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# **REVIEW ARTICLE**

# Cell Death & Disease

# **Open Access**

# Disruption of ER–mitochondria signalling in fronto-temporal dementia and related amyotrophic lateral sclerosis

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### Abstract

Fronto-temporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are two related and incurable neurodegenerative diseases. Features of these diseases include pathological protein inclusions in affected neurons with TAR DNA-binding protein 43 (TDP-43), dipeptide repeat proteins derived from the *C9ORF72* gene, and fused in sarcoma (FUS) representing major constituent proteins in these inclusions. Mutations in *C9ORF72* and the genes encoding TDP-43 and FUS cause familial forms of FTD/ALS which provides evidence to link the pathology and genetics of these diseases. A large number of seemingly disparate physiological functions are damaged in FTD/ALS. However, many of these damaged functions are regulated by signalling between the endoplasmic reticulum and mitochondria, and this has stimulated investigations into the role of endoplasmic reticulum-mitochondria signalling in FTD/ALS disease processes. Here, we review progress on this topic.

## Facts

- ER—mitochondria signalling is disrupted by a number of FTD/ALS-linked insults. These include TDP-43, FUS, mutant SOD1, and loss of the Sigma-1 receptor.
- For TDP-43 and FUS this disruption involves breaking of the VAPB–PTPIP51 ER–mitochondria tethering proteins via activation of GSK3β.

## **Open questions**

- How do TDP-43 and FUS activate GSK3β?
- How does GSK3β regulate the VAPB–PTPIP51 interaction; is it via direct phosphorylation of one or both of these tethering proteins?

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Do other FTD/ALS insults also perturb ER

 mitochondria contacts and signalling via disruption
 of the VAPB–PTPIP51 tethers? In particular, do
 pathogenic dipeptide repeat proteins derived from
 mutant C9ORF72 damage the VAPB–PTPIP51
 tethers and if so, does this involve GSK3β?

- Are ER-mitochondria contacts and the VAPB -PTPIP51 tethers damaged in human disease tissues?
- Is damage to ER-mitochondria signalling and the VAPB-PTPIP51 tethers an early pathogenic feature?
- Can ER-mitochondria signalling and the VAPB -PTPIP51 tethers be targeted pharmacologically?

# Fronto-temporal dementia and amyotrophic lateral sclerosis are related diseases

Fronto-temporal dementia (FTD), also known as fronto-temporal lobar degeneration, is characterised by neurodegeneration and neuronal loss in frontal and anterior temporal brain lobes. This leads to language impairment as well as behavioural and personality changes<sup>1</sup>. FTD is the second most common cause of presenile

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dementia after Alzheimer's disease<sup>2</sup>. Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease. It involves degeneration of lower motor neurons in the brainstem and spinal cord, and of upper motor neurons in the motor cortex which together leads to progressive paralysis and muscle wasting. Survival time from symptom onset is only about 3 years<sup>3</sup>. There is no cure nor even effective disease-modifying treatments for either FTD or ALS.

Although originally classified as different diseases, FTD and ALS are now known to be clinically, genetically and pathologically linked. Approximately 15% of FTD patients display clinical ALS features and up to 15% of ALS patients develop symptoms consistent with a clinical definition of FTD<sup>4,5</sup>. Moreover, recent genetic and pathological studies have confirmed these links<sup>2</sup>.

Both FTD and ALS have strong genetic components, and mutations in a large number of genes are now known to be causative for inherited familial forms of these diseases. Indeed, there are now over 80 genes that have been linked to genetic forms of FTD/ALS and related motor neuron disorders<sup>6</sup> (and see http://alsod.iop.kcl.ac.uk). Some of these mutant genes are more closely linked to either FTD or ALS. For example, mutations in MAPT, which encodes the microtubule-associated protein Tau, and PGRN, which encodes Progranulin, are linked almost exclusively to FTD. Likewise, mutations in SOD1 that encodes the anti-oxidant enzyme Cu/Zn Superoxide dismutase-1 (SOD1) primarily causes ALS. However, mutations in a number of other genes cause dominantly inherited forms of both FTD and ALS. These include TARDP and FUS/TLS that encode the nucleic acid binding proteins TDP-43 and FUS, and C9ORF72 whose encoded protein has been linked to autophagy<sup>2</sup>.

