

Lead Exposure Exacerbates Amyloid-β-induced Lysosomal Dysfunction Via GSK-3-TFEB Signaling In Human Neuronal Cells

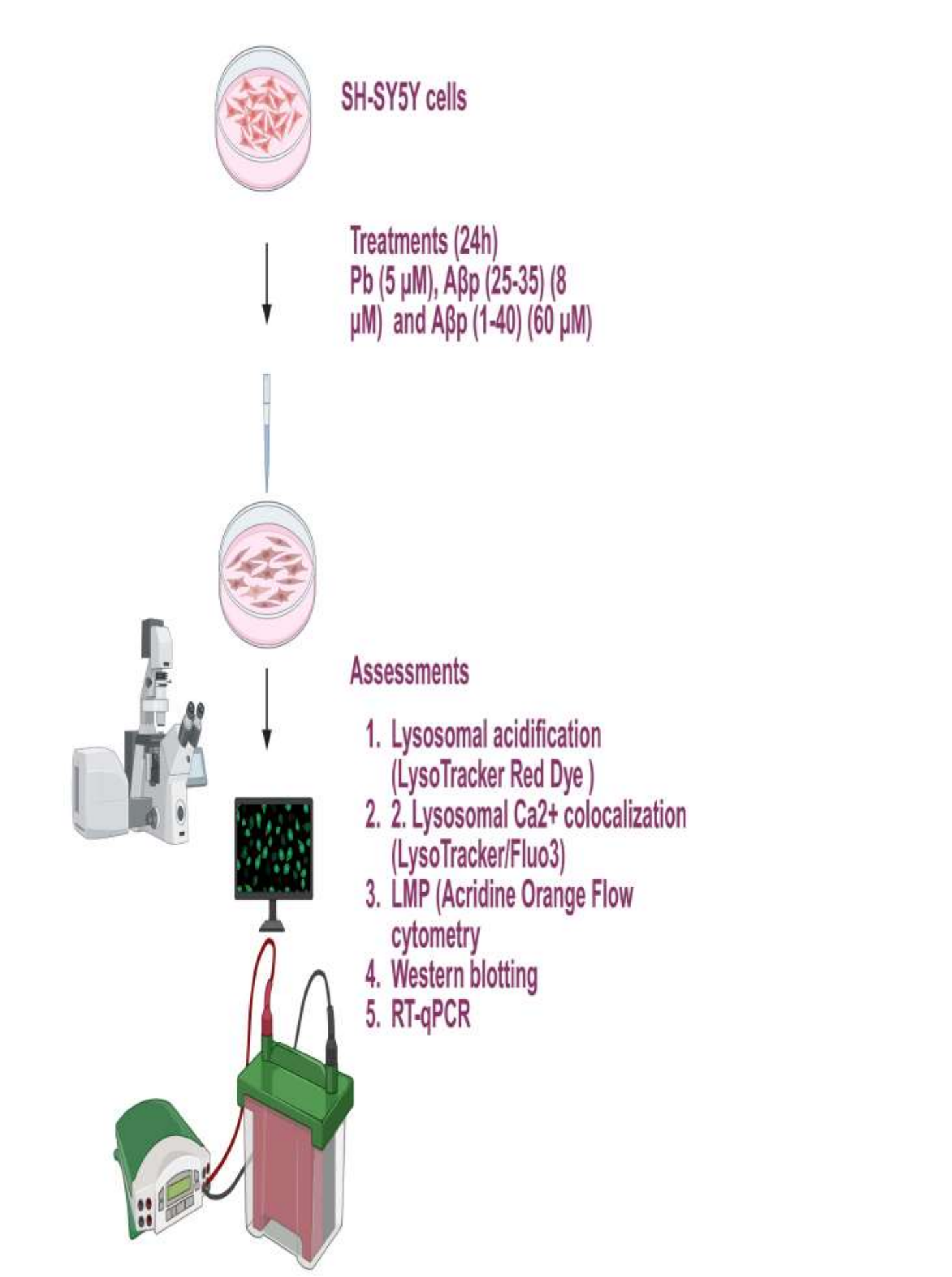
Shrabani Das, Suresh Challa. Poster Code: aaic2026.1490261
Cell Biology Division, ICMR-National Institute of Nutrition, Hyderabad, India.

