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Fused in sarcoma (FUS): An oncogene goes awry in neurodegeneration

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ABSTRACT

Fused in sarcoma (FUS) is a nuclear DNA/RNA binding protein that regulates different steps of gene expression, including transcription, splicing and mRNA transport. FUS has been implicated in neurodegeneration, since mutations in *FUS* cause familial amyotrophic lateral sclerosis (ALS-FUS) and lead to the cytosolic deposition of FUS in the brain and spinal cord of ALS-FUS patients. Moreover, FUS and two related proteins of the same protein family (FET family) are co-deposited in cytoplasmic inclusions in a subset of patients with frontotemporal lobar degeneration (FTLD-FUS). Cytosolic deposition of these otherwise nuclear proteins most likely causes the loss of a yet unknown essential nuclear function and/or the gain of a toxic function in the cytosol. Here we summarize what is known about the physiological functions of the FET proteins in the nucleus and cytoplasm and review the distinctive pathomechanisms that lead to the deposition of only FUS in ALS-FUS, but all three FET proteins in FTLD-FUS. We suggest that ALS-FUS is caused by a selective dysfunction of FUS, while FTLD-FUS may be caused by a dysfunction of the entire FET family. This article is part of a Special Issue entitled 'RNA and splicing regulation in neurodegeneration'.

Introduction

FUS, also known as Translocated in liposarcoma (TLS), was identified about 20 years ago as a fusion oncogene in human myxoid liposarcomas (Crozat et al., 1993; Rabbitts et al., 1993). In these cancers, an aberrant chromosomal translocation fuses the N-terminus of FUS to a transcription factor, such as CHOP, giving rise to a fusion oncogene (Crozat et al., 1993; Rabbitts et al., 1993). In the following decade, research on FUS was mainly focused on these fusion oncogenes and the mechanisms by which they cause oncogenic transformation (Kovar, 2011). About 15 years later, researchers interested in neurodegeneration suddenly took an interest in FUS, when mutations in *FUS* were reported to cause familial ALS and deposition of FUS in pathological protein inclusions (Kwiatkowski et al., 2009; Vance et al., 2009). Shortly afterwards, FUS inclusions were also found in the brains of a subset of FTLD patients, however in the absence of *FUS* mutations (Munoz et al., 2009; Neumann et al., 2009a, 2009b). Insoluble protein deposits are observed in almost all neurodegenerative disorders, and the disease-characterizing proteinaceous components of these inclusions provided tremendous insights into the underlying disease mechanisms (Haass and Selkoe, 2007).

ALS and FTLD: related yet distinct neurodegenerative disorders

ALS and FTLD are considered to be related disorders with overlapping clinical symptoms, genetics and neuropathology. ALS, also known as Lou Gehrig's disease, is the most frequent motor neuron disease and is caused by degeneration of upper and lower motor neurons (Kiernan et al., 2011). The most prominent clinical symptom is muscle weakening and atrophy throughout the body. Due to progressive muscle wasting, ALS patients experience increasing difficulties in moving, swallowing, speaking and breathing. Eventually patients become paralyzed and usually die from infections or respiratory failure. FTLD is the second most common cause of dementia in the presenile age group (<65 years) and is caused by degeneration of frontal and temporal cortical neurons. Clinically, this syndrome is characterized by progressive alterations in personality, behavior disturbances and/or language problems (Rademakers et al., 2012). Memory is typically well preserved in the initial phase of FTLD, which distinguishes it from Alzheimer's disease (AD). It is well-established that ALS and FTLD form a clinical disease continuum (Lomen-Hoerth et al., 2002; Murphy et al., 2007), since up to 15% of ALS patients meet the clinical criteria of FTLD and 30–50% have subtle cognitive deficits. Likewise, up to 15% of FTLD patients meet the

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clinical criteria for ALS and up to one third have at least minor motor neuron dysfunction.