Interestingly, a number of these encoded proteins linked to familial FTD, ALS, and FTD/ALS also form pathologies of these diseases. Thus, Tau and SOD1 inclusions are seen in FTD and ALS respectively while TDP-43 and FUS inclusions form major pathologies in FTD/ALS<sup>2,7</sup>. Mutations in C9ORF72 are causative for large numbers of familial FTD/ALS cases (up to about 30% FTD, 50% ALS and 80% FTD/ALS cases)<sup>8-14</sup>. The C9ORF72 mutations involve expansion of an intronic hexanucleotide GGGGCC repeat and this repeat has been shown to be translated to generate dipeptide repeat proteins (DPRs) by a process termed repeat-associated non-ATG translation<sup>15–17</sup>. These DPRs are either poly- Gly-Pro, Pro-Ala, Gly-Ala, Pro-Arg or Gly-Arg and are deposited in FTD/ ALS cases<sup>15–17</sup>. Some of these DPRs have been shown to be neurotoxic<sup>18</sup>. Interestingly, genetic forms of FTD/ALS caused by the C9ORF72 mutations also often present with TDP-43 pathology and transgenic c9orf72 mice or mice expressing DPRs can develop TDP-43 pathology<sup>7,19-23</sup>. Together, these data suggest a link between DPRs and

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TDP-43. However, while DPR toxicity is the favoured disease mechanism for mutant *C9ORF72*, alternative hypotheses have been proposed. These involve haploinsufficiency and loss of c9orf72 function, and also the formation of RNA foci involving the GGGGCC repeat. These foci may sequester mRNA binding and/or other proteins to disrupt proper expression of heterologous genes<sup>2</sup>. Nevertheless, together these data show that there is some convergence of genetic and pathological phenotypes in FTD/ALS.

# FTD/ALS is characterised by damage to a variety of cellular functions and many of these are regulated by signalling between the ER and mitochondria

A number of physiological functions are perturbed in FTD/ALS<sup>2,3,24,25</sup>. These include damage to organelles and in particular mitochondria and the ER. Indeed, altered bioenergetics and activation of the unfolded protein response (UPR) are major features of FTD/ALS<sup>26-28</sup>. Disruption to Ca<sup>2+</sup> homeostasis and changes to lipid metabolism are also seen in both diseases<sup>29,30</sup>. Axonal transport is a process by which proteins and organelles are transported to and from synapses and neurons are heavily dependent on this process. This is because most proteins are synthesised in cell bodies which then need to be transported to their final destinations including synapses; this transport can involve relatively long distances. Damage to axonal transport is a common feature of FTD/ ALS<sup>31,32</sup>. Defective autophagy is also strongly implicated in FTD/ALS and some mutant genes linked to autophagy such as those encoding optineurin, ubiquilin-2, and SQSTM1/p62 are causative for familial forms of FTD/ ALS<sup>33,34</sup>. Damage to autophagy may contribute to the failure of affected neurons to clear pathological protein aggregates in disease<sup>27,35</sup>. Mitophagy is specialised form of autophagy that involves the clearance of damaged mitochondria<sup>36</sup>. As stated above, damage to mitochondria contributes to FTD/ALS and so perturbations to mitophagy can lead to a failure to eliminate such damaged organelles. Finally, inflammatory responses are seen in FTD/ALS where reactive morphologies to astrocytes and microglia are prominent features along with the presence of inflammatory mediators and cytokines. It is generally believed that such inflammatory responses contribute to the disease process<sup>37,38</sup>. Indeed, anti-inflammatory agents can be protective in transgenic models of ALS<sup>39</sup>.

The biological conundrum is how so many apparently disparate physiological processes are damaged collectively. The therapeutic challenge is selecting which of these different processes to prioritise for drug discovery.

A number of recent studies have investigated signalling between ER and mitochondria in FTD/ALS. ER-mitochondria communication involves close physical contacts



(10–30 nm distance) between the two organelles such that up to approximately 20% of the mitochondrial surface is tightly apposed to ER-membranes<sup>40</sup> (Fig. 1a). These regions of ER are termed mitochondria-associated ER membranes (MAMs)<sup>24,41–45</sup>.

