BOOK OF ABSTRACTS

U.PORTO

INVESTIGAÇÃO JOVEM DA UNIVERSIDADE DO PORTO

16.ª EDIÇÃO

ENCONTRO DE INVESTIGAÇÃO JOVEM UNIVERSIDADE DO PORTO

10.11.12
MAIO 2023

REITORIA DA
UNIVERSIDADE
DO PORTO

U.PORTO

iUP INVESTIGAÇÃO JOVEM DA UNIVERSIDADE DO PORTO

TÍTULO | *TITLE*

Livro de Resumos do 16.º Encontro de Investigação Jovem da U.Porto / *Book of Abstracts Young Researchers Meeting of U.Porto*

Universidade do Porto

Vice-Reitor para a investigação e Inovação

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ISBN

978-989-746-356-3

Design

Serviço de Comunicação e Imagem da U.Porto

20702 | Targeting mitochondrial TERT to overcome therapeutic resistance

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Abstract

Reactivation of telomerase is a common process in most human tumours [1, 2], usually due to re-expression of its catalytic subunit, the telomerase reverse transcriptase (TERT), contributing to cell immortalization [3]. In thyroid cancer (TC), it was demonstrated that TERT reactivation is often associated with distant metastases, therapy resistance and shorter survival rates of patients [4], however TERTs' canonical functions are not enough to explain these clinical associations. Some works have been proposing a possible non-canonical function of TERT, specifically in mitochondria, as it can translocate into this organelle due to the presence of a N-terminal target mitochondrial sequence (MTS) [1]. In mitochondria, TERT seems to contribute to: protection of mtDNA under oxidative stress; decrease in the production of ROS and apoptosis; increase in mitochondrial membrane potential; and improvement of cellular respiration [5].

Our hypothesis is that the translocation of TERT into mitochondria, in TC cells, may indicate a mechanism of response to oxidative stress caused by cancer therapeutics. Therefore, in this project we are evaluating TERTs' impact in mitochondria in a CRISPR-Cas9 altered TC cell line which lacks the MTS region of TERT (preventing its translocation into this organelle) in comparison with control cells. Currently, we are characterizing the altered cells regarding cell growth and viability (Trypan Blue Exclusion and PrestoBlue Assays), cell cycle profile and proliferation (Flow Cytometry with PI, BrdU Incorporation Asssay). We will further evaluate the effects of these alterations in mitochondrial functions, namely oxidative stress (specific dyes), apoptosis (Flow Cytometry with Annexin V/PI), and metabolism (Seahorse Analyser) as well as in the cellular response to therapeutic drugs.

Overall, this study will allow to evaluate the relevance of mitochondrial TERT-related functions as they might contribute to the discovery of novel targets and therapeutic opportunities for TC patients.

Keywords: thyroid cancer; TERT; therapy resistance; non-canonical functions; mitochondria.

Acknowledgments

This work is supported by the project “Cancer Research on Therapy Resistance: From Basic Mechanisms to Novel Targets”—NORTE-01-0145-FEDER-000051, and by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, and by European Regional Development Fund (ERDF) under the project "The Porto Comprehensive Cancer Center" with the reference NORTE-01-0145-FEDER-072678 - Consórcio PORTO.CCC – Porto.Comprehensive Cancer Center Raquel Seruca. Further support from European Thyroid Association through ETA Project Research Grants 2020. Additional funding was obtained from the project: “Unravel familial non-medullary thyroid cancer aetiology: A Genetic Orphan Disease”, ref. - 2022.05763.PTDC, financed by national funds through FCT – Fundação para a Ciência e a Tecnologia, I.P. We also thank the “Projecto de investigação patrocinado pela SPEDM 2020” from Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo (SPEDM).

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