TIM16 inhibition enhances sensitivity to Paclitaxel and decreases calcitonin secretion by reducing mitochondrial membrane potential in a human medullary thyroid carcinoma cell line

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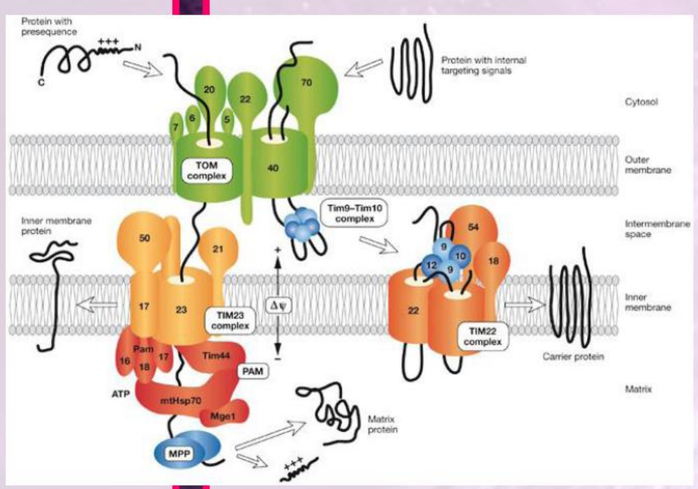
Background

TIM 16, a protein of the translocase complex TIM 23 of the mitochondrial inner membrane, is encoded by the Magmas a gene. Magmas silencing has been associated with a greater sensitivity to apoptotic stimuli in pituitary adenoma cell lines. We recently demonstrated that in a human medullary thyroid carcinoma cell line (TT) compound 5, a TIM 16 inhibitor, was not cytotoxic but enhanced the proapoptotic effects of staurosporine.

Aim

The aim of our study is to verify whether mithocondrial function is involved in compound 5 effects.

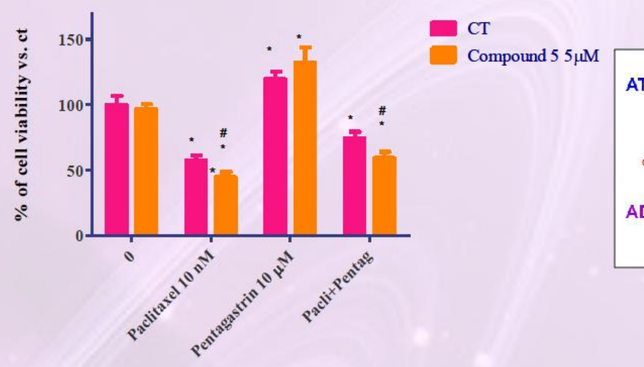


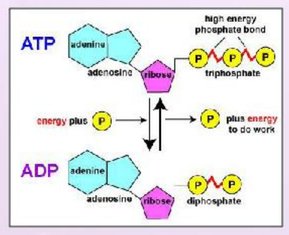
Materials and methods

To evaluate cell viability we performed ATPlite assay, while Caspase 3/7 assay was used to determine apoptotic activation. ELISA test was used for calcitonin detection in cell culture medium, while TMRM assay was employed to evaluate mitochondrial membrane potential (MMP).

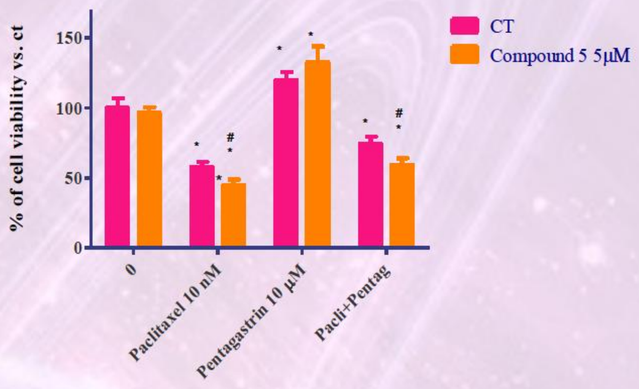
Results

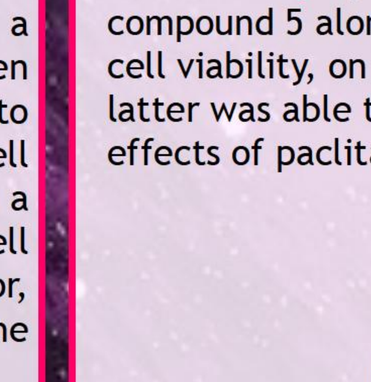
Paclitaxel 10 nM was able to reduce **cell viability** by 40%, while compound 5 alone had no effects on cell viability, on the contrary the latter was able to increased the effects of paclitaxel by nearly 14%.



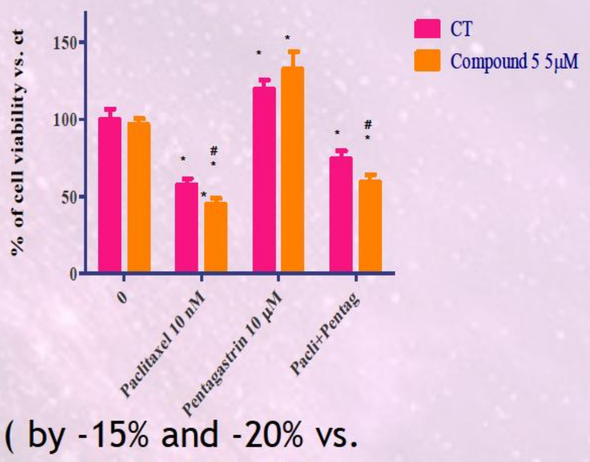


Paclitaxel increased **caspase 3/7 activity** by 130%, moreover compound 5 was able to increased the apoptotic effects of paclitaxel by 130%.

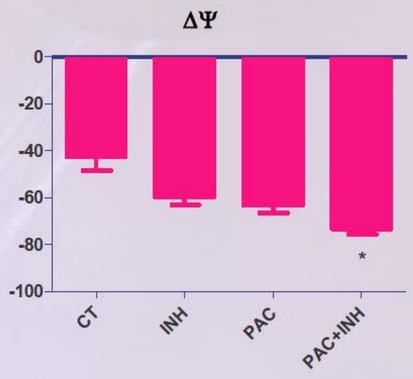


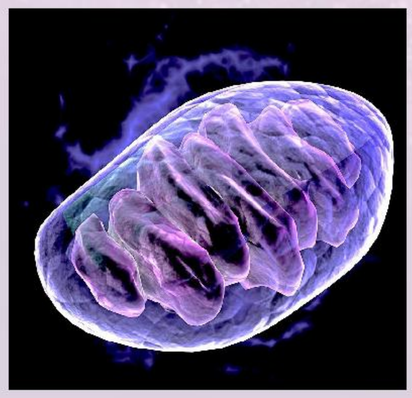


We found that compound 5 was able to reduce basal and pentagastrin induced calcitonin secretion



Furthermore, compound 5 and Paclitaxel decreased MMP (by -15% and -20% vs. CT, respectively), and their combination was even more potent (- 50% vs. CT).





Conclusion

compound 5 could represent a tool to increase the effects of chemotherapeutic agents and to control hypercalcitoninemia in medullary thyroid carcinoma

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