Recent advances in the neuropathology and genetics of ALS/FTLD have started to reveal the molecular basis for the observed clinical overlap (van Langenhove et al., 2012). In 2006, TAR DNA binding protein of 43 kDa (TDP-43) was identified as the main component of the cytoplasmic protein inclusions in most ALS and FTLD cases (Arai et al., 2006; Neumann et al., 2006). Based on the homology between TDP-43 and FUS, mutations in the latter gene were identified in familial ALS patients (Kwiatkowski et al., 2009; Vance et al., 2009), and the FUS protein was found to be deposited in cytoplasmic inclusions in ALS patients with *FUS* mutations (Kwiatkowski et al., 2009; Vance et al., 2009) as well as in rare cases of TDP-43-negative FTLD (Munoz et al., 2009; Neumann et al., 2009a, 2009b). Thus, ALS and FTLD share the same pathological protein aggregates, which are reflected in a new protein-based classification and nomenclature of FTLD/ALS (Mackenzie et al., 2010a) (Fig. 1). Moreover, in 2011, abnormal expansion of a hexanucleotide repeat (GGGGCC) in the *C9orf72* gene was identified as a common genetic cause of both FTLD and ALS (Dejesus-Hernandez et al., 2011; Gijselinck et al., 2012; Renton et al., 2011). Recently, it has been shown that although the hexanucleotide repeat is located in a non-coding region of *C9orf72*, it is translated into so-called dipeptide repeat (DPR) proteins, leading to widespread neuronal aggregates of DPR proteins in *C9orf72* mutations carriers {Mori, 2013 #1394}{Ash, 2013 #1396}.

Despite these commonalities in the molecular pathology and genetics of ALS and FTLD, some genetic mutations and protein deposits are unique to either FTLD or ALS (Fig. 1). For example mutations in *tau* (*MAPT*) or *progranulin* (*PGRN*) cause a pure FTLD phenotype, whereas mutations in *superoxide dismutase 1* (*SOD1*), *TARDBP* (the gene encoding for TDP-43) or *FUS* usually cause a pure ALS phenotype (Mackenzie et al., 2010b). Moreover, pathological inclusions in ALS-FUS and FTLD-FUS patients both contain FUS, but otherwise have a distinct protein composition (see Table 1) (Dormann et al., 2012; Neumann et al., 2011, 2012), suggesting that they arise by different pathomechanisms. In this review we will focus on the distinct protein deposition in ALS-FUS and FTLD-FUS and discuss the divergent pathomechanisms that underlie these two FUSopathies.

Table 1
Proteins deposited in cytoplasmic inclusions in ALS-FUS and FTLD-FUS.

Deposited protein	ALS-FUS	FTLD-FUS	References
FET family			
FUS	✓	✓	Vance et al. (2009); Kwiatkowski et al. (2009); Neumann et al. (2009a)
Methylated FUS	✓	–	Dormann et al. (2012)
EWS	–	✓	Neumann et al. (2011); Davidson et al. (2012)
TAF15	–	✓	Neumann et al. (2011); Davidson et al. (2012)
Transport receptor			
Transportin 1	–	✓	Brelstaff et al. (2011); Davidson et al. (2012); Neumann et al. (2012); Troakes et al. (in press)
Stress granule proteins			
PABP-1	✓	✓	Dormann et al. (2010); Baumer et al. (2010)
eIF4G	✓	✓	Dormann et al. (2010)
TIA-1	n.d.	✓	Fujita et al. (2008)
Ribosomal protein S6	n.d.	✓	Fujita et al. (2008)
Protein degradation machinery			
Ubiquitin	✓	✓	Neumann et al. (2009a); Seelaar et al. (2010)
p62	✓	✓	Neumann et al. (2009a); Baumer et al. (2010); Seelaar et al. (2010)

Summary of proteins co-deposited along with the disease-signifying FUS protein in cytoplasmic inclusions in ALS-FUS and FTLD-FUS patients. The arginine methylation status of FUS and the co-deposited proteins differ between ALS-FUS and FTLD-FUS, suggesting that the two diseases are caused by distinct pathomechanisms.

