Intratumoral mast cell infiltration and recurrence of hepatocellular carcinoma in patients undergoing orthotopic liver transplantation.

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Introduction

Tumor-infiltrating immune cells are highly relevant for prognosis and identification of immunotherapy targets in hepatocellular carcinoma (HCC). We have recently suggested IgE activated mast cells as potentially relevant for HCC outcome (Rohr-Udilova et al. 2018). This suggestion was based on immune cell profiling using CIBERSORT method (Newman et al. 2015) together with immunohistochemical (IHC) staining for tryptase in ten HCC patients. Although mast cells have been previously detected in HCC, their activation status, however, has not been evaluated in details.

Aim

Here, we aimed to verify the previously suggested relevance of mast cells for tumor recurrence in a larger HCC cohort of Austrian patients.

Conclusion

OLT-HCC patients with low mast cell density in tumor tissue have a higher risk for HCC recurrence, which is of prognostic importance. The underlying mechanisms and the impact of MCs on HCC biology require further investigation.

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Results

Mast cells were detectable in 93% of tumor tissues (160 out of 172) and in all available corresponding surrounding tissues (n=149). Based on tryptase staining, tissue morphometric analysis allowed us to quantify mast cell density as a number of cells per mm2 of tissue slide (Fig 1A).

A lower density of intratumoral mast cells (median density cut-off: 3.9 cells/mm2) correlated significantly with a higher HCC recurrence rate (Fig.2, hazard ratio: 2.12, 95% confidence interval: 1.1-4.2; log-rank Mantel-Cox test p=0.03) and was associated with a larger tumor size (Spearman correlation coefficient r=0.237, p=0.001). Moreover, the mean number of tumors was significantly increased in patients with low density of intratumoral mast cells (Fig. 1B, 2.7±0.2 cm vs. 2.2±0.1 cm; p=0.04 unpaired t-test, Welch correction).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Males, n</td>
<td>151</td>
</tr>
<tr>
<td>Females, n</td>
<td>21</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>55.2±7.9</td>
</tr>
<tr>
<td>Mean tumor size, cm</td>
<td>3.94±3.56</td>
</tr>
<tr>
<td>Mean number of tumors, n</td>
<td>2.44±1.65</td>
</tr>
</tbody>
</table>

Tumor grading: T1, n = 28; T2, n = 121; T3, n = 23

Underlying disease: HCV, n = 70; ALD, n = 49; HBV, n = 22; HADV, n = 4; HBV/HCV coinfected, n = 4

Vascular invasion: Beyond Milan criteria, n = 15; Beyond "up to 7" criteria, n = 23

Fig. 1. (A) An example of mast cell tryptase IHC staining in human hepatocarcinoma tumor surrounding tissue. Some (but not all) tryptase positive cells are highlighted by arrows. (B) Intratumoral mast cell density and tumor multiplicity in HCC patients.

Methods

The Austrian HCC patient cohort included 172 patients who underwent orthotopic liver transplantation (OLT) at the General Hospital of Vienna (Table 1). Tissue arrays from HCC tumor tissues and corresponding surrounding tissues have been stained immunohistochemically for mast cell marker tryptase as described in (Rohr-Udilova et al. 2018). Tissue array core diameter was 2 mm, two cores per tumor and one core per corresponding surrounding tissue were analysed for each patient. Tryptase-positive cells were quantified by tissue morphometric analysis and correlated retrospectively with patient survival.

Fig. 2. HCC recurrence and intratumoral mast cells. Density of mast cells in tissues was quantified by computational tissue morphometric analysis in 172 patients; median value (3.9cells/mm2) was used as a cut-off. Log-rank (Mantel-Cox) test was applied.

References