

Nanoscale Chirality Regulates Amyloid-β42 Proteostasis by Restoring Autophagy–Lysosomal Function

#4057

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Nanoscale chirality restores Aβ42 proteostasis by simultaneously suppressing amyloid fibrillation and rescuing autophagy–lysosomal dysfunction without pharmacological intervention.

INTRODUCION

Amyloid-β42 (Aβ42) aggregation and proteostasis failure are central pathological features of Alzheimer’s disease (AD). Current therapeutic strategies primarily target Aβ production or clearance through pharmacological approaches. We investigated whether nanoscale material chirality, independent of biochemical activity, can regulate amyloid assembly and neuronal proteostasis.

METHODS

Topology-defined chiral mesoporous silica nanofibers were synthesized without drug loading or surface functionalization. Their effects on Aβ42 aggregation were evaluated by ThT kinetics and electron microscopy. Neuronal responses were assessed in SH-SY5Y cells exposed to Aβ42 aggregates formed in the presence or absence of chiral nanofibers. Mitochondrial function and autophagy–lysosomal flux were examined using imaging, biochemical assays, and ultrastructural analyses.

RESULTS

- 1. Chiral nanofibers significantly inhibited Aβ42 fibrillation and redirected aggregation toward less toxic non-fibrillar species, resulting in reduced intracellular accumulation and neurotoxicity.
- 2. Chiral nanofibers reduced cell apoptosis, alleviated oxidative stress, and restored Aβ42-impaired autophagy–lysosomal flux, thereby maintaining neuronal proteostasis.

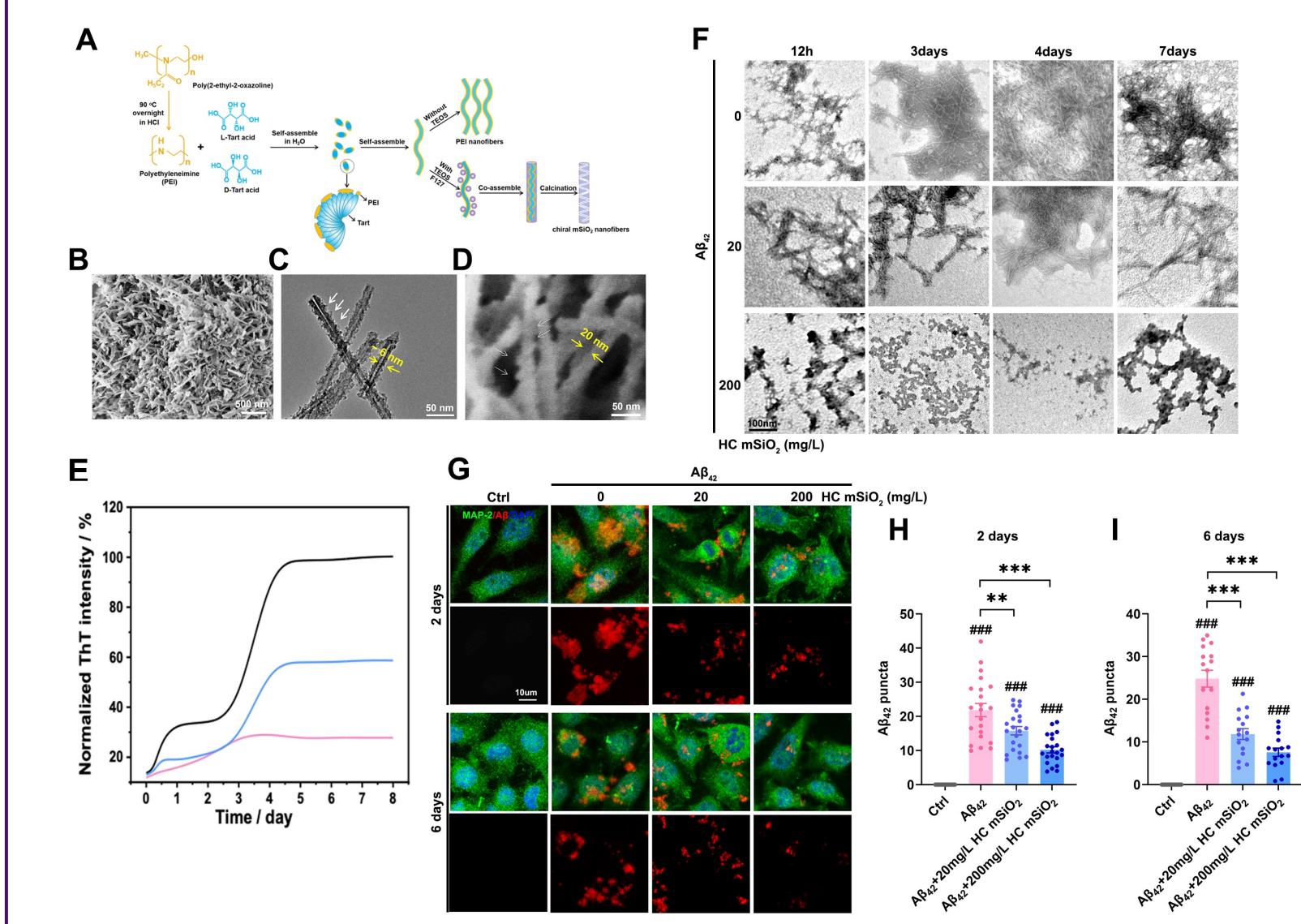


Figure 1: L-HC mSiO₂ nanofibers mitigated Aβ42 fibrillation and insoluble Aβ42 aggregations in SH-SY5Y cells.

