A POTENTIAL INHIBITOR OF HOMOLOGOUS RECOMBINATION DNA REPAIR IN TRIPLE-NEGATIVE BREAST CANCER

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Introduction

Triple-negative breast cancers (TNBC) are hard-to-treat tumors associated with drug resistance [1]. Although defects in homologous recombination (HR) DNA repair can predispose individuals to develop TNBC, this vulnerability can be exploited to selectively induce cancer cell death. In fact, this is the basis of poly-ADP-ribose polymerase inhibitors (PARPis), as olaparib [1]. PARPis are in the frontline of BRCA1/2-deficient breast cancer targeted therapy. However, the commonly reported resistance of cancer cells to PARPis has become a major clinical concern. The combination of other HR inhibitors with PARPis may represent a promising strategy to overcome this therapeutic limitation [2].

In this work, the small molecule XGAc was identified as a potential HR inhibitor with anticancer activity against TNBC.

Methods

The growth inhibitory activity of compound XGAc was evaluated by sulforhodamine B (SRB), after 48 h of treatment, in human immortalized BC cells, and compared to cisplatin and olaparib chemotherapeutics. The effect of 1.5-6 μM XGAc on cell cycle progression (by propidium iodide staining) and apoptosis (by annexin V staining) was evaluated by flow cytometry analysis after 48h treatment. The modulation of key HR DNA repair protein levels by 3-6 μM XGAc was assessed by immunoblotting, after 48h treatment.

Results

Growth inhibitory activity

<table>
<thead>
<tr>
<th>IC₅₀ (µM)</th>
<th>MDA-MB-231</th>
<th>MDA-MB-468</th>
<th>HCC1937</th>
<th>HFF1</th>
</tr>
</thead>
<tbody>
<tr>
<td>XGAc</td>
<td>1.13±0.26</td>
<td>3.23±0.80</td>
<td>2.72±0.68</td>
<td>30.30±4.19</td>
</tr>
<tr>
<td>Olaparib</td>
<td>5.08±1.70</td>
<td>43.01±5.89</td>
<td>30.51±1.35</td>
<td>36.00±1.15</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>12.12±1.15</td>
<td>2.34±0.35</td>
<td>8.62±0.93</td>
<td>9.31±0.93</td>
</tr>
</tbody>
</table>

Effect on cell cycle progression and apoptosis induction

Cell cycle analysis: Effect of 1.5-6.0 μM XGAc on cell cycle progression of MDA-MB-231 and HCC1937 cells, after 48h treatment. Data are mean ± SD (n=3). *p<0.05 compared to control (DMSO).

Apoptosis analysis: Effect of 1.5-6.0 μM XGAc on apoptosis induction of MDA-MB-231 and HCC1937 cells, after 48h treatment. Data are mean ± SD (n=3). *p<0.05 compared to control (DMSO).

Modulation of key HR DNA repair players protein levels

Immunoblotting: Effect of 3-6 μM XGAc on protein expression of HCC1937 and MDA-MB-231 cancer cells, after 48h of treatment. (n=3)

Conclusion

These data support the promising application of XGAc in TNBC therapy by inhibiting HR DNA repair.

Further studies are underway to validate these results.

References:

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