CellPress

Review

Common Molecular Pathways in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are age-related neurodegenerative diseases in which predominantly motor neurons and cerebral cortex neurons, respectively, are affected. Several novel ALS and FTD disease genes have been recently discovered, pointing toward a few overarching pathways in ALS/FTD pathogenesis. Nevertheless, a precise picture of how various cellular processes cause neuronal death, or how different routes leading to ALS and FTD are functionally connected is just emerging. Moreover, how the most recent milestone findings in the ALS/FTD field might lead to improved diagnosis and treatment is actively being explored. We highlight some of the most exciting recent topics in the field, which could potentially facilitate the identification of further links between the pathogenic ALS/FTD pathways related to autophagy, vesicle trafficking, and RNA metabolism.

Amyotrophic Lateral Sclerosis and Frontotemporal Dementia – Components of a Phenotypic Neurodegenerative Disease Spectrum

Classic **amyotrophic lateral sclerosis (ALS**; see Glossary) and **frontotemporal dementia (FTD**) represent parts of a spectrum of classical neurodegenerative diseases with an incidence of approximately 2–3/100 000 and 3–4/100 000 per year, respectively [1,2]. ALS is a multisystem degenerative condition clinically characterized by the predominant loss of motor neurons and progressive weakness of voluntarily innervated muscles, including muscles of the respiratory apparatus. This leads to almost complete **paresis** after a few years, and death occurs usually from respiratory failure [3]. By contrast, FTD comprises a group of disorders with a principally different clinical phenotype, caused by degeneration of **cortical neurons** and **basal ganglia**. This results not only in cognitive and language deficits but also changes in personality and behavior [4]. FTD is therefore distinct from the 'classical' Alzheimer's disease (AD) type of dementia. It is frequently also termed frontotemporal lobar degeneration to specify that the disease phenotype goes beyond dementia and cognitive defects.

Despite the distinct neurological and psychiatric symptoms, ALS and FTD are tightly linked [4]. Case reports of a co-occurrence of ALS and FTD symptoms in the same patients date back to the 19th century, while the view of ALS in most textbooks after World War II was that of a pure motor neuron disease. The connection between both diseases was gradually rediscovered in the 1980s. In 2006, Neumann *et al.* [5] showed that ALS and FTD comprised cytoplasmic protein deposits consisting of the protein **transactive response DNA-binding**

Trends

The link between amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), described in the 19th century based on clinical observations, has been (re)discovered and confirmed by both neuropathological and genetic findings.

Recent results from human genetics have revealed common functional pathways in ALS/FTD pathogenesis. Protein products of most ALS genes act in pathways regulating autophagy and vesicle trafficking, RNA metabolism, or cytoskeleton dynamics. The functional role of impaired DNA damage repair remains to be shown.

Selective autophagy connects at least four different ALS/FTD genes in one putative functional pathway [*TBK1*, *SQSTM1*/p62, *OPTN*, and chromosome 9 open reading frame 72 (*C9ORF72*)].

RNA granules are regulated by liquid-phase transition involving RNA proteins with disordered, aggregation-prone protein domains. This principle provides a plausible explanation on how RNA-binding protein mutations and protein aggregation could be linked to RNA dysregulation, and subsequently, to neuronal degeneration.

New genetic mouse models based on recently discovered ALS genes are currently being evaluated.

protein 43 kDa (TDP-43). Finally, in 2008, mutations in the *TARDBP* gene [coding for TAR DNA-binding protein 43 (TDP-43)] were identified as causative for both ALS and FTD, sometimes even in the same family or in the same patient [6,7]. The identification of *TARDBP* as a shared ALS/FTD gene was followed by a wave of discoveries continuing until the present day, revealing that mutations in several other genes such as chromosome 9 open reading frame 72 (*C9ORF72*) [8,9], *VCP* [10], or *TBK1* [11] could cause both ALS and FTD. ALS and FTD have thus been increasingly regarded as part of a disease spectrum [4]. These illnesses have been further linked by an overlapping neuropathology, mainly characterized by TDP-43-positive cytoplasmic neuronal inclusions in most ALS, and a large proportion of FTD brains [5]. These discoveries have led to a completely different understanding of ALS and FTD in recent years, with research in these pathologies developing into one of the most active fields of neurological science. Nonetheless, the cellular basis of ALS and FTD remains unknown.

In this review, we summarize some of the current knowledge on the latest development of ALS and FTD and discuss the common downstream mechanisms of known ALS genes and the putative common denominators on how they are functionally linked. We also examine how the **premanifest phase** of ALS and FTD might be characterized, and how otherwise physiological age-related events might contribute to disease manifestation of a pre-existing disease predisposition. Will it be possible to generate more innovative and predictive ALS disease models (*in vitro* and *in vivo*) based on recent genetic and cell biological discoveries? (Box 1 and Outstanding Questions).

Human Genetics and Neuropathology of ALS – Guideposts to Molecular Events

Overall, a positive family history for ALS or FTD is recognized in approximately 5% of all ALS patients [1,12], but a higher contribution of genetic factors can be assumed, given that inheritance may be missed due to incomplete penetrance or because of an **oligogenic** mode

Box 1. The Clinician's Corner

Neuropathology and human genetics have led to the (re)discovery that amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are tightly linked diseases.

Both diseases can be caused by the same mutation in different members of one same family, and comorbidity in a same patient is frequent. This has also led to a new definition of 'familial' ALS/FTD, already assumed when one family member has ALS and another one presents dementia or 'psychosis' (as FTD patients may be misdiagnosed with schizophrenia).

Known ALS and FTD genes explain more than half of familial ALS/FTD cases in Caucasian populations, which can improve genetic counseling, also because it is increasingly recognized that typical phenotypes and disease courses can be assigned to specific genes (e.g., often times representing more aggressive disease courses in chromosome 9 open reading frame 72 (*C9ORF72*) mutation carriers, or in advanced age-onset *TBK1* loss-of-function mutation carriers). According to their frequency, familial patients should usually be screened first for mutations in *C9ORF72* and *SOD1* (superoxide dismutase 1), and then *TBK1*, *TARDBP*/TDP-43 (TAR DNA-binding protein 43 gene/transactive response DNA-binding protein 43 kDa), and *FUS*, until whole-genome sequencing finds its way into clinical routines.

Recent discoveries in the ALS/FTD field have outlined a few overarching cell biological topics that seem to play a central role in disease causation, specifically protein quality control, RNA regulation, and cytoskeletal dynamics.

Novel pathogenic insights will hopefully lead to innovative, ALS/FTD-relevant experimental *in vitro* and *in vivo* paradigms to be used for therapeutic compound screening and evaluation of novel treatment approaches.

As a consequence of ALS genetic research, a first genotype-dependent therapy, which is based on intrathecally delivered improved antisense oligonucleotides, is currently being tested in Phase I clinical trials.

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