FUS: a multifunctional nuclear protein

FUS is a 526 amino acid multidomain protein with an N-terminal transcriptional activation domain, multiple nucleic acid binding domains and a C-terminal nuclear localization signal (NLS) (Fig. 2a). The N-terminal SYGQ-rich domain functions as a potent transcriptional

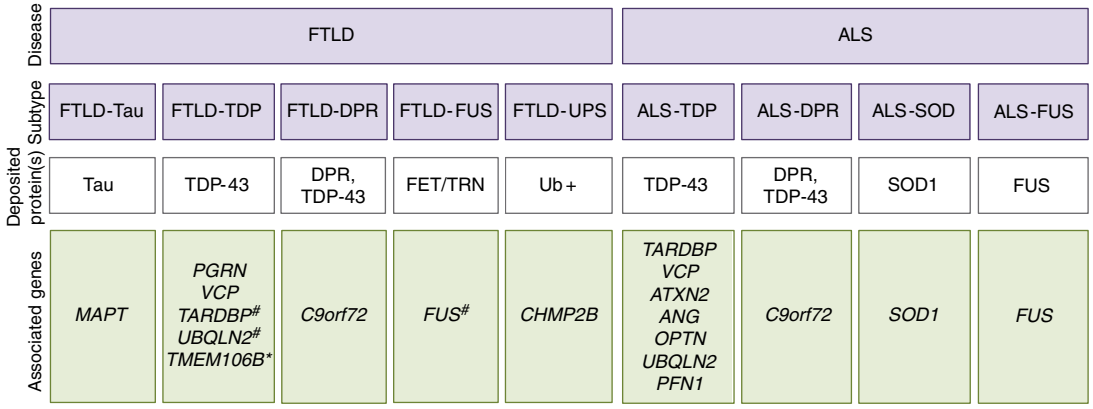

Fig. 1. New molecular classification of FTLD and ALS. FTLD and ALS are divided into different neuropathological subtypes (purple) based on the disease-signifying deposited protein in pathological inclusions (white). Genetic defects associated with a certain subtype are indicated below (green). The most frequent subtypes of FTLD are FTLD-tau and FTLD-TDP (~30–40% each). About 10–20% show deposition of dipeptide repeat proteins (DPR) and TDP-43 (FTLD-DRP) and about 10% show a co-deposition of FET proteins and Transportin (TRN) (FTLD-FUS). Rare cases (<1%) are labeled with antibodies to the ubiquitin-proteasome system (UPS) only (FTLD-UPS). A large proportion of FTLD cases are familial and are frequently linked to mutations in *tau* (*MAPT*), *progranulin* (*PGRN*) and *C9orf72* and more rarely to *valosin-containing protein* (*VCP*). #Mutations in *TARDBP*, *FUS* and *ubiquilin 2* (*UBQLN2*) usually cause ALS and are only rarely found in patients with FTLD. *TMEM106B is a genetic modifier of PGRN expression, since genetic variants in *TMEM106B* protect from or delay the onset of FTLD in individuals with *PGRN* mutations. The most frequent ALS subtype is ALS with TDP-43 pathology (ALS-TDP, ~80%). The vast majority of these cases are sporadic, but some familial cases are caused by mutations in *TARDBP*, *VCP*, *ataxin 2* (*ATXN2*), *angiogenin* (*ANG*), *optineurin* (*OPTN*), *UBQLN2* and *profilin 1* (*PFN1*). About 10–20% of all ALS cases have DPR and TDP-43 pathology and are caused by hexanucleotide repeat expansion in *C9orf72* (ALS-DPR). About 5% of all ALS cases have SOD1 pathology and are caused by mutations in *SOD1* (ALS-SOD), and around 1% have FUS-positive inclusions and are caused by *FUS* mutations (ALS-FUS).

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