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Modulation of P-Glycoprotein, toxic xenobiotics and its relevance for spermatogenesis

Maria S. Dias^{1,2,3*}, Carolina P. Amorim^{1,4}, Fernando Remião^{1,2}, Marco G. Alves^{3,4}

¹UCIBIO—Applied Molecular Biosciences Unit, REQUINTE, Toxicology Laboratory, Biological Sciences Department Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal

²Associate Laboratory i4HB—Institute for Health and Bioeconomy, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal

³Biotechnology of Animal and Human Reproduction (TechnoSperm), Institute of Food and Agricultural Technology, University of Girona, ES-17003 Girona, Spain

⁴Unit of Cell Biology, Department of Biology, Faculty of Sciences, University of Girona, ES-17003 Girona, Spain

*✉ maria.sousa.dias@outlook.pt

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Resumo

Introduction: For reproduction to be sustained, it is necessary to preserve fertility and, in parallel, decrease exposure to all compounds capable of causing damage in this process. With the development of modern societies, new products such as xenobiotics appeared. These compounds are used in medicine, tobacco or even a solvent used in a factory. The mechanisms of action of xenobiotics will have serious consequences for a variety of target organs and processes and can target spermatogenesis, the process of production of sperm, that occurs in the seminiferous tubule. For a correct process of spermatogenesis, it is necessary that Sertoli Cells (SCs) that form the blood-testicular barrier (BTB) are accomplishing their physical, immunological and metabolic support functions. With the suggestion that P-gp (P-glycoprotein), an efflux transporter, plays an important role in the assembly and reassembly of BTB, it is necessary to study if its modulation in SCs can have effects in spermatogenesis.

Objectives: To understand if there are different responses and different resistances in BTB in contact with xenobiotics and if P-gp has a role in these processes and can be used as a therapeutic strategy and protect some

important processes such as spermatogenesis. **Material and methods:** This study was carried out with human SCs from testicular biopsies of men with conserved spermatogenesis but anejaculation (n=6). To evaluate the presence of ABCB1 transcripts (gene encoding for P-gp), we performed a conventional PCR. To study P-gp modulation we use Zosuquidar, a P-gp inhibitor, concentrations (in µg/mL): 1; 2,5 and 5; and Rhodamine 123, a P-gp (in µg/mL): 1; 5 and 10. We further aim to understand if the different treatments affect SCs physiology and function, we study the cytotoxicity of these compounds through the SRB (Sulforhodamine B) and LDH (lactate dehydrogenase) assays. **Results:** By conventional PCR we identified ABCB1 transcripts in SCs. The results show that the concentrations that are not toxic to SCs are 1 µg/mL of Zosuquidar and 1 µg/mL of Rhodamine 123. **Conclusion:** After unraveling the concentrations of the P-gp inhibitor and substrate that are not toxic we can, in the future, use these concentrations to do studies to evaluate P-gp activity and modulation by Flow Cytometry, to understand whether the modeling of this protein can be related to male (in)fertility and/or therapeutic purposes.

Keywords: spermatogenesis; hemato-testicular barrier; sertoli cells; membrane transporters; P-glycoprotein

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