NEW SYNTHETIC RALOXIFEN-LIKE DI(HETERO)ARYLAMINES INDUCE APOPTOSIS AND INHIBIT THE ESTROGEN RECEPTOR IN BREAST CANCER CELLS

S. Pires[1], E. Silva[2], M.J.R.P. Queiroz[3], A. Preto[1] and O.P. Coutinho[1]

[1]CBMA – Molecular and Environmental Biology Centre, Department of Biology, University of Minho, Braga, Portugal; [2]School of Pharmacy, University of London, UK; [3]Centre of Chemistry, Department of Chemistry, University of Minho, Braga, Portugal.

Breast cancer is the most common form of cancer in women in the western world, and in spite of some decline in death rates in recent years it is still the second most common cause of death from cancer, in women (1).

For more than three decades, the estrogen receptor (ER) has been the most important biomarker of breast cancer, largely due to the substantial benefit that endocrine therapy provides in the treatment of ER positive tumors, in women of all ages (2). Endocrine therapies currently available include selective estrogen receptor modulators (SERMs), like tamoxifen and raloxifene (3). Raloxifene acts as an estrogen antagonist in the breast by competitive binding to the ER, inhibiting estrogen-induced breast tissue proliferation and preventing the growth of mammary tumors. In addition, it shows no increase in incidence of endometrial cancer, which is an advantage compared to tamoxifen (4). The successes of these endocrine therapies, however, are often limited. So, it is important to continue searching for new strategies and/or drugs that overcome resistance problems and that can be potent enough with fewer adverse effects.

In this work, we studied the effect of two new synthetic di(hetero)arylamines, named MJQ2 and MJQ3 (which have in common with raloxifene a benzothiophene ring), in cell proliferation and apoptosis of two different cell lines from breast cancer: MCF-7 (ER positive) and MDA-MB-231 (ER negative).

Our results showed that both diarylamines induce apoptosis without significant necrosis (evaluated by Hoechst-PI staining), at the IC50 concentration that inhibits cell proliferation (evaluated by the SRB assay). The results obtained with TMRM, a marker of mitochondrial membrane potential, suggest that mitochondrial disruption can be involved in this apoptotic process. These effects are more pronounced in the MCF-7 cell line (ER positive), suggesting that the presence of the ER might be important in the response to these compounds. Confirmation of their interaction with the ER was obtained in the E-Screen assay, where a clear antagonism of the proliferative effects of the hormone 17β-estradiol was observed with both compounds, at non-toxic concentrations.

The overall results suggest that these new synthetic “raloxifene-like” drugs might have potential to be further developed as alternative hormonal or adjuvant therapies for breast cancer.

Supported by the FCT research project PTDC/QUI/68382/2006 (FCOMP-01-0124-FEDER 007441).

References

1) Chang H.R. (2010). *Cancer* 116(12): 2857-2867; 2) Hartman J., *et al.*(2009). *Steroids* 74(8): 635–641; 3) Briest S. and Stearns V. (2009). *Clinical Advances in Hematology & Oncology* 7(3): 185-192; 4) Rey J. *et al.* (2009). *The Open Orthopaedics Journal* 3:14-21.