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Understanding the influence of altered lipid metabolism on TDP-43 pathology: a protocol for a systematic review and meta-analysis

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Tatiana Langerova[1], Holly Spence[1], Fergal Waldron[1], Jenna Gregory[1]

[1]University of Aberdeen

Jenna Gregory
University of Aberdeen

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Abstract

Background: TDP-43 aggregation is the hallmark pathology seen at post-mortem in the majority of Amyotrophic lateral sclerosis (ALS) cases. Lipid metabolism has been shown to be disrupted in ALS including evidence for systemic metabolic disruptions in ALS patients as well as lipid peroxidation changes noted at the single cell level. The temporal nature of lipid dysregulation during disease course and the role that lipid dysregulation may play in potentiating TDP-43 pathology is unclear.

Aim: The aim of this review is to analyse existing literature assessing the interplay between altered lipid metabolism and TDP-43 pathology in ALS, and investigate possible relationships between the two.

Methods: This protocol describes the strategy for a proposed systematic review and meta-analysis to identify, evaluate and analyse studies examining lipid changes in relation to TDP-43 pathology.

Summary: This review will aid our understanding of ALS-associated pathobiology through detailed analysis of molecular processes underlying the influence of lipids on TDP-43 behaviour in ALS.

Understanding the influence of altered lipid metabolism on TDP-43 pathology: a protocol for a systematic review and meta-analysis

Tatiana Langerova*, Holly Spence, Fergal M. Waldron, Jenna M. Gregory*.

[1]Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK.

*Correspondence to **t.langerova.23@abdn.ac.uk** or **jenna.gregory@abdn.ac.uk**

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Introduction

TAR DNA-binding protein (TDP-43) is a nucleic acid binding protein and a member of the heterogeneous nuclear ribonucleoprotein family. It is encoded by the TARDBP gene on chromosome 1, and is normally located in the nucleus or sometimes in the cytoplasm. TDP-43 plays several roles in cellular function, including RNA metabolism and transport, protein synthesis regulation, gene editing, DNA repair and stress granule formation. Through a combination of post-translational events, including aggregation, cleavage, ubiquitination and hyperphosphorylation, pathological TDP-43 inclusions are formed in the cytoplasm (Majumder et al., 2018; Liao et al., 2022; Tamaki and Urushitani, 2022). ALS is a clinically and genetically heterogeneous condition; however, there are some common pathologies which can be seen across the majority of cases. These include TDP-43 aggregation together with mitochondrial dysfunction, neuroinflammation, oxidative stress, iron imbalance and more (Ilieva et al., 2023; Fu et al., 2023). This review attempts to identify potential convergent pathogenic pathways to understand how to target therapeutics to all patients.

Increasing evidence suggests that lipid metabolism has an essential role in neurodegenerative disease, including Alzheimer's disease (AD), Parkinson's disease (PD), ALS and others. There are multiple symptoms and characteristics

of ALS patients that point toward altered lipid composition. Firstly, patients experience general metabolic changes, such as reduced body weight (irrespective of muscle atrophy and dysphagia), loss of appetite, increased metabolism, and consequential reduction in fat storage (Ngo et al., 2019; Janse Van Mantgem et al., 2020; Fayemendy et al., 2021). Next, abnormalities in energy metabolism have been reported, such as glucose intolerance and insulin resistance (Burg and Van Den Bosch, 2023). Moreover, dyslipidaemia is often reported, however the specific parameters vary in literature. Some studies report increased blood cholesterol levels or increased low-density lipoprotein cholesterol (LDL) (Dorst et al., 2011; Ahmed et al., 2018), but these findings are often contradicted (Yang et al., 2013). Literature seems to be more uniform when reporting changes in triglyceride levels which are usually increased in ALS (Ahmed et al., 2018; Phan et al., 2023). This increase was even suggested to prolong survival (Dorst et al., 2011). ALS animal models mirror these findings, confirming the involvement of hypermetabolism and dyslipidaemia in ALS (Dupuis et al., 2004; Kim et al., 2011), as well as the protective effect of high-fat diet supplementation (Fergani et al., 2007).

Another important factor of lipid abnormalities is the involvement of lipid peroxidation in neurodegeneration. Lipid peroxidation is the formation of oxidised lipids which can result in ferroptosis and inflammation if dysregulated. Lipid peroxidation markers have been found in serum, spinal fluid samples and tissue samples of ALS patients (Shibata et al., 2001; Simpson et al., 2004; Baillet et al., 2010). Again, animal models complement these findings, reporting lipid peroxidation markers in plasma and neuromuscular tissue (Peng et al., 2022; Mukhamedyarov et al., 2023). The role of lipid peroxidation in TDP-43 aggregation remains unclear. In PD, lipid peroxidation is an essential pathological process, directly associated with α-synuclein aggregate toxicity (Angelova et al., 2015; Ludtmann et al., 2018). This review aims to evaluate whether lipid peroxidation has the same effect on TDP-43 aggregation and toxicity, as it is the case with α-synuclein in PD.

