#343: Angiogenic and T-effector subgroups identified by gene expression profiling (GEP) and propensity for PBRM1 and BAP1 alterations in clear cell renal cell carcinoma (ccRCC)

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Background:
Predictive biomarkers for optimal treatment selection in RCC are lacking. Gene expression data from IMmotion151 and Javelin Renal 101 clinical trials generated anti-angiogenic and immune signatures that warrant further validation. We aimed to describe the genomic and gene expression profiles in a multi-institutional database of patients with ccRCC, and its association with other biomarkers of interest.

Methods:
• Whole transcriptome sequencing was performed for ccRCC patient samples submitted to a commercial CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ) from February 2019 to September 2020.
• Tumor GEP and hierarchical clustering based on the validated 66-gene signature (D’Costa et al, 2020) were used to identify patient subgroups.
• Samples from both primary tumors and metastatic sites were included.

Results:
• A total of 316 patients with ccRCC, median age 62 (range 32-90), 71.8% male, were included. Tissue samples were obtained from primary tumor (46.5%), lung (12.3%), bone (9.5%), liver (4.7%) and other metastatic sites (27%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All cases</th>
<th>‘Angiogenic’ subgroup</th>
<th>‘Mixed’ subgroup</th>
<th>‘T-effector’ subgroup</th>
<th>P-value (Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, N cases (% of total)</td>
<td>316 (100%)</td>
<td>76 (24.1%)</td>
<td>62 (19.6%)</td>
<td>162 (51.3%)</td>
<td>0.0350 (Mann-Whitney U)</td>
</tr>
<tr>
<td>Median Age, years</td>
<td>62 (10.6)</td>
<td>62 (10.6)</td>
<td>62 (10.6)</td>
<td>62 (10.7)</td>
<td>32.86</td>
</tr>
<tr>
<td>Age Range, years</td>
<td>32-90</td>
<td>32-90</td>
<td>32-90</td>
<td>32-90</td>
<td>38.83</td>
</tr>
<tr>
<td>Female/Male, N cases (% Female/Male)</td>
<td>89/227 (28.2%/71.8%)</td>
<td>21/65 (26.7%/72.3%)</td>
<td>19/62 (30.6%/69.4%)</td>
<td>45/117 (38.5%/61.5%)</td>
<td>0.0009 (Chi-square)</td>
</tr>
<tr>
<td>Metastatic/Primary, N cases (% Metastatic/Primary)</td>
<td>170/146 (53.8%/46.2%)</td>
<td>42/55 (76.4%/23.6%)</td>
<td>42/55 (76.4%/23.6%)</td>
<td>88/54 (63.6%/36.4%)</td>
<td>0.0863 (Chi-square)</td>
</tr>
</tbody>
</table>

Table 1 – Baseline patient and tumor characteristics.

• Gene expression analysis identified angiogenic (24.1%), mixed (51.3%) and T-effector (24.7%) subgroups (Figure 1).
• Angiogenic subgroup tumors compared to those with T-effector subgroup tumors were more likely to be older (63 versus 60 years, p=0.035) and female (40.8% versus 16.7%, p=0.0009) (Table 1).
• PBRM1 mutations were more common in the angiogenic subgroup (62.0% vs 37.5%, p=0.0034) while BAP1 mutations were more common in the T-effector subgroup (18.6% versus 3.0%, p=0.0035) (Figure 1).

Conclusions:
• Our hierarchical clustering results based on the 66-gene expression signature were concordant with results from prior studies;
• Angiogenic tumors were more likely to be found in patients who were older or female, and were more likely to harbor gastro-intestinal metastases, stromal cell population and PBRM1 mutations;
• BAP1 mutations and Immunotherapy markers such as TMB and dMMR/MSI-H (not significant), PD-L1 and Immune cell population were more frequent in the “T-effector” signature;
• These findings have potential predictive value and require further validation in prospective clinical trials.

Results:
• Markers associated with immune checkpoint inhibition such as PD-L1 (p=0.0021 [exploratory]), TMB (not significant), and dMMR/MSI-H status (not significant) were more frequent in the T-effector subgroup (Figure 2).
• Pancreatic/small bowel (Gastrointestinal; GI) metastases were more frequently ‘angiogenic’ compared to primary tumors (75% versus 23.8%, p=0.0103 [exploratory]) (Figure 3).

Figure 1 – Hierarchical clustering of gene expression signature

Figure 2 – Predictive biomarkers of Immunoresponse response.

Figure 3 – Distribution of subtypes among specimen sites. *p-value (exploratory) < 0.05.

Figure 4A

Figure 4B

Figure 4 – Analysis of ccRCC tumor microenvironment by Microenvironment Cell Population (MCP) counter. Immune cell population (e.g. T cells, cytotoxic lymphocytes) abundance and immune checkpoint genes (e.g. PDCD1, C0274, CTLA4, LAG3) were coordinately increased in the T-effector subgroup, while stromal cell population (endothelial cells, fibroblasts) abundance was increased in the Angiogenic subgroup.

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