RNA expression-based hypoxia score as a prognostic and predictive biomarker in hepatocellular carcinoma (HCC)

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Methods

- Solid tumors across a range of tissues (N=91516) were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome), including 1382 HCC tumors.
- Mutation prevalence (-Mt) was calculated for pathogenic SNVs/indels.
- PD-L1 expression (SP142; +: ≥2+, ≥5%) tested by IHC.
- HS based on RNA expression of 15 genes and normalized across a range of solid tumors was implemented as previously described (Bhandari et al, 2019). Tumors were defined as HS high (-H), medium (-M) and low (-L) by a combination of hierarchical clustering and empirically setting thresholds.
- A transcriptomic signature associated with immunotherapy response (T-cell inflamed score) was applied.
- Fisher’s Exact2 test were applied as appropriate with p-values adjusted for multiple comparisons (p < 0.05).
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Results

- In HCC, RNA expression-based HS high is associated with a higher prevalence of TP53-Mt and a lower rate of CTNNB1-Mt.
- High HS is also associated with a more inflamed immune microenvironment.
- HS high tumors had worse OS.
- There was no significant difference in survival when segmenting HS-high, medium and low tumors by the first-line treatments that they received.

Conclusions

- HS is a potential prognostic biomarker in HCC that merits validation in orthogonal data sets and prospective studies.

Contact Dr. Ashton Connor (aconner@houstonmethodist.org) for additional information

Background

- Hepatocellular carcinoma (HCC) has rising incidence and mortality rates.
- Tumor hypoxia is important in HCC pathogenesis but has not been effectively translated into practice.
- We studied whether an RNA expression-based hypoxia score (HS) can serve as a prognostic and predictive biomarker in HCC.

Figure 1: (A) Hierarchical clustering created a pan-tumor preliminary grouping of HS high, medium and low tumors (columns are z-score normalized HS genes and rows are all available tumors, red represents higher expression, blue lower). (B) Distribution of hypoxia scores for HCC in the three clusters, thresholds were then empirically set for our three HS categories (yellow dashed lines).

Figure 2: (A) landscape of genomic alteration in HCC (all statistically significant alterations are shown in addition to TSC1 and PTEN-Mt) (B) Prevalence of PD-L1 positivity (C) Prevalence of T cell-inflamed tumors.

Table 1: Demographic data for HCC tumors

<table>
<thead>
<tr>
<th>HCC</th>
<th>HS High</th>
<th>HS Med</th>
<th>HS Low</th>
<th>q-value</th>
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<tbody>
<tr>
<td>Count (N)</td>
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<td>194</td>
<td>903</td>
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<tr>
<td>Median Age</td>
<td>[13-80]</td>
<td>[19-89]</td>
<td>[13-89]</td>
<td>0.530</td>
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<tr>
<td>% Male</td>
<td>76.1%</td>
<td>73.2%</td>
<td>77.5%</td>
<td>0.865</td>
</tr>
</tbody>
</table>

Table 2: Study Highlights

- Low HS has lower OS.
- High HS is associated with a more inflamed immune microenvironment.
- HS high tumors had worse OS.
- There was no significant difference in survival when segmenting HS-high, medium and low tumors by the first-line treatments that they received.

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