“Teamwork to beat breast cancer”

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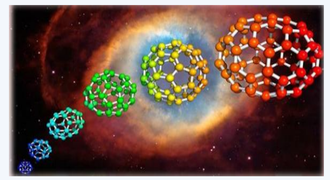

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INTRODUCTION

Basal-like breast cancer is considered unmet medical entity, as patient outcome in advanced stages is short, even receiving the most appropriate treatment. These tumors are characterized by a high grade of genetic instability and a notable impairment of DNA repair processes. In this context, DNA damaging agents like platinum compounds have positioned as key therapies for the treatment of basal-like. However, resistance to these agents appear after a given period of time.

In the complex procedure of control DNA damage, the serine/threonine kinase Chk1 is a key protein, required for checkpoint mediated cell cycle arrest integrating signals from ATM and ATR. Chk1 detects cells with DNA damage, and triggers the activation of mechanisms of DNA repair, causing cell arrest in G1. Targeting these mechanisms has become one interesting therapeutic option because then cells cannot repair the DNA modification.

Here, we explore the interaction of Chk1 inhibitor rabusertib with DNA damaging agents used in clinical for breast cancer. In addition, we evaluate the role of these agents to overcome platinum resistance.

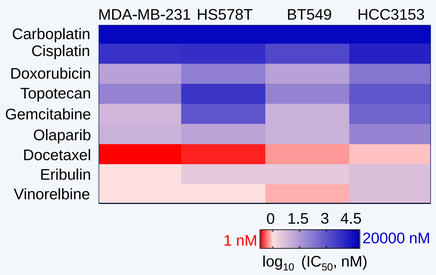
MATERIAL AND METHODS

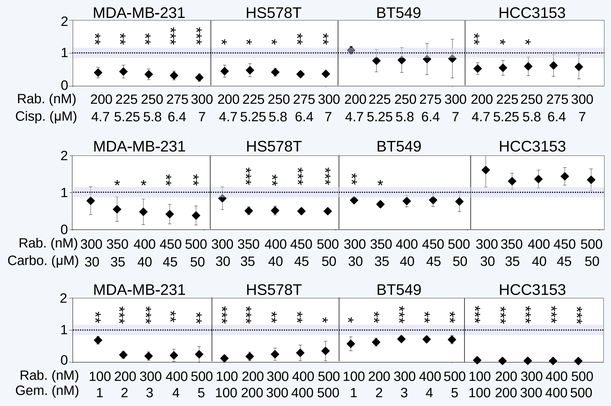
- Cell lines used in our study were MDA-MB-231, HS578T, BT549 y HCC3153. Cisplatin-resistant breast cancer cells (MDA-MB-231R) were generated.
- MTT, synergistic assays and clonogenic assays were used to study the influence of Chk1 inhibitor and chemotherapies, alone and in combination, on cell viability and proliferation.
- Matrigel embedded 3D cultures were used to study the effect of these drugs on cell migration and invasion.
- The effect on cell death was studied by flow cytometry and caspase activity assays.
- We used Western Blot studies to confirm the biochemical effect of DNA damage at a protein level.

RESULTS

Synergistic interactions of Chk1 inhibitors with standard of care therapies used for breast cancer

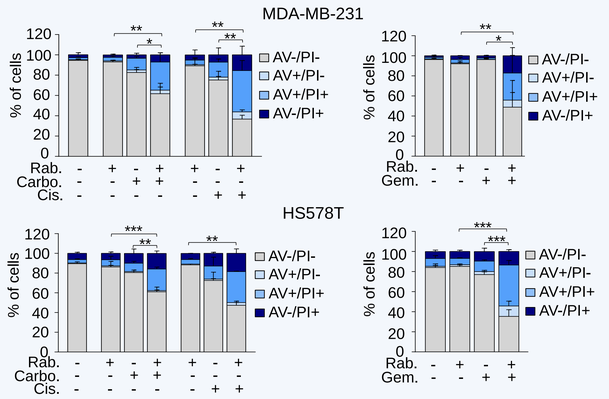
Cellular models	Standard of care therapies	
	1st line	2nd and 3rd line
MDA-MB-231 HS578T BT549 HCC3153	Doxorubicin Docetaxel Cisplatin / Carboplatin	Eribulin Gemcitabine Topotecan Vinorelbine Olaparib





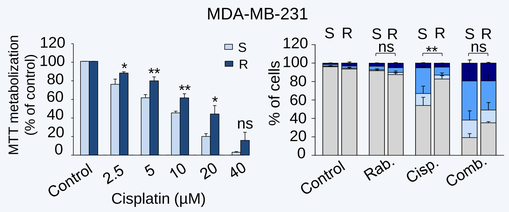
Chk1 inhibition reduces cell growth and migration in combination with platinum compounds

Combination of platinum agents and gemcitabine with rabusertib markedly induces cell death

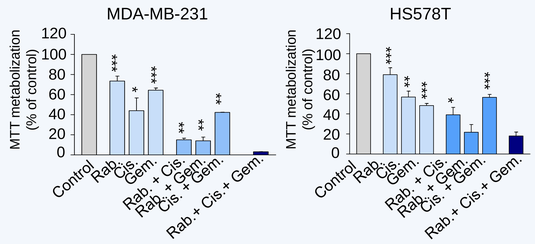


Induction of apoptosis by the combination of platinum agents with rabusertib was mainly mediated by activation of caspases.

Inhibition of Chk1 reverts resistance to platinum compounds



Chk1 inhibition enhances the effect of standard-of-care chemotherapies



CONCLUSIONS

- ✓ Inhibition of Chk1 has a strong synergistic interaction with DNA damaging agents, mainly platinum compounds but also gemcitabine.
- ✓ Induction of apoptosis by the combination of platinum agents with rabusertib was mainly mediated by activation of caspases.
- ✓ Resistance to cisplatin can be overcome by inhibition of Chk1 kinase.

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