(A–D) Schematic diagram of the synthesis route for hemp rope structured chiral mesoporous silica nanofibers (L-HC mSiO₂ nanofibers, A). Optical and transmission electron microscopy images of the linear PEI (B–D). (E) Thioflavin T (ThT) fluorescence assay. (F) TEM images of Aβ42 in the absence and presence of varying concentrations of L-HC mSiO₂ nanofibers. Scale bar = 100 nm. (G–I) The insoluble Aβ42 aggregations in SH-SY5Y cells induced by Aβ mixtures with or without L-HC mSiO₂ nanofibers. ###p<0.001 vs Ctrl group; **p<0.01, ***p<0.001 vs Aβ42 group.

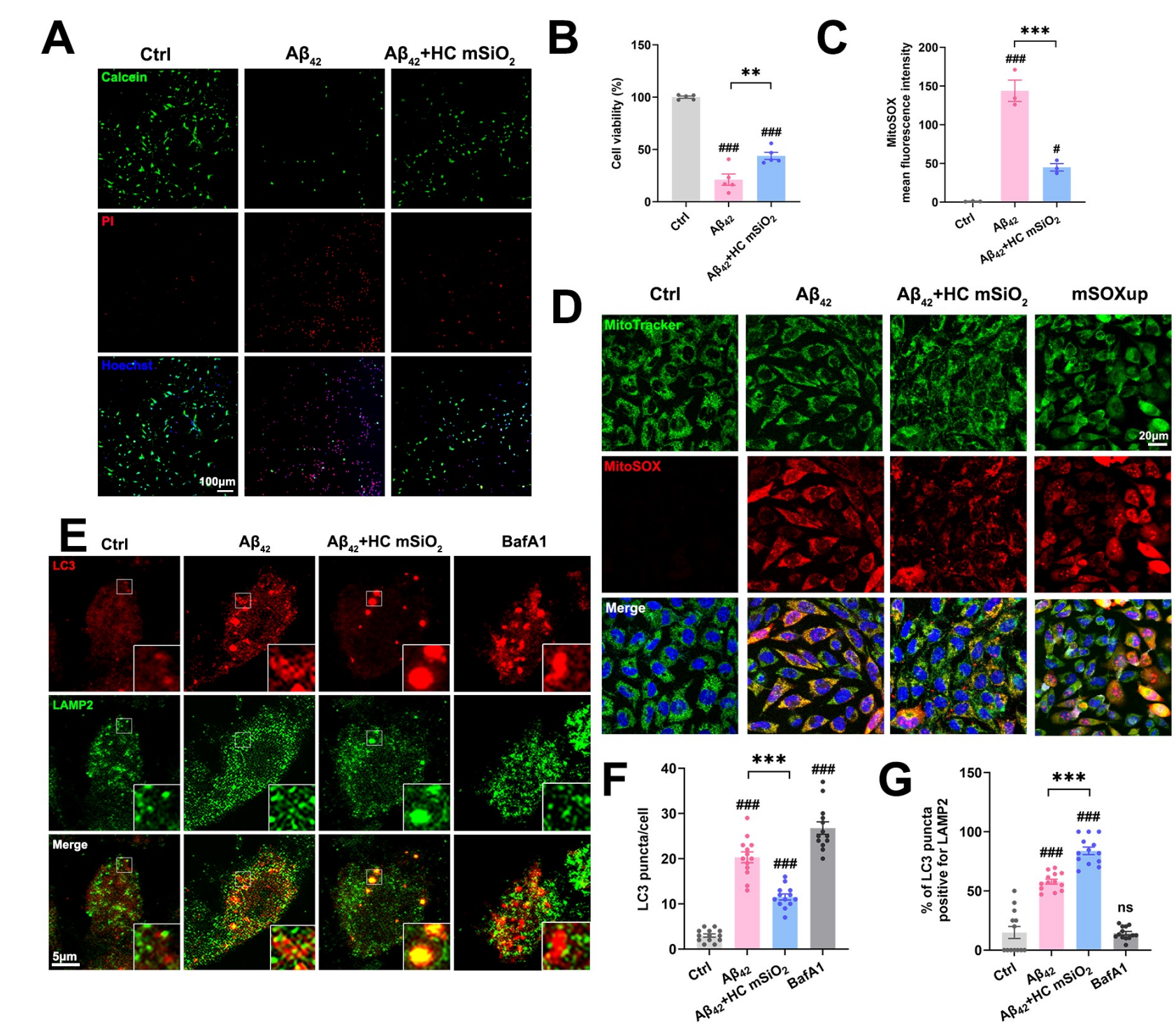


Figure 2: L-HC mSiO₂ nanofibers mitigated cell injury, mitochondrial impairment and autophagy flux in SH-SY5Y cells

(A, B) Calcein/PI staining in SH-SY5Y cells 48h after treatment with fibrillated Aβ42 solutions with or without 20mg/L L-HC mSiO₂ nanofibers. Scale bar: 100 μm. (C, D) Mitochondrial ROS levels from different groups. (E–G) Representative immunofluorescence images and quantification of the number of autophagosomes (red vesicles) and autolysosomes (red vesicles colocalized with green vesicles). Bafilomycin A1 (BafA1) treatment was used as the positive control. #P<0.05, ###P<0.001 vs Ctrl group. **p<0.01, ***p<0.001 vs Aβ42 group

CONCLUSION

Nanoscale chirality functions as a physical regulator of proteostasis, coupling amyloid remodeling with restoration of autophagy–lysosomal clearance.

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