

Lithium Isotopes Differentially Influence
β-amyloid Assembly And Mitochondrial Toxicity

P1-488

Petr Zach², Monica Bucciantini³, Manuela Leri³, Daniele Nosi¹

¹Department of Experimental and Clinical Medicine, University of Florence. Largo Brambilla 3, 50134, Florence, Italy

²Institute of Anatomy, Third Faculty of Medicine, Ruská 87, Prague, 100 00, Czech Republic

³Department of Experimental and Clinical Biomedical Sciences, University of Florence, Viale Morgagni, 50 - 50134 Florence, ITALY

Objective: To investigate whether the nuclear properties of lithium isotopes (⁶Li and ⁷Li) differentially modulate Aβ aggregation, aggregate structure and downstream pathogenic mechanisms.

Aggregation and Structure: ⁶Li delays Aβ aggregation and promotes structurally heterogeneous aggregate populations, whereas ⁷Li accelerates nucleation and favors the formation of highly ordered fibrillar assemblies.

Neuroprotection: Both lithium isotopes reduce Aβ-induced cytotoxicity and oxidative stress in SH-SY5Y cells, indicating the generation of aggregate species with reduced neurotoxic potential.

Isotope-Dependent Cellular Interaction: ⁶Li-derived aggregates exhibit enhanced cellular association and intracellular trafficking, suggesting increased accessibility to proteostatic clearance pathways. In contrast, ⁷Li-derived aggregates remain predominantly extracellular.

Proposed Mechanism: Lithium isotopes remodel the structural landscape of Aβ aggregates, leading to distinct pattern of cellular interactions and biological outcomes. These findings reveal a previously unrecognized role of isotope-specific nuclear properties in amyloid assembly, cellular handling of aggregates, and proteotoxicity.

INTRODUCTION

METHODS

RESULTS

CONCLUSIONS

REFERENCES

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and is characterized by the accumulation of β-amyloid (Aβ) aggregates, oxidative stress, synaptic dysfunction, and progressive neuronal loss.

