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TDP-43 Liquid-Liquid Phase Separation (LLPS) Deficiency Attenuates Amyloid Beta Deposition in the 5XFAD Transgenic Mouse Model of Alzheimer's Disease

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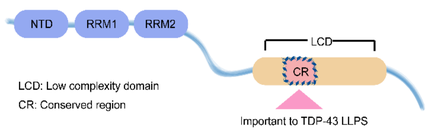
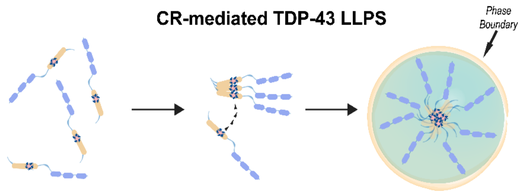
Background

TAR DNA-binding protein 43 (TDP-43) can be found within the cell nucleus in most tissues and is a fundamental component to protein production, as it works to slice and reconfigure mRNA molecules. Recently, TDP-43 inclusions have been identified as a prevalent proteinopathy in the brains of individuals diagnosed with Alzheimer's Disease (AD). However, despite the growing body of evidence demonstrating the important role of TDP-43 in AD pathogenesis, whether and how TDP-43 proteinopathy and other AD pathological hallmarks interact remain largely unknown. Furthermore, TDP-43 has a high propensity to undergo liquid-liquid phase separation (LLPS), a biological process necessary for the condensation of proteins, nucleic acids, and other biomolecules.

TDP 43



CR-mediated TDP-43 LLPS



Purpose of research

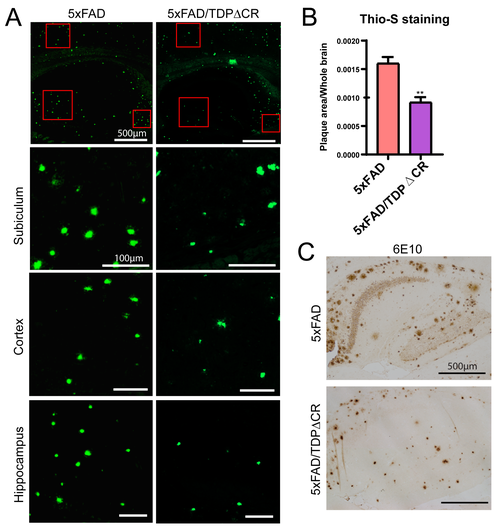
The correlation between TDP-43 LLPS and AD deposition is an intriguing, yet currently unexplored area of interest. The purpose of this study is to investigate whether and how TDP-43 and its phase separation are involved in amyloid deposition in APP transgenic mice for Alzheimer's Disease.

Methods

We crossed our recently generated mice expressing endogenous LLPS-deficient murine TDP-43 with the widely used 5XFAD transgenic mouse model. Different approaches were then performed to assess amyloid deposition and associated neuroinflammation.

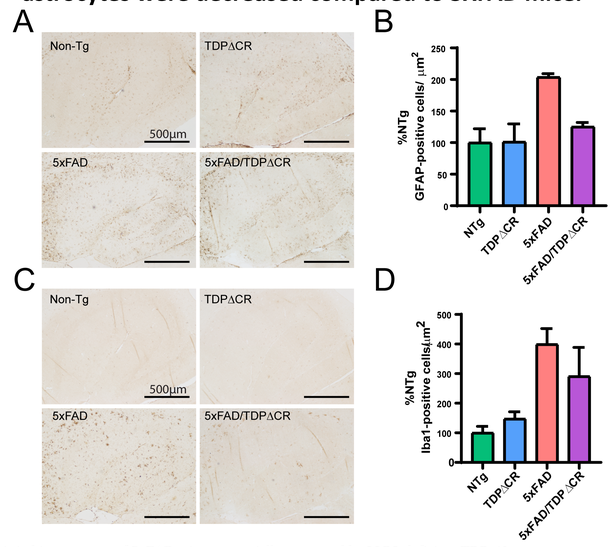
Results

1. The amyloid beta deposition in the brain of 5XFAD transgenic mouse model of Alzheimer's Disease is alleviated by TDP-43 deficiency.