Altogether, significant metabolic changes and pathological lipid peroxidation illustrate the relevance of lipids in the pathology of ALS. Despite this, the interplay between lipids and TDP-43 behaviour was not thoroughly investigated in literature. This review will address this research gap and examine available literature about TDP-43's interaction with various lipids. Subsequently, this literature will be evaluated and statistically analysed to produce comprehensive conclusions about the role of lipids in TDP-43 pathology. We hope that this may provide a platform for future targeted therapeutics or even lifestyle advice that could improve the lives of people affected by ALS.

Approach

A systematic review will be performed to identify and evaluate literature assessing the relationship between lipids and TDP-43. Human, animal, cell, and in vitro studies investigating this interplay will be considered. A meta-analysis will be performed to evaluate outcomes that have been reported in 2 or more studies. Outcomes will be compared on forest plots. Human, animal, and cell studies will be compared separately.

Objectives

Intervention studies (PICOS Framework)

Population: Human, animal, cell, and in vitro studies.

Intervention: Pharmacological, genetic, environmental, dietary interventions targeting lipid metabolism.

Comparison: Intervention groups compared to suitable control.

Outcome measures: Including but not limited to treatment efficacy (assessed in 2 or more studies) as determined by:
Primary outcome measures:
(1) Survival (human and animal)

Secondary outcome measures:
(1) Biochemical (e.g. encompassing fat composition and/or TDP-43 pathology)

Study design: Human, animal, cell, and in vitro studies where interventions target lipid metabolism

Non-intervention studies
This study will also summarise non-intervention studies (e.g. hypothesis generating experiments, characterisation studies), for example where an in vitro experiment has characterised TDP-43 aggregation in a lipid rich environment, or human study where lipid composition has been measured in context of TDP-43 burden.

Methods

Searches
Three databases (PubMed, Embase and MEDLINE) will be used (search terms specified below). The searches were performed on December 12, 2023. No restriction on language or publication date was implemented.

Search terms
Pubmed: (("fatty acid" OR lipid OR fat)) AND (TDP*43): n=132
MEDLINE and **Embase** (via Ovid) (("fatty acid" OR lipid OR fat)) n=338
Selected resources to search:
- Ovid MEDLINE(R) ALL 1946 to December 7, 2023
- Embase (1974 to 2023 December 12)

Screening

Firstly, all selected sources will be uploaded to EndNote where duplicates will be filtered out. Next, the SYrF (Systematic Review Facility: syrf.org.uk) will be used for screening. Initially, titles and abstracts will be screened for inclusion criteria, exclusion criteria and quality characteristics specified below. This initial screening and the subsequent data extraction will be done by two independent reviewers. A third reviewer will be employed if reviewer concordance is <0.66. Where data are missing authors may be contacted or calculated based on available information. The outcome of the screening will be presented in a PRISMA diagram.

Inclusion and Exclusion Criteria

Inclusion criteria:

- All studies investigating lipid composition, function, or pathological behaviour in relation to cytoplasmic TDP-43 aggregation.
- Human, animal, cell, and in vitro studies.

Exclusion criteria:
- Narrative reviews, letters, commentaries.
- Non-peer reviewed work: conference abstracts and posters, preprints.

Quality Checklist:

General reporting checklist:
- Peer reviewed publication
- Conflicts of interest statement
- Compliance with animal welfare regulations where appropriate
- Eligibility criteria specified

Experiment reporting checklist:
- Sample size calculation (power calculation)
- Appropriate sample size
- Appropriate control group
- Random group allocation
- Group allocation concealment
- Blinded outcome assessment
- Target engagement assessment

Data and statistics reporting checklist:
- Data extractability: e.g. data reported in article/supplementary data, or requiring manual extraction/inference
- Statistical test appropriateness
- Statistical test reported
- Exact sample numbers reported or reported as a range

Study characteristics to be extracted

Study characteristics that will be extracted will include (1) study ID (first author last name followed by year of publication with numerical suffix if more than one study was published by that name in that year, e.g. Name 2019 (1) and Name 2019 (2)); (2) study title and journal of publication; (3) model/organism; (4) lipid type investigated; (5) means of lipid and TDP-43 pathology measure (6) findings (outcome measure metrics and narrative summary of findings); (7) timing (e.g. developmental or pre-symptomatic); (8) sample size.

Statistical Analysis

Outcome measures will be plotted for each subgroup as detailed above. Each of the studies identified will be included on a forest plot. Given the possibility of variability in methodologies used for these studies a random effects model will

be used for analysis. Cell, animal, and human data will be treated separately. Where possible continuous variables will be compared as standardised mean differences (SMD) and survival as odds ratios. SMD will be compared using Hedges g statistic, to account for bias from small sample sizes. Survival summary measures and SMDs will be reported as odds ratios with 95% confidence intervals. Studies will also be coded into similar groups using qualitative methodologies. Where two or more studies have assessed the same quantitative variable, a quantitative analysis as described above will be conducted. All data will be made available at publication. Heterogeneity will be assessed for all quantitative outcome measures using I2 values, and a funnel plot and Egger's regression test will be used to assess publication bias.

Conflicts of interest

Authors declare no conflicts of interest.

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