KEY TAKEAWAY: Combined exposure to Lead (Pb) and Aβ peptides (25-35 and 1-40) profoundly impairs lysosomal acidification, Ca²⁺ homeostasis and membrane integrity through suppression of TFEB-CLEAR signalling, highlighting a molecular mechanism by which environmental Pb exposure may accelerate Alzheimer’s disease-related pathology

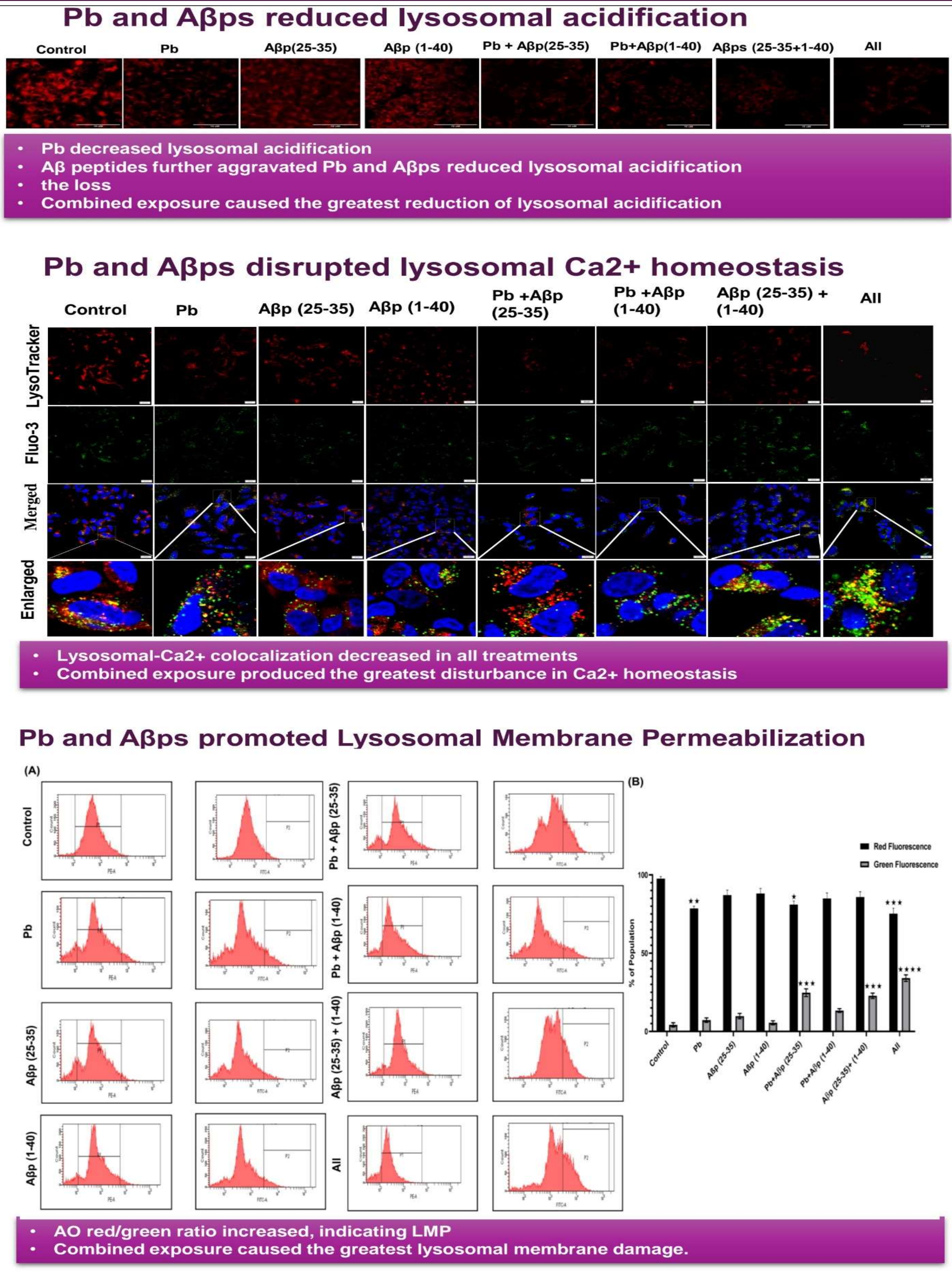
INTRODUCTION

- Pb is a pervasive environmental neurotoxicant.
 - Aβ peptides disrupt neuronal proteostasis and promote AD pathology.
 - Lysosomal dysfunction is an early and critical event in AD
- Hypothesis
- Pb potentiates Aβ-induced lysosomal dysfunction, leading to failure of lysosomal homeostasis, and promoting AD pathogenesis.