The reason for investigating ER—mitochondria signalling is that many of the damaged cell functions described above that characterise FTD/ALS are regulated by this signalling. Indeed, ER—mitochondria cross-talk is known to impact upon the following.

- ER-mitochondria contacts facilitate phospholipid exchange between the two organelles. This is important as the enzymes that synthesise certain lipids are present in either organelle and so precursor exchange is required for the production of these lipids<sup>24,41-45</sup>. Indeed, MAMs have been shown to be a specialised type of lipid raft (also known as detergent-resistant membranes)<sup>46</sup>.
- ER-mitochondria contacts facilitate Ca<sup>2+</sup> exchange between the two organelles and in particular uptake of Ca<sup>2+</sup> by mitochondria following its release from ER stores via inositol 1,4,5-trisphosphate (IP3) receptors. Such Ca<sup>2+</sup> uptake is required by mitochondria for generating ATP via the tricarboxylic acid cycle since several mitochondrial dehydrogenases are Ca<sup>2+</sup> regulated<sup>47</sup>. However, excessive uptake of Ca<sup>2+</sup> by mitochondria can lead to opening of the mitochondrial permeability transition pore and signalling for apoptosis<sup>24,41-45</sup>.
- ER-mitochondria contacts are required for mitochondrial biogenesis since mitochondrial fission occurs at contact sites and mitochondrial DNA synthesis is regulated by these contacts<sup>48-50</sup>.

- 4. ER-mitochondria contacts regulate intracellular trafficking of both mitochondria and ER since a proportion of ER is co-transported with mitochondria through cells<sup>51</sup>. Moreover, the Ca<sup>2+</sup> sensor mitochondrial Rho GTPase (Miro), which mediates attachment of mitochondria to kinesin-1 motors for transport, localises to ER-mitochondria contact sites<sup>52–55</sup>. In neurons, this trafficking includes axonal transport.
- ER-mitochondria contacts are linked to autophagy<sup>56-61</sup>. Notably, several groups have shown that delivery of Ca<sup>2+</sup> from ER stores to mitochondria at MAM regulates autophagosome formation<sup>61-69</sup>.
- ER-mitochondria contacts are linked to ER stress and the UPR. Several ER protein folding chaperones are present in MAM, disrupting ERmitochondria contacts induces the UPR, and chemical induction of the UPR increases ERmitochondria associations<sup>70-72</sup>. Moreover, vesicle-associated membrane protein associatedprotein B (VAPB), which functions as an ER -mitochondria tethering protein (see below), is strongly linked to ER stress responses<sup>73,74</sup>.
- ER-mitochondria signalling is linked to formation of the inflammasome, a multiprotein complex involved in the initiation of inflammatory processes and in particular, proteolytic maturation of the pro-inflammatory cytokine interleukin-1β. Notably, mitochondriaderived reactive oxygen species induce recruitment of the NOD-like receptor NLRP3, a key component of the inflammasome to MAM<sup>75</sup>.





Thus, damage to ER-mitochondria signalling represents a plausible route for explaining many pathological features of FTD/ALS.

## **ER-mitochondria tethering proteins**

Crucial to understanding both the normal roles of ER -mitochondria signalling and any abnormal role in disease is knowledge of the mechanisms by which regions of ER are recruited to mitochondria. It is now generally accepted that this recruitment involves scaffolding proteins that function to tether the two organelles. A number of tethering proteins have now been identified (Fig. 2). In yeast, proteins of the ER-mitochondria encounter structure (ERMES) function to connect the two organelles but ERMES proteins are yeast specific and no homologues

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have been found in mammals<sup>76</sup>. In mammals, the interaction between ER-located IP3 receptors and the mitochondrial voltage-dependent anion channel (VDAC) via Grp75 was originally proposed as a functional tether but loss of IP3 receptors does not affect ER-mitochondria contacts, which argues against a direct tethering role<sup>40</sup>. Homo- and heterotypic interactions between ER-located mitofusin-2 and mitochondrial mitofusin-1/2 have also been proposed as tethers<sup>77,78</sup> but other groups have disputed these findings (see Filadi et al.<sup>41</sup> for further discussion on this topic).

