p53 isoforms: a major pronostic marker of the metastasis risk

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Market needs

- Metastases: cause of cancer death
- Pronostic marker: prediction of relapse/metastases
- Therapeutic option: guided by the risk
- Europe: > 446,000 new cases/y colorectal cancer (CRC), > 463,000 /breast
- Biomarker in oncology: 15 Md $ in 2013 (35 Md $ in 2018)
- Urgent need of specific biomarkers of metastasis
A biomarker predicts the risk of recidive

Primary tumor

Biomarker: Personalized therapy

Weak risk: Chemotherapy reduced
- No biomarker: Colorectal cancer
  - 70% overtreatment

High risk: Intensified chemotherapy
- No biomarker: Breast cancer
  - 30% inadequate treatment

Stratification: Targeted therapy

Increased survival rate
Alternative splicing generates modified proteins

Gene

Pre-mRNA

mRNA

Protein

Major

Isoform A

Isoform B

Alternative splicing as an unexplored program in oncology
p53: a key role in cancer

- The most tumor suppressor studied
- The most frequent mutated gene in cancer
- Inactivated function in almost all tumors

Mutated p53 → Mutation → Alternative Splicing → Isoforms: modified p53

• p53
• p53β
• p53γ
• Δ40p53
• Δ40p53β
• Δ40p53γ
• Δ133p53
• Δ 133p53β
• Δ 133p53γ

Mutated p53: Unreliable biomarker

Isoforms: Robust biomarker of metastasis risk
A clinical biomarker to predict high risk of relapse in advanced breast cancer

- **p53 isoform test:**
  - Associated with reduced disease free survival (DFS) and global survival, independently of p53 mutations
  - Predicts high risk of relapse
  - High specificity (93%)
  - Help guide treatment decision-making in selecting which patients should benefit from additional therapy
Opportunity to position p53 isoforms test in breast cancer

Newly diagnosed early invasive breast cancer

High risk node negative

Metastatic breast cancer or locally advanced

ER positive (Luminal A)

HER2 positive

Triple negative

• Needs:
  • Luminal A: hormone sensitive cancer (70% of breast tumors)
  • 30% (undetectable) of relapse/metastases in 4 years
  • Predict risk of relapse or treatment failure in Luminal A
  • Adapt treatment strategy
A clinical biomarker to predict high risk of relapse in advanced rectal cancer

- Needs:
  - Single chemotherapy treatment
  - 70% overtreatment
  - Adapt treatment strategy

- p53 isoform test:
  - Associated with reduced disease free survival (DFS) and global survival, independently of p53 mutations
  - Predict high risk of relapse
  - High specificity (95%)
  - Help guide treatment decision-making in selecting which patients should benefit from additional therapy
  - All patients may benefit from this test
Competitive position

- Colorectal cancer: no test available
- Breast cancer

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Oncotype DX/Mammaprint</th>
<th>p53 isoform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature</td>
<td>Multiplex</td>
<td>Monogenic</td>
</tr>
<tr>
<td>Specificity</td>
<td>Weak (63% Oncotype DX)</td>
<td>High(93%)</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Non-identifiable</td>
<td>Identifiable</td>
</tr>
<tr>
<td>Associated targeted therapy</td>
<td>Impossible</td>
<td>Potential Targeting</td>
</tr>
<tr>
<td>Cost</td>
<td>High (4000 $ Oncotype DX)</td>
<td>Reduced (estimated cost &lt; 25 €)</td>
</tr>
<tr>
<td>Sample</td>
<td>Paraffin (Oncotype DX) / Frozen (Mammaprint)</td>
<td>Paraffin and frozen</td>
</tr>
</tbody>
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Positioning in the value chain development

Identification | Hit | Scientific Validation | Lead | Pre-Clinical optimization | Clinical trials

Research | Development | Clinic

- Reliable and robust method (qPCR)
- High sensitivity and specificity
- Original mechanism
- Highly relevant target
- Meets a market need

- Needs of resources
- Optimization detection kit
- Design of clinical trials
- Partnership/Investors
IP Status

• Scope of patents protection:

1. Method of detection (prediction)

2. Method to assess cancer aggressiveness (pronostic)

3. Method to determine resistance to therapy (chemoresistance)

4. Method to screen anti-metastatic compounds (theranostic)

• Patents:


Team: Dynamic of cancer invasion
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