Scientific Letters

Poster Communication 53

Unraveling the role of telomeres and telomerases in the response to neurotoxicants

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Abstract

Background: Telomeres are repetitive DNA sequences that protect chromosome ends and whose length is maintained by telomerase activity [1]. While telomere dynamics are well characterized in proliferating cells, their role in post-mitotic cells such as neurons remains poorly explored [2]. Particularly, the impact of telomere attrition or telomerase dysfunction on the cellular response to neurotoxicants is largely unknown. **Objective:** We aimed to investigate whether telomere shortening increases the susceptibility of neuronal cells to the toxic effects of common environmental neurotoxicants (i.e., HgCl2, acetaldehyde). **Methods:** The effects of $HgCl_2$ (0-100µM) and acetaldehyde (0-10mM) on the metabolic activity (MTT reduction assay) and lysosomal integrity (Neutral Red uptake) of SH-SY5Y human neuroblastoma cells were assessed by determining IC10 and IC50 for each neurotoxicant. These assessments were performed either 24h after exposure to the neurotoxicants or following a 72h pre-treatment with 1µM XAV939, a tankyrase-1 inhibitor that limits telomerase access to telomeres, promoting telomere shortening [3]. Relative telomere length in XAV939-treated treated alone and in combination with biologically relevant, subtoxic concentrations of $HgCl_2$ (10 and 25 µM) or acetaldehyde (0.1 and 5 mM) was measured using quantitative real-time PCR. **Results:** Our findings revealed that $HgCl_2$ and acetaldehyde reduced the metabolic activity and lysosomal integrity of SH-SY5Y cells in a concentration-dependent manner. Also, $HgCl_2$ shifted the IC10 from 26 to 15 µM for metabolic activity and from 21 to 6 µM for lysosomal integrity in XAV939-treated cells, compared to cells not exposed to XAV939, suggesting that shortened telomeres may have increased the cells' susceptibility to $HgCl_2$. In turn, XAV939 pretreatment did not alter the impact of acetaldehyde on those parameters. Notably, XAV939-induced telomere shortening was confirmed by qPCR analysis. Interestingly, our data showed that 100µM acetaldehyde and 10 µM $HgCl_2$ reduced the cells' telomere length to 45% and 77% of control levels, respectively, at the same time point. **Conclusions:** Our preliminary findings suggest that telomere shortening increases SH-SY5Y cells vulnerability to the toxic effects of $HgCl_2$, evidencing a possible involvement of telomere-related mechanisms in the response to neurotoxicants. However, further research is required to confirm the importance of such mechanisms in neurotoxicity-related responses.

Keywords: Telomere shortening; Neurotoxicity; Telomerase inhibition

Funding

This work was funded within the scope of the project ALCOHOLAGEING (Operation No. 15705; COMPETE2030-FEDER-00680600), funded by the European Regional Development Fund (ERDF) through the Innovation and Digital Transition Programme (COMPETE 2030) and by National Funds from Fundação para a Ciência e Tecnologia, I.P. (FCT) (FCT) under Call No. MPr-2023-12. The work was further supported by FCT, in the scope of the project UID/04378/2025 (DOI identifier 10.54499/UID/04378/2025), and UID/PRR/04378/2025 (DOI identifier 10.54499/UID/PRR/04378/2025), of the Research Unit on Applied Molecular Biosciences - UCIBIO and the project LA/P/0140/2020 (DOI identifier 10.54499/LA/P/0140/2020) of the Associate Laboratory Institute for Health and Bioeconomy - i4HB. JPS also acknowledges FCT for the researcher contract (under Scientific Employment Stimulus) 2021.01789.CEECIND/CP1662/CT0014, respectively.

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