More recently, binding of the integral ER protein VAPB and the outer mitochondrial membrane protein, protein tyrosine phosphatase interacting protein 51 (PTPIP51) has been shown to tether ER with mitochondria<sup>79,80</sup> (see Fig. 3



for VAPB and PTPIP51 domain structures). VAPB binds to PTPIP51 in many different biochemical assays and modulating VAPB and PTPIP51 expression induces appropriate changes in ER—mitochondria contacts (Fig. 1b). Moreover, manipulating VAPB or PTPIP51 expression alters Ca<sup>2+</sup> exchange between the two organelles which is a physiological readout of ER—mitochondria contacts<sup>79–81</sup>. Others have now replicated and extended these findings<sup>82–86</sup>. Thus, PTPIP51 may also interact with the oxysterolbinding protein-related proteins ORP5 and ORP8 to regulate ER—mitochondria contacts<sup>83</sup>.

Finally, the tail-anchored, PDZ-domain-containing outer mitochondrial membrane protein SYNJ2BP was shown to bind to the ribosome-binding protein 1 and this interaction may act to selectively mediate signalling between mitochondria and rough ER<sup>87</sup>. A number of other proteins have also been linked to ER-mitochondria signalling, including B-cell receptor-associated protein 31 (Bap31) and fission protein 1 (Fis1), FUN14 domain-containing protein 1 (FUNDC1) and calnexin, and phosphofurin acid cluster sorting protein 2 (PACS2), but whether these are bonafide tethering proteins or regulators of ER-mitochondria signalling is unclear<sup>24,41,59,70,88</sup>.

## ER-mitochondria signalling and the VAPB-PTPIP51 tethers are disrupted in FTD/ALS

A number of studies have now investigated how FTD/ ALS insults affect ER-mitochondria signalling. Both TDP-43 and FUS have been shown to disrupt ER-mitochondria interactions and this is associated with decreased binding of VAPB to PTPIP51<sup>80,89</sup>. TDP-43 and FUS also perturb Ca<sup>2+</sup> exchange between ER and mitochondria (which is consistent with a loosening of ER -mitochondria associations) and mitochondrial ATP production which is dependent upon this  $Ca^{2+}$ exchange<sup>80,89</sup>. Moreover, the effects of TDP-43 and FUS on ER-mitochondria contacts and the VAPB-PTPIP51 tethers are linked to activation of glycogen synthase kinase-3 $\beta$  (GSK3 $\beta$ ) (Fig. 4)<sup>80,89</sup>. GSK3 $\beta$  activation disrupts binding of VAPB to PTPIP51 and GSK3ß inhibitors correct FUS induced damage to ER-mitochondria signalling<sup>80,89</sup>. GSK3β is strongly associated with neurodegenerative disease. For example, GSK3ß is activated in induced pluripotent stem cell neurons derived from Alzheimer's disease patients and regulates Aß production, and phosphorylates Tau so that it resembles that seen in dementia<sup>90–92</sup>.

Other studies have linked loss-of-function mutations in the Sigma-1 receptor to familial FTD, ALS and other forms of motor neuron disease<sup>93-99</sup>. The Sigma-1 receptor is an ER protein enriched in MAM that facilitates IP3 receptor-mediated delivery of Ca<sup>2+</sup> from ER stores to mitochondria; as such the Sigma-1 receptor enhances mitochondrial ATP production<sup>100–102</sup>. The Sigma-1 receptor gene resides on chromosome 9 and it has been suggested that the disease-causing mutations in some of these families may involve C9ORF72 (which also resides on chromosome 9) and not the mutant Sigma-1 receptor<sup>103</sup>. However, further mutations in the Sigma-1 receptor have been linked to FTD and motor neuron disease and some of these have formally excluded the involvement of mutant C9ORF7293,94,97,98. Moreover, a variety of experimental studies have provided mechanistic data to link loss of the Sigma-1 receptor to FTD/ALS. Firstly, Sigma-1 receptor knockout mice display features of ALS. Secondly, loss of Sigma-1 receptor exacerbates disease in other transgenic mouse models of ALS and can induce features of FTD/ALS in cellular models. Finally, Sigma-1 receptor agonists have proved beneficial in some models of FTD/ALS<sup>93,94,104-109</sup>. Notably, disease mutant Sigma-1 receptor variants and loss of the Sigma-1 receptor have all been shown to reduce ER-mitochondria contacts and signalling although the mechanisms underlying these effects are not known (Fig. 4)<sup>93,94,98</sup>. Finally, ALS mutant SOD1 has also been shown to reduce ER-mitochondria contacts and signalling, and this is linked to a selective loss of the Sigma-1 receptor from MAM<sup>94</sup>. Thus, four different FTD/ALS-linked genetic insults, TDP-43, FUS, the Sigma-1 receptor and mutant SOD1, have all been shown to disrupt ER-mitochondria contacts and signalling and where investigated (TDP-43

and FUS) this involves breaking of the VAPB–PTPIP51 tethers<sup>80,89,93,94,98</sup>.

