Antecedents / State Of The Art

Telomeres, telomerase and cancer

Telomeres are repetitive sequences of nucleotides at the ends of each chromosome in order to prevent them for degradation during replication.

Human telomerase is a ribonucleoprotein composed of a catalytic protein subunit with reverse transcriptase activity (hTERT) and a template-containing RNA component (hTR). Its function is to synthesize multiple tandem repeats of telomeric DNA, which counter stability to telomeres length.

Telomerase is active in germ line cells and becomes deactivated during differentiation. Oncogenically transformed cells that lack telomerase activity can bypass senescence but then die during crisis. However, cancer cells with active telomerase can continue to proliferate and become unaffected by senescence (fig.1).

Figure 1. The telomere hypothesis for cellular mortality. Figure from Shay JW, et al (2011).

Telomers are active during tumor progression

The majority of human solid tumors contain regions of hypoxia, which is caused by reduced oxygen delivery to the cells. This sets off a series of events that take advantage of normal cellular stress response machinery intended to relieve cells of their stressful environment through altered gene expression.

Transcriptional regulation by hypoxia-inducible factor 1α (HIF-1α) represents the most important mechanism mediating adaptive response to a O₂-reduced environment.

A link between hypoxia and telomerase regulation

Previous studies have demonstrated telomerase activity up-regulation under hypoxic conditions in solid tumors (ovarian carcinoma and colon adenocarcinoma).

Transcriptional activation of hTERT and hTERT gene promoters under hypoxia is caused by HIF-1α. It results in telomerase up-regulation which in turn affects cancer cell proliferation and cell survival in different solid cancer tissues.

General Aims

1. To investigate the role and regulation of human telomerase RNA (hTR) in basal-like and claudin-low breast carcinoma cell lines cultured under hypoxic condition.

2. To assess the role of hypoxia along hTR regulation and tumoral transformation of non-carcinogenic breast cell lines

Material And Methods

Stress treatments

Use of cell lines (table 1):

<table>
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<tr>
<th>Condition</th>
<th>Cell line</th>
<th>ER</th>
<th>PR</th>
<th>HER2</th>
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<tbody>
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<td></td>
<td>MDA-MB-231</td>
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Table 1. Molecular features of breast cancer cell lines chosen for this study.

Measurement of telomerase activity

- Method 1: Telomeric Repeat Amplification Assay (TRAP)
- Method 2: Reverse Transcriptase PCR

Telomerase activity during tumor development

- Telomerase activity inhibitors as adjuvant therapy to improve the efficiency of chemotherapeutic agents.

Study of hTR regulation mechanisms in this cell lines and condition might be useful for developing a new therapeutic approach.

Project Benefits And Social Impact

- Hypoxic condition in tumors is crucial for tumor progression and leads to:
  - Basal like and claudin-low breast cancer cell lines growth cannot be inhibited by neither anti-estrogen therapy or trastuzumab (used as breast cancer treatment)

Need to improve treatments

Tumor growth and progression

Scientific community

- Better understanding of telomerase regulation mechanisms.
- Interesting for therapeutic approaches development

Research findings will be shared with:
  - a) Researchers
  - b) Higher education

References: