoga FTD-a vezana je uz niz mutacija u GRN-u, FUS/TLS-u, rijetko VCP-u i drugim genima. TDP-43 i FUS/TLS imaju velike strukturne i funkcionalne sličnosti, koje najvjerojatnije impliciraju izmijenjeno procesiranje RNA kao glavni događaj u patogenezi ALS-a. Kliničko preklapanje simptoma FTD-a i ALS-a nadopunjuje se preklapajućom neuropatologijom, s unutarstaničnim inkluzijama koje se sastoje od proteina tau povezanog s mikrotubulima, TDP-43 i rjeđe FUS-a ili nepoznatih ubikvitiniranih proteina. Nadalje, pojavljuju se novi terapijski pristupi koji ciljaju na SOD1, TDP-43 ili GRN proteine. Ovaj pregledni rad daje uvid u nova saznanja o molekularnim mehanizmima obiju bolesti koja bi se potencijalno mogla pretvoriti u nove mogućnosti liječenja.

KLJUČNE RIJEČI: *bolest motornih neurona; C9orf72; demencija; FTLD; FUS/TLS; genetika; ponavljajući sljedovi nukleotida; TARDBP; TDP-43*