Novel Approaches to Targeting Cancer Stem Cells

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Rosen and Jordan, Science 324:1670, 2009

Microarray Analysis of Gene Expression in CD29\textsuperscript{H}CD24\textsuperscript{H} Cells

- CD133 (Prominin1, a marker for both neural and brain CSCs, as well as for small intestine and blood stem cell)
- CD49f (alpha 6 integrin, known mammary stem cell marker)
- Dnmt2 (polycomb genes pluripotency and epigenetics)
- Bmi1 (polycomb genes pluripotency and epigenetics)
- Ezh2 (polycomb genes pluripotency and epigenetics)
- Brca1 (DNA damage repair and checkpoint genes)
- Chek1 (DNA damage repair and checkpoint genes)
- Bub1

Do CSCs React Differently to DNA Double Strand Breaks?

- DNA damaging therapeutics, such as ionizing radiation (IR), kill tumor cells by inducing DNA double strand breaks (DSBs)
- Different subpopulations of tumor cells may utilize different DNA repair mechanisms

Radioresistance of CSC-enriched Mammospheres

Fig. 2. CSC models. (A) The intrinsic model suggests that specific subpopulations within a tumor spindle hold the functional properties of CSCs. (B) The extrinsic model proposes that tumor cells are functionally equivalent and display heterogeneous behaviors as a function of extrinsic (microenvironmental) cues.

Rosen and Jordan, Science 324:1670, 2009
Altered DNA Damage Repair in CSCs

The ALDH+ Subpopulation Repairs DSBs More Efficiently Than the ALDH- Subpopulation

Since the CSCs that evade radiation and chemotherapy treatment may lead to tumor recurrence and relapse, how can we target them?

Mammosphere Survival Significantly Decreases with XRT and Hyperthermia

Hyperthermia is a Potent Radiosensitizer

- Hyperthermic stress can alter tumor cell survival both in vivo and in vitro
- With many tumor types, hyperthermia (41° C-43° C) increases and synergizes the therapeutic response to combination therapy
Hyperthermia Prevents Repair of Double Strand Breaks
Atkinson et al Science Trans Med, 2010

Gold Nanoshells
- Dielectric silica core
- Thin gold coating
- Light absorbed by the free electrons on the gold is converted to heat.
- Core-shell ratio determines the optical characteristics
- Biocompatibility (silica, noble metal surface)
- Acceptable toxicity for high concentration (up to 3% of body weight) of gold in the body
- Robust structure
- Less susceptible to chemical/thermal denaturation

Tumour Targeting by EPR Effect

Using Gold Nanoshells for Hyperthermia
- Hyperthermia is generated by near-infrared illumination of gold nanoshell-laden tumors to precisely heat cancer cells

Sample Temperature Profile

CD29<sup>hi</sup>/CD24<sup>hi</sup> Cells Decrease with Combination Treatment
Tumor Formation Decreases with Radiation Plus Hyperthermia Treatment

<table>
<thead>
<tr>
<th>Tumor Initiation Cell Frequency (TIC) 95% CI</th>
<th>10,000</th>
<th>1,000</th>
<th>100</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIC</td>
<td>1/447  (240-836)</td>
<td>1/97 (50-190) *</td>
<td>1/1995 (960-3984) *</td>
<td></td>
</tr>
</tbody>
</table>

T1 Tumors Treated with 6 GY Radiation plus 20 min 42°C C Fail to Repair DNA DS Breaks

ALDH+ Cells are Sensitive to Radiation with the Addition of Hyperthermia

Mechanisms of Thermal Effects
Dear Prof Rosen,

I was most interested to see that your recent paper http://stm.sciencemag.org/content/STM was picked up by some of our non-specialist media here in the UK (for example see here http://www.dailymail.co.uk/health/article-1324247/Breast-cancer-bullet-treatment-use-metastatic-human-hair.html). I would like to read the full paper – would you be able to forward it on please?

Yours sincerely, Trevor

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