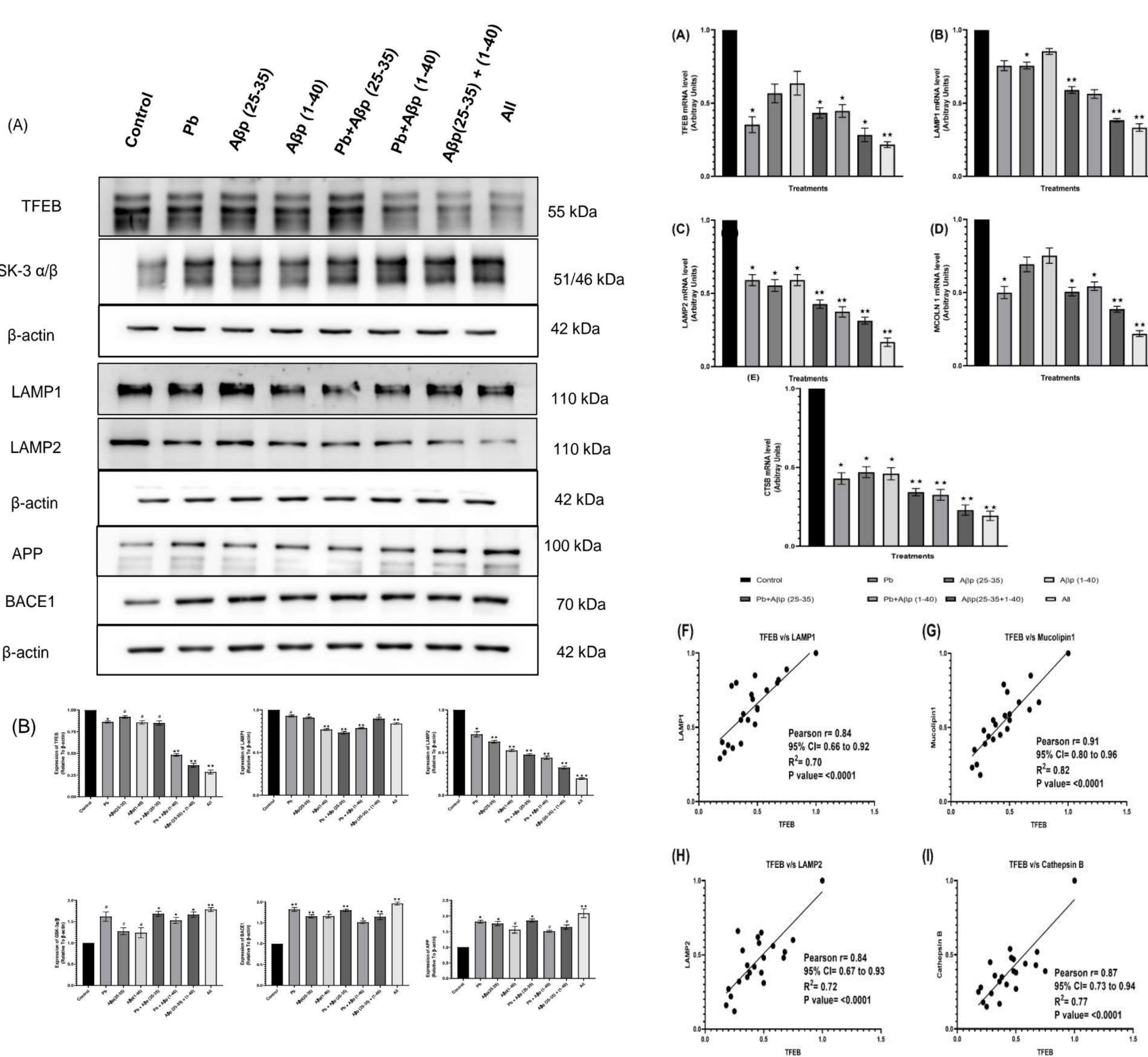
METHODS



RESULTS

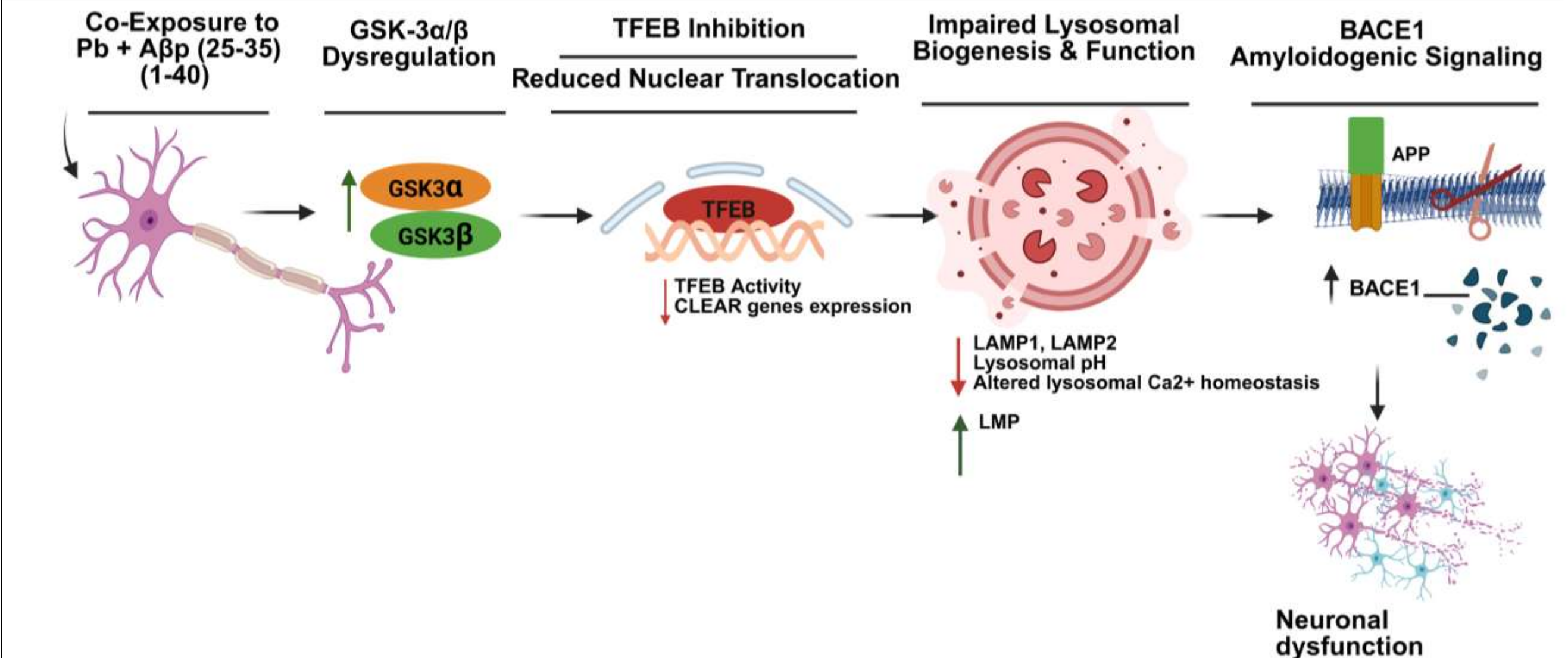


Pb and Aβ suppressed TFEB-CLEAR signalling and altered AD-related proteins



- Pb + Aβ decreased GSK-3 α/β and TFEB levels
- LAMP1/2 decreased, while BACE1 and APP increased
- CLEAR genes (TFEB, Mucolipin1, LAMP1, LAMP2, CTSB) were downregulated
- Data are Mean ± SEM (n=3). *p< 0.05, **p<0.01, ***p<0.001

Proposed Mechanism



CONCLUSIONS

- Pb potentiates Aβ peptide toxicity, causing profound lysosomal dysfunction
- Combined exposure impairs lysosomal acidification, Ca²⁺ homeostasis, and membrane integrity
- Suppression of TFEB-CLEAR signaling may be a key mechanism linking environmental Pb exposure to AD pathogenesis.

REFERENCES

Ayyalasomayajula, Neelima, Madhuri Bandaru, Prasanna Kumar Dixit, Rajanna Ajumera, Chellu S. Chetty, and Suresh Challa. 2020. 'Inactivation of GAP-43 due to the Depletion of Cellular Calcium by the Pb and Amyloid Peptide Induced Toxicity: An in Vitro Approach'. *Chemico-Biological Interactions* 316 (January): 108927. <https://doi.org/10.1016/j.cb.2019.108927>.