Interestingly, mutations in VAPB also cause some forms of ALS and related motor neuron diseases<sup>2,3</sup>. The best characterised mutant involves a proline to serine substitution at amino acid 56 VAPB-P56S<sup>110</sup>. Compared to wild-type, VAPB-P56S displays increased binding to PTPIP51<sup>79</sup>. This is in apparent contrast to other FTD/ALS mutant proteins which reduce ER–mitochondria contacts and the VAPB–PTPIP51 interaction<sup>80,89,93,94,98</sup>. However, VAPB-P56S expression is markedly lower than wild-type and also reduces total VAPB levels<sup>73,111</sup>. Thus, despite its increased binding to PTPIP51, the overall effect of VAPB-P56S may be to reduce ER–mitochondria contacts. Interestingly, reduced levels of VAPB are seen in sporadic ALS patients<sup>112</sup>.

### Is damage to ER-mitochondria signalling and MAM a 'driver' of disease, or a response to damage of other physiological processes?

The above studies that demonstrate damage to ER -mitochondria signalling in FTD/ALS provide a plausible mechanism for explaining many disease features. Thus, primary insults such as TDP-43, FUS, loss of the Sigma-1 receptor and mutant SOD1 may damage ER-mitochondria signalling which in turn perturbs other downstream cellular functions such as Ca<sup>2+</sup> homeostasis, lipid metabolism, axonal transport, mitochondrial function and ER stress. In this scenario, damage to ER-mitochondria signalling represents a driver of the disease process and therapeutic correction of this damage may correct many disease features (Fig. 4). However, an alternative possibility is that alterations to ER-mitochondria signalling in disease represent a physiological response to other damaged features. Clearly, if targeting ER-mitochondria signalling is to be a valid drug target for FTD/ALS, then it is important to properly discriminate between these possibilities.

A number of lines of evidence suggest that disruption to ER-mitochondria signalling is a driver of disease. Firstly, mutations in VAPB cause some familial forms of ALS and these mutants reduce VAPB levels; selective reduction of VAPB is also seen in spinal cords of sporadic ALS patients<sup>110–112</sup>. Such loss of VAPB impairs ER-mitochondria communication<sup>79,80</sup>. Secondly, mutant loss of the Sigma-1 receptor, a key MAM protein also causes familial FTD/ALS and enhancing Sigma-1 receptor function is protective in FTD/ALS models<sup>93,94,98</sup>. Thirdly, overexpression of VAPB to restore ER-mitochondria tethering and signalling<sup>61,80</sup> is protective in mutant SOD1 transgenic mice<sup>113</sup>. Finally, Parkinson's disease-related  $\alpha$ -synuclein disrupts the VAPB-PTPIP51 tethers and overexpression of VAPB to correct this disruption also corrects a-synucleinlinked damage to  $Ca^{2+}$  homeostasis<sup>114</sup>.

Future studies to address these issues further will involve determining whether ER-mitochondria contacts are perturbed in human FTD/ALS tissues and whether any damage is an early disease feature; early pathogenic changes are believed to be the most important. However, such studies are likely to be compromised by the quality of preservation in most post-mortem tissue. Utilising neurons derived from induced pluripotent stem cells carrying FTD/ALS associated mutations provides an alternative route. In a complementary fashion, determining whether damaged ER-mitochondria contacts and signalling are early pathogenic events in transgenic mouse models of FTD/ALS will be of major value. Finally, investigating whether experimental correction of damaged ER-mitochondria contacts corrects other disease features will provide evidence as to whether targeting the ER-mitochondria axis is a valid drug target for FTD/ALS.

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### **Competing interests**

The authors declare that they have no competing financial interests.

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