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CHARACTERIZATION OF PORPHYRINS AS A NEW CLASS OF SELECTIVE INHIBITORS FOR THE ABCG2 TRANSPORTER

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INTRODUCTION

Multidrug resistance is the main cause of chemotherapy failure in cancer cells and the overexpression of the ABCG2 transporter is closely related with this phenomenon. A common approach to overcome the resistance is the development of new inhibitors based on substrates scaffold. For this transporter, there is no available inhibitor for clinical trials due to the high toxicity showed by the tested compounds. Porphyrins are known as classic ABCG2 substrates and here we described one porphyrin with high capacity of inhibition, selective to the ABCG2 and with an interesting toxicity profile.

MATERIAL AND METHODS

The screening, inhibition curves and selectivity assays were performed by flow citometry. Confocal microscopy allowed the visualization of the inhibition profile. MTT assays were used to perform a long-term cell viability assay (72 hours) and the reversion of the resistance phenotype in stably transfected cells and cancer cells lineages. Conformational antibody and ATPase activity measurements were used to verify allosteric modifications on the protein.

RESULTS

Experiments showed that this porphyrin was a selective inhibitor of ABCG2, with an IC_{50} of 1.6 µM. This concentration is 30 fold lower than the IG_{50} (50 µM) showing a very good toxicity profile. The porphyrin was able to fully inhibit the ABCG2 mediated transport with different substrates. The interaction between the porphyrin and ABCG2 caused a small ATPase stimulation but a significantly increase on 5D3 conformational antibody binding. A mixed inhibition mechanism was verified by Hannes-Wolf linearization. Interestingly, different from the classical porphyrins, this compound was not transported by ABCG2 and, at 10 µM, was able to fully revert the resistance phenotype in cells overexpressing ABCG2 transporter, including cancer cell lines.

CONCLUSIONS

In this work we described the first porphyrin capable of inhibit the ABCG2 transporter, leading to a new class of selective ABCG2 inhibitors with an

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