Bandaru, Lakshmi Jaya Madhuri, Neelima Ayyalasomayajula, Lokesh Murumulla, Prasanna Kumar Dixit, and Suresh Challa. 2022. 'Defective Mitophagy and Induction of Apoptosis by the Depleted Levels of PINK1 and Parkin in Pb and β-Amyloid Peptide Induced Toxicity'. *Toxicology Mechanisms and Methods* 32 (8): 559–68. <https://doi.org/10.1080/15378516.2022.2054749>.

Bandaru, Lakshmi Jaya Madhuri, Lokesh Murumulla, Bindu Lasya C, Krishna Prasad D., and Suresh Challa. 2023. 'Exposure of Combination of Environmental Pollutant, Lead (Pb) and β-Amyloid Peptides Causes Mitochondrial Dysfunction and Oxidative Stress in Human Neuronal Cells'. *Journal of Bioenergetics and Biomembranes* 55 (1): 79–89. <https://doi.org/10.1007/s10863-023-09956-9>.

Carling, Philippa J., Brent J. Ryan, William McGuinness, et al. 2023. 'Multiparameter Phenotypic Screening for Endogenous TFEB and TFEB3 Translocation Identifies Novel Chemical Series Modulating Lysosome Function'. *Autophagy* 19 (2): 692–705. <https://doi.org/10.1080/15548827.2022.2095834>.