RNA-sequencing reveals immunotherapeutic targets in gynecological cancer

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Background

We performed expression immune profiling and microsatellite instability testing of endometrioid and serous carcinomas to identify immunotherapeutic targets and characterize their immune microenvironment.

Methods

Microsatellite instability and RNA-seq of 395 immune-related genes were performed in 37 endometrioid and 53 serous carcinomas (Table 1).

Table 1: Patient and specimen characteristics.

<table>
<thead>
<tr>
<th>Specimen number</th>
<th>Ovarian primary</th>
<th>Uterine primary</th>
<th>Vaginal primary</th>
<th>Fallopian primary</th>
<th>Cervical primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid</td>
<td>37</td>
<td>34</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serous</td>
<td>53</td>
<td>38</td>
<td>31</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Average BMI</td>
<td>38</td>
<td>35</td>
<td>38</td>
<td>53</td>
<td>64</td>
</tr>
<tr>
<td>FIGO grade III</td>
<td>27% (10/36 cases)</td>
<td>70% (35/50 cases)</td>
<td>0% (0/4 cases)</td>
<td>33% (11/34 cases)</td>
<td>33.2% (11/33.2)</td>
</tr>
</tbody>
</table>

Table 2: p-values and differential expression direction (compared to reference population) of IFN and IFN-related genes in endometrioid and serous carcinomas. Serous carcinomas overexpressed an abundance of IFN-related genes. p-values are a result of Wilcoxon ranked sum test comparisons.

Figure 1: Schematic of comparison scheme.

Figure 2: Boxplots of differentially expressed checkpoint genes. Medians and ranges of RNA-rank in endometrioid/serous sets and corresponding comparison populations are shown. VTCN1, IDO1, and components of the mTOR pathway (data not shown) were overexpressed in both endometrioid and serous carcinomas. CD276 and NTSE were overexpressed in the endometrioid set while LAG3 was overexpressed in the serous set. p-values are a result of Wilcoxon ranked sum test comparisons.

Figure 3: Heat map of RNA-seq rank unsupervised clustering of both endometrioid and serous data sets. Four clusters emerged. There was no correlation between microsatellite instability status and expression of any gene in either endometrioid or serous cancers (data not shown). When ranks of both endometrioid and serous sets were subjected to unsupervised clustering, four distinct clusters resulted with trends emerging for histology and primary site Histologic attributes and CD8 RNA-rank are also shown.

Figure 4: The four clusters (1 through 4) contain a decreasing proportion of endometrial primary and endometrioid carcinomas. The reverse trend is seen with ovarian primaries and serous carcinomas.

Results and Conclusions

- There is relatively high RNA-expression of VTCN1 (B7-H4) and IDO1 in endometrioid and serous carcinomas
- NTSE (ADOR2A ligand) and CD276 (B7-H3) RNA is relatively overexpressed in endometrioid carcinomas, and LAG3 in serous carcinomas
- These markers may play a role in immune suppression in gynecological cancers and are potential immunotherapeutic targets
- Based on unsupervised clustering and the disparate upregulation of IFN-related genes the immune microenvironments of endometrial/ovarian and endometrioid/serous carcinomas have distinct elements