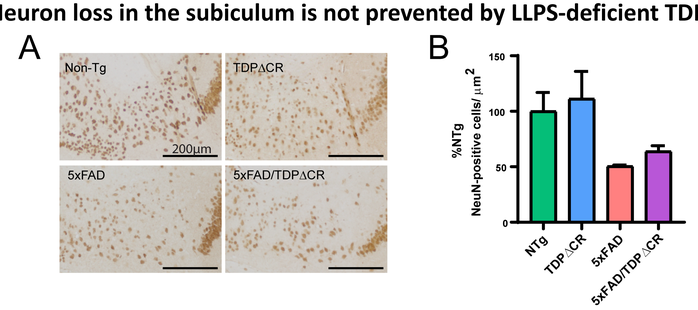
TDP-43 with inhibited liquid-liquid phase separation properties attenuate the amyloid plaques in the brain of 5xFAD mice.
(A) Representative images of dense core plaques (Thio-S) in the subiculum, cortex, and hippocampus of 5xFAD mice and 5xFAD/TDPΔCR mice.
(B) Quantification of plaque load of Thio-S positive plaques in whole brain, presented by the ratio of plaque area to whole brain area, n=2.
(C) Representative images of immunohistochemistry staining of 6E10 at hippocampus of Non-Tg, TDPΔCR, 5xFAD, and 5xFAD/TDPΔCR mice. Data is analyzed with Student's t-test and shown in means ± s.e.m., **p<0.01.

2. In the hippocampus of 5XFAD/TDPΔCR mice, the number of activated microglia and astrocytes were decreased compared to 5XFAD mice.



Microgliosis and astrogliosis in hippocampus of 5xFAD mice are partially prevented by LLPS-deficient TDP-43
(A) Representative images of immunohistochemistry staining of GFAP, and Iba1, respectively, at hippocampus of Non-Tg, TDPΔCR, 5xFAD, and 5xFAD/TDPΔCR mice.
(B) Quantification of immunohistochemistry staining of GFAP and Iba1 at hippocampus area of Non-Tg, TDPΔCR, 5xFAD, and 5xFAD/TDPΔCR mice, presented by the ratio of number of GFAP-positive or Iba1-positive cells to the area of hippocampus, n=2-4. Data is analyzed with One-Way of Variance (ANOVA) followed by Tukey's multiple comparison test, shown in means ± s.e.m., *p<0.05.

3. Neuron loss in the subiculum is not prevented by LLPS-deficient TDP-43.



Phase separation-deficient TDP-43 does not protect the brains of 5xFAD mice from the loss of neurons at subiculum area.
(A) Representative images of immunohistochemistry staining of NeuN at subiculum of Non-Tg, TDPΔCR, 5xFAD, 5xFAD/TDPΔCR mice.
(B) Quantification of immunohistochemistry staining of NeuN at subiculum area of Non-Tg, TDPΔCR, 5xFAD, and 5xFAD/TDPΔCR mice, presented by the ratio of number of NeuN-positive cells to the area of subiculum, n=2-5. Data is analyzed with One-Way of Variance (ANOVA) followed by Tukey's multiple comparison test, shown in means ± s.e.m.

Conclusion

When compared to 5XFAD mice, 5xFAD mice expressing LLPS-deficient TDP-43 showed significantly reduced amyloid deposition throughout the brain. Neuroinflammation, as evaluated by GFAP and Iba1 expression, was also alleviated by LLPS-deficient TDP-43. For the first time, our study demonstrates the likely role TDP-43 LLPS plays in amyloid deposition. And, targeting TDP-43 LLPS may serve as a novel therapeutic approach to Alzheimer's Disease treatment.

Acknowledgements

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