Immunohistochemical study of Aurora kinase B proves association with differentiation and expression of crucial progression markers in gastroenteropancreatic neuroendocrine neoplasms

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Objective
Gastroenteropancreatic neuroendocrine neoplasm (GEP-NENs) are rare and heterogeneous in their tumor biology. Therapeutic options to prevent growth and dissemination are still not satisfactory. As shown previously, survivin and aurora kinases (members of the mitotic chromosomal passenger complex) play a role in cell cycle progression [1]; FOXM1 is a transcription factor that regulates G2/M progression and is associated with grading and metastasis in GEP-NENs [2]. Aurora kinases, survivin and Ki-67 have been described as transcriptional targets of FOXM1. Here, we immunohistochemically analyzed this protein network as potential tumor markers.

Methods
Tumor tissues from 78 patients were studied immunohistochemically with A11 (Aurora kinase B) antibody (>5%; positive) and correlated by the formerly established immunohistochemical analysis of survivin [3]. Additional 28 tissues were studied with anti-FOXM1 antibody and further 22 with anti-STAT3-antibody. The expression pattern was correlated with follow up data such as tumor progression, time of death and cause of death.

Results
The immunohistochemical analysis of Aurora kinase B revealed an association with survivin, as both nuclear scores were positively correlated (p=0.000). We further found associations with the cytosolic localization of STAT3. Aurora kinase B expression was related to high FOXM1 expression (p=0.05). In accordance with the strong association of survivin/FOXM1 expression with grading and differentiation, we found cytosolic Aurora kinase B almost exclusively in G1/G2 tumors, nuclear Aurora kinase B expression in G3 tumors (both: p=0.000).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivin nuclear expression</th>
<th>STAT3 cytoplasmic expression</th>
<th>FOXM1 expression</th>
<th>Differential</th>
<th>Tumor size</th>
<th>Functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aurora B nuclear immunoreactivity</td>
<td>N=78</td>
<td>P=0.001</td>
<td>N=55</td>
<td>N=56</td>
<td>inversely</td>
<td></td>
</tr>
<tr>
<td>Aurora B cytoplasmic immunoreactivity</td>
<td>N=22</td>
<td>P=0.001</td>
<td>N=28</td>
<td>N=78</td>
<td>inversely</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4: Clinicopathological data of included patients

Conclusion
Our study shows that the expression of Aurora kinase B is associated with differentiation, progression and aggressiveness of GEP-NENs. We could demonstrate strong association of Aurora kinase B, FOXM1 and survivin with grading and the Ki67 proliferation status. Therefore this set of markers should be evaluated prospectively in order to better define subtypes of neuroendocrine tumors, especially in the heterogenous G3 tumor group (G3 NEN vs G3 NEC). Moreover, with this work we speculate that regulators of the G2/M cell cycle transition could be generally interesting as new targets to individualize therapeutic strategies in this tumor entity in the future.