Expression of GRP78 protein is increased in pancreatic ductal adenocarcinoma, pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm

Xianzhong Ding, Brandon Trac, and Xiuzhen Duan

Department of Pathology
Loyola University Medical Center
Maywood, IL 60153
USA
• Poor prognosis
• Lack of responsiveness to conventional therapy

**PANCREATIC DUCTAL ADENOCARCINOMA**
Precursor Lesions of Pancreatic Adenocarcinoma

- Pancreatic intraepithelial neoplasia (PanIN)
- Mucinous cystic neoplasm (MCN)
- Intraductal papillary mucinous neoplasm (IPMN)
According to the Response Evaluation Criteria in Solid Tumors (RECIST), for pancreatic cancer patients treated palliatively with gemcitabine and nab-paclitaxel:

- No complete responses were observed
- Partial response in 37% of patients
- Progressive disease in 22% of patients
GRP78

- Glucose-Regulated Protein 78 (GRP78)
- Heat Shock Protein 70 (HSP70) family
- A major endoplasmic reticulum (ER) chaperone protein
- Critical for protein quality control of ER
- GRP78 is preferably required for
  - cancer cell survival
  - Promotes tumor progression
  - Enhances drug resistance
Endoplasmic Reticulum Stress in the Tumor Microenvironment
(glucose starvation, hypoxia, protein malfolding)

Apoptosis

↑GRP78

Genistein (soy)
EGCG (green tea)
Versipelostatin (microbes)
AB$_5$ subtilase toxin (bacteria)
IL-24 (immune cells)

GRP78 binding peptide
Kringle 5
Activated α-2 macroglobulin

Tumor progression:
• Survival
• Immune resistance
• Proliferation, metastasis

Biomarker for:
• Tumor behavior
• Treatment response

Tumor cell resistance to:
• Chemotherapy
• Anti-angiogenesis therapy
• Anti-hormonal therapy

Drug resistance of:
• Dormant cancer cells
• Tumor endothelial cells
AIMS

• **GRP78 expression in human pancreatic ductal adenocarcinoma**

• **GRP78 expression in precursor lesions of human pancreatic ductal cancer**
  – Pancreatic intraepithelial neoplasia
  – Intraductal papillary mucinous neoplasm

• **GRP78 and pancreatic cancer growth**
GRP78 IMMUNOHISTOCHEMISTRY

- Benign pancreatic ducts
- Low grade IPMN
- High grade IPMN
- Invasive ductal adenocarcinoma
**GRP78 PROTEIN EXPRESSION LEVEL**

<table>
<thead>
<tr>
<th></th>
<th>Normal ducts</th>
<th>IPMN-LG</th>
<th>IPMN-HG</th>
<th>panIN-HG</th>
<th>PDAC</th>
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<tbody>
<tr>
<td>Total</td>
<td>38</td>
<td>26</td>
<td>9</td>
<td>32</td>
<td>20</td>
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<tr>
<td>No or weak staining (0-1+)</td>
<td>37</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Strong staining (2-3+)</td>
<td>1</td>
<td>19</td>
<td>9</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>% of strong staining</td>
<td>3%</td>
<td>73%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
GRP78 siRNA INHIBITS PANCREATIC CANCER CELL PROLIFERATION

% growth inhibition

PANC-1

HPAF

Control siRNA

GRP78 siRNA

Control siRNA

GRP78 siRNA
GRP78 KNOCKDOWN ENHANCES ANTICANCER EFFECT OF GEMCITABINE
SUMMARY AND CONCLUSIONS

- GRP78 is up-regulated in human pancreatic ductal adenocarcinoma and its precursor lesions
- Blockade of GRP78 inhibits pancreatic cancer cell proliferation
- GRP78 knockdown enhances anti-cancer effect of gemcitabine
- Prognosis?