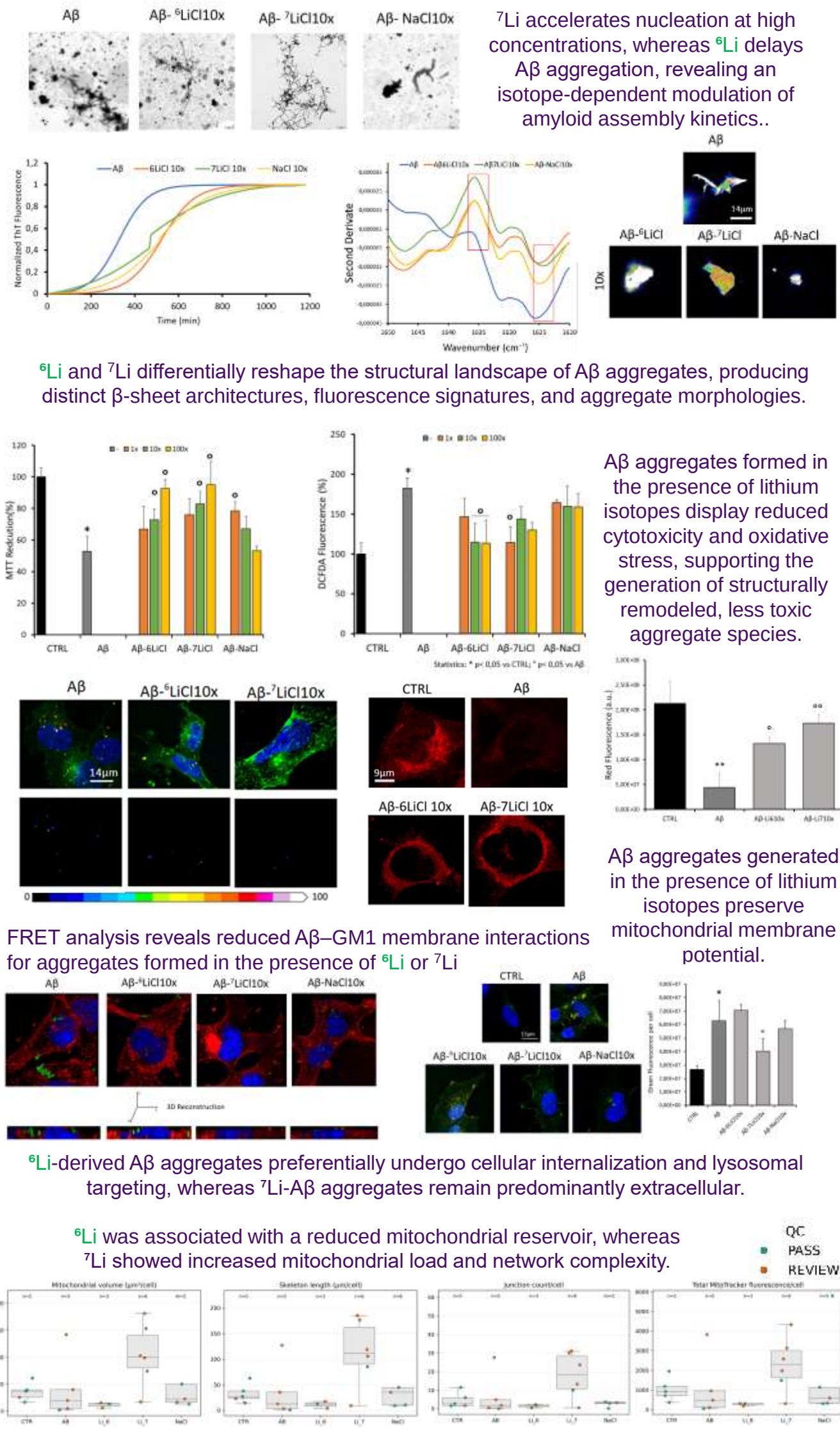
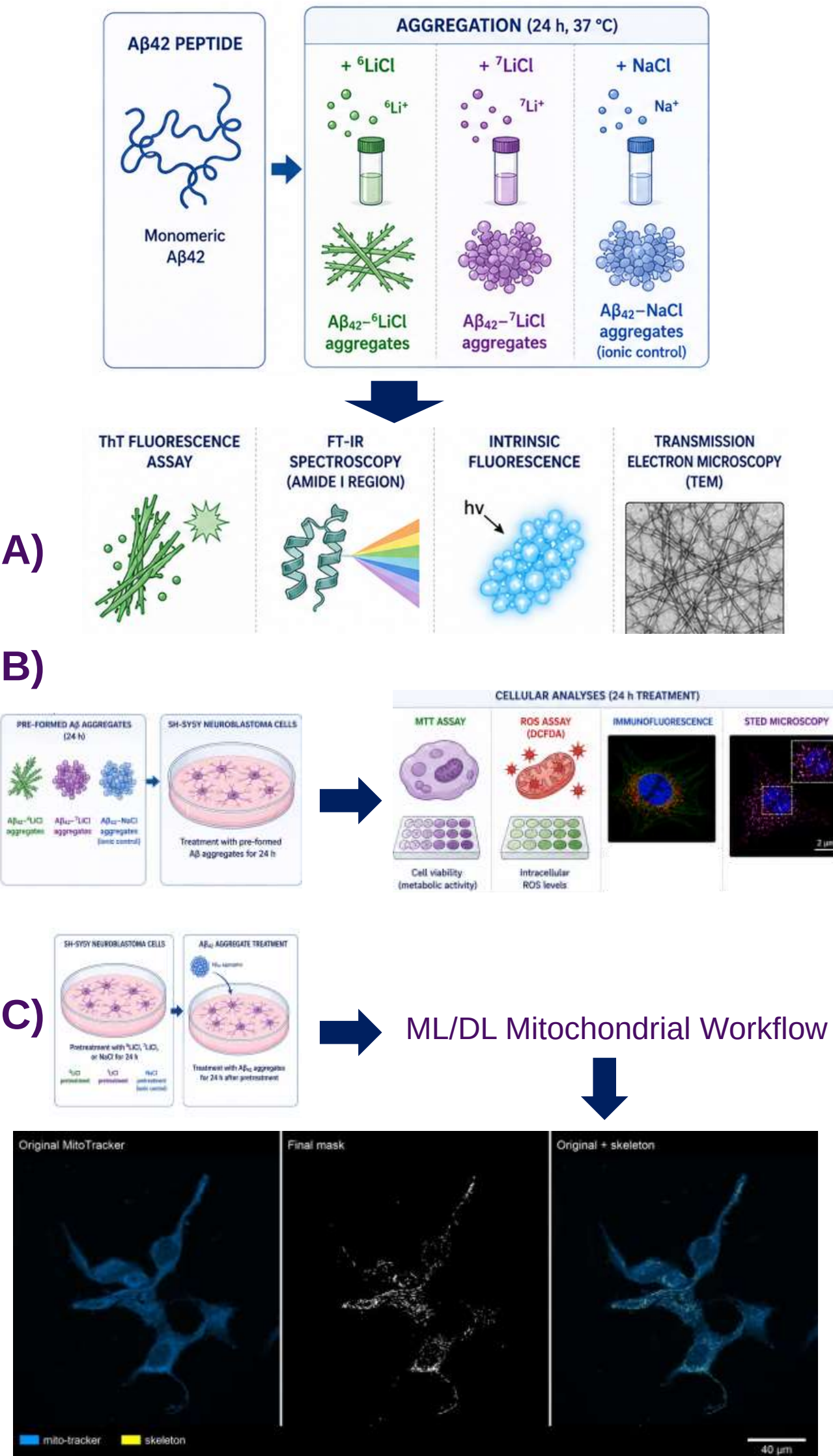
Despite decades of research, effective disease-modifying therapies remain elusive. Lithium has emerged as a promising candidate for AD treatment due to its neuroprotective, anti-inflammatory, and antioxidant properties.

