Inositol-requiring enzyme-1 (IRE1) blockade affects triple-negative breast cancer chemotherapy sensitivity and prevents chemotherapy-related cardiotoxicity

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**Background**

Inositol-requiring enzyme-1 (IRE1) Signaling

- Arm of the unfolded protein response (UPR) pathway that plays a crucial role in tumor development.
- IRE1 is mostly known for endo nucleus activities, the activation results in the unconventional splicing of XBP1-U to form the active transcription factor XBP1-S that lead to cancer cell proliferation.

**Aim of study**

Determine the role of IRE1 targeting on mediating TNBC chemotherapy response and preventing therapy-related cardiac toxicity.

**Results**

**Triple Negative Breast Cancer (TNBC)**

Doxorubicin cardiotoxicity

- Acute
- Chronic
- Cardiac dysfunction

**Inositol-requiring Enzyme-1 (IRE1) Signaling**

- Hypothesis: IRE1 is involved in TNBC and doxorubicin cardiotoxicity.

**Background Results**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DOX</th>
<th>IRE1 morpholino +DOX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ejection Fraction</strong></td>
<td>4 week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.03%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOX</td>
<td>25.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRE1 morpholino +DOX</td>
<td>3.35%</td>
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</tbody>
</table>

**Aim of study**

- Determine the role of IRE1 targeting on mediating TNBC chemotherapy response and preventing therapy-related cardiac toxicity.

**Results**

**Tumor Volume (mm³)**

<table>
<thead>
<tr>
<th></th>
<th>Control n=10</th>
<th>DOX n=8</th>
<th>IRE1 morpholino n=7</th>
<th>IRE1 morpholino +DOX n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (Days)</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>21</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td></td>
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</tr>
</tbody>
</table>

**Tumor Weight (grams)**

- Control
- IRE1 morpholino
- IRE1 morpholino +DOX

**Fractional Shortening (%)**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DOX</th>
<th>IRE1 morpholino +DOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 week post DOX</td>
<td>70</td>
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</tbody>
</table>

**Inflammation in obesity**

- Hyperinsulinemia
- Hypertension
- Inflammation

**Cancer cell proliferation**

- Inflammation in obesity

**Cardiac dysfunction**

- Acute
- Chronic