Hypoexpression of Galectin-4 Inhibits Invasive Behavior of Primary Pancreatic Adenocarcinoma Cells And Is Associated With Modulation of Wnt/β-catenin Signalling And Reduced Lymph Node Metastasis

Niccola Funel
Oncotarget. 2014;5(14):5335-49

Department of Translational Research and The New Technologies in Medicine and Surgery AIRC-Start-Up, Pisa, Italy
Galectins

- carbohydrate-binding proteins that can recognize carbohydrates attached to proteins/lipids — known as glycoconjugates — on cell surfaces and extracellular matrices.

- have many functions, including mediation of cell adhesion, cell–cell interactions, and modulation of cellular communication.

<table>
<thead>
<tr>
<th>Type</th>
<th>Structure</th>
<th>Galectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>One CRD</td>
<td><img src="image1.png" alt="One CRD" /></td>
<td>1,2,5,7,10,11,13,14,15</td>
</tr>
<tr>
<td>Two CRD</td>
<td><img src="image2.png" alt="Two CRD" /></td>
<td>4,6,8,9,12</td>
</tr>
</tbody>
</table>

Cell–cell and cell-matrix interactions

Receptor-receptor interaction

Signal transduction
Gal-4 is a 323-amino acid (36 kDa) protein predominantly expressed in the luminal epithelia of the gastrointestinal tract, from the tongue to the large intestine.

Gal-4 shows a significantly higher expression in IPMN and in PDAC compared to normal pancreas [Bauer A et al., Panreatology 2009].

BUT...

Gal-4 expression is high in PaTu-S, which shows poor migratory properties, whereas much lower Gal-4 levels are observed in the highly metastatic cells PaTu-T.

Belo et al., PLoS ONE 2013
This study was aimed at

1) Evaluating the expression of Gal-4 in PDAC tissues selected according to their lymph node metastatic status (N0 vs. N1)

2) Evaluating the role of Gal-4 in the metastatic potential of primary PDAC cells and orthotopic models

1) Investigating the therapeutic potential of targeting the cross-link with the Wnt signaling pathway
Gal-4 expression in PDAC patients

- Gal-4 expression is associated with lack of tumor invasion in the lymph nodes.
- Patients with low Gal-4 expression had a significantly higher LNR than patients with high Gal-4 expression.
Gal-4 expression in PDAC primary cells

- Gal-4 is differentially expressed in primary PDAC cells, as well as in their originator tissues.
- PDAC-1 had markedly higher expression of Gal-4 protein with respect to PDAC-2.
Gal-4 expression in PDAC orthotopic models with differential metastatic potential

- PDAC-1 tumors showed a strong staining for Gal-4, while the PDAC-2 tumors had only a weak staining.

- Macroscopic metastases were observed in all the livers of the PDAC-2 mice, while no liver metastases were detected in 33% of the mice of the PDAC-1 group.

- LNR ratio in the PDAC-2 models was 1.4-fold higher than in PDAC-1.
Modulation of Gal-4 expression alters the migratory and invasive behavior of PDAC cells.

Modulation of Gal-4 in our gain- and loss-of-function models support the role of Gal-4 in the inhibition of migration and invasion.
Gal-4 reduced β-catenin levels and sensitizes PDAC cells to the Wnt inhibitor ICG-001

Gal-4 inhibits metastasis by down-regulation of β-catenin and Wnt signaling target genes, in colon rectal cancer [Satelli et al., Int J Cancer 2011]
Gal-4 emerged as a novel tumor suppressor in PDAC, since elevated Gal-4 levels correlated with reduced lymph node metastasis, \textit{in vitro} migratory/invasive behavior and \textit{in vivo} metastasis.

Possibly, Gal-4 cross-links axin, \(\beta\text{-cat}\) and APC, thereby enhancing degradation of \(\beta\text{-cat}\). Furthermore, Gal-4 is shown to inhibit the IL-6/NF-\(\kappa\)B/STAT3 pathway and to induce expression of the Wnt signaling inhibitor Naked1. Collectively, these effects of Gal-4 might contribute to reduced cell migration and sensitization to ICG-001 activity.
Acknowledgements