Several studies have shown that lithium can reduce Aβ production and aggregation, attenuate tau hyperphosphorylation through GSK-3β inhibition, improve mitochondrial function, and enhance neuronal survival. Epidemiological and preclinical evidence further suggests that chronic lithium exposure may be associated with a reduced risk of dementia and slower cognitive decline.

Naturally occurring lithium consists of two stable isotopes, Lithium-6 (⁶Li) and Lithium-7 (⁷Li), which differ in atomic mass and nuclear spin.

While lithium's biological activity has traditionally been attributed to its chemical properties, emerging evidence suggests that isotope-specific nuclear effects may influence molecular interactions and cellular responses.

Objective: To investigate whether ⁶Li and ⁷Li differentially modulate Aβ aggregation, aggregate structure, cellular interactions, and mitochondrial function, thereby uncovering a potential isotope-dependent regulation of amyloid pathogenicity and neurotoxicity.



- ⁶Li and ⁷Li differentially modulate Aβ aggregation, generating structurally distinct aggregate populations characterized by specific biophysical signatures and morphologies.
- Despite promoting β-sheet-rich assemblies, lithium-modified Aβ aggregates display reduced cytotoxicity and oxidative stress, indicating the formation of less toxic aggregate states.
- Enhanced cellular uptake and lysosomal targeting of ⁶Li-Aβ aggregates reveal isotope-dependent effects on aggregate trafficking and clearance.
- ⁶Li and ⁷Li pre-treatment elicit divergent mitochondrial responses in Aβ-exposed SH-SY5Y neuroblastoma cell line, with ⁶Li associated with a reduced mitochondrial reservoir and ⁷Li with increased mitochondrial network load and complexity.

⁶LiCl and ⁷LiCl differentially modulate Aβ aggregation, generating structurally distinct aggregate populations characterized by specific biophysical signatures and morphologies.

Despite promoting β-sheet-rich assemblies, lithium-modified Aβ aggregates display **reduced cytotoxicity and oxidative stress**, indicating the formation of less toxic aggregate states.

Lithium-induced structural remodeling alters Aβ interactions with cellular membranes and intracellular trafficking, leading to **isotope-dependent biological responses**.

Overall, the effects of lithium on Aβ are **isotope-dependent**, highlighting a previously unrecognized role of nuclear isotope properties in modulating amyloid assembly and proteotoxicity.

doi:10.3389/fphys.2023.1200119

doi:10.1016/j.neulet.2021.136044

doi:10.3233/JAD-230568

doi:10.3389/fphar.2024.1408462

doi:10.3389/fpsy.2025.1664092

doi:10.18388/abp.2020_5493

doi:10.1007/s12011-014-9949-z

CONTACT

University of Florence

Charles University

ALZHEIMER'S ASSOCIATION

AAIC 26