A bioinformatics approach to evaluating the therapeutic value of galectin-1 and galectin-3 inhibitors in cancer.

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Introduction

Galectins are a family of beta-galactoside-binding lectins that control numerous cellular processes in health and disease, including fibrosis, carcinogenesis and tumour immune evasion. Evidence is starting to emerge that blockade of more than one galectin may provide additional benefit within the oncology arena due to the overlapping biological functions associated with these lectins. Due to the rich and robust external datasets associated with the two most previously studied galectins, we initially investigated the potential therapeutic benefit of a dual blockade approach of Galectin-1 (Gal-1) and Galectin-3 (Gal-3). This insilico exercise initially investigated both the independent and overlapping tumour invasion / metastasis mechanisms associated with Gal-1 and Gal-3. This was then followed by determining which cancer types are most likely to benefit from a combined Gal-1/3 inhibition based on both protein and gene expression patterns and the correlating survival analysis.

Methods

Two datasets were mined for bioinformatics analysis. Firstly, The Cancer Genome Atlas Program (TCGA) which contains gene expression data from cancers and normal tissue samples from a cohort of 11,000 patients, encompassing 33 different tumour types. Available clinical metadata was used to examine associations between Galectin-1 (Gal-1) and Galectin-3 (Gal-3) expression and clinical and pathological parameters. Secondly, the Clinical Proteomic Tumour Analysis Consortium (CPTAC) uses mass spectrometry to profile protein levels in cancer, including all those assessed in the TCGA cohort. Cancer types were ranked based on the association of Galectin expression with clinical or pathological parameters with a negative prognostic value.

Conclusions

Data analysis indicated a select number of cancers that may benefit from therapeutic blockade of both Gal-1 and Gal-3. Pancreatic Adenocarcinoma (based on both gene and protein expression) was a clear top ranking cancer of interest and follow up is currently ongoing around this indication

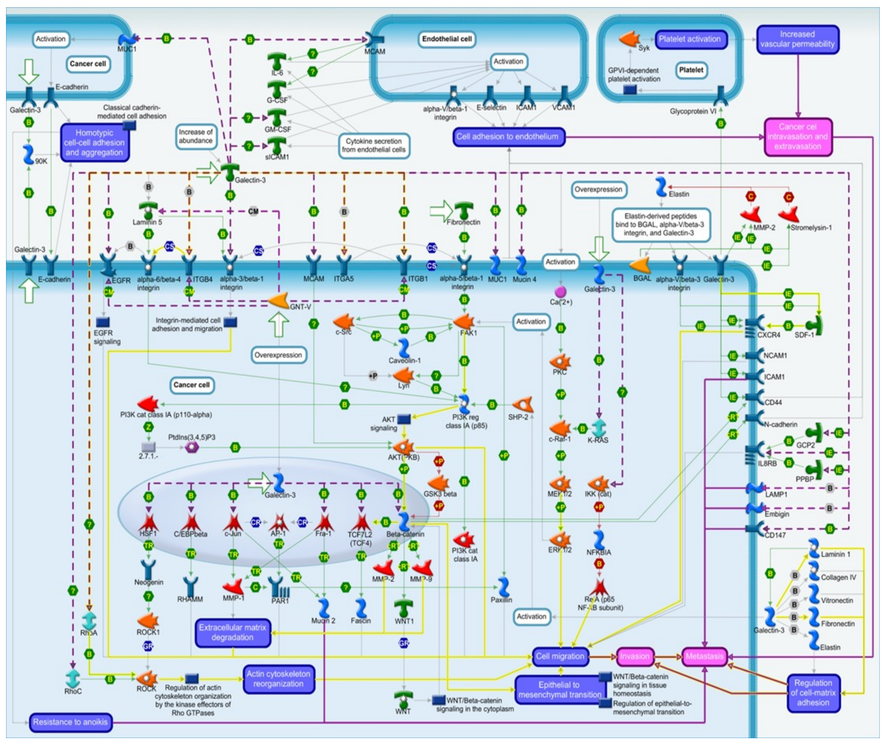
The interactions between Gal-1 and Gal-3 are complex, and a combined blockade approach may be more beneficial due to the different but synergistic roles these galectins play in carcinogenesis and tumour invasion. In addition to our data showing that both are highly expressed in particular cancers, others have shown inhibition of both Gal-1 and Gal-3 is essential for successful treatment of acute lymphoblastic leukaemia in response to chemotherapy[1]. Although the value of galectin inhibitors as single target therapies, in oncology indications, is yet to be determined, our initial analysis has indicated the cancer types most likely to benefit from a combined Gal-1/3 inhibition approach.

References

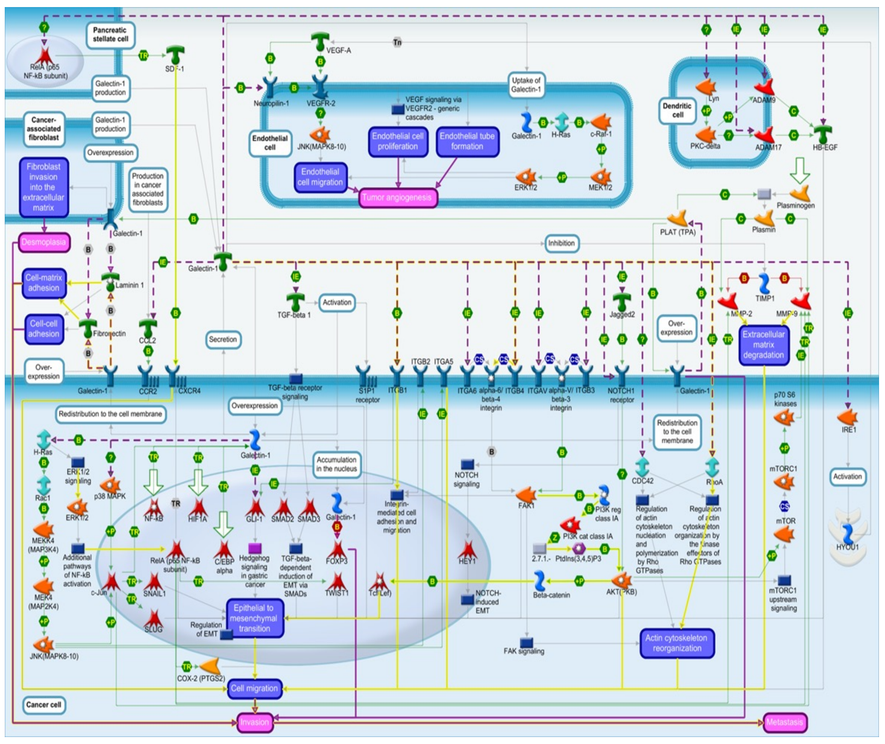
1. Fei et al. 2022. Galectin-1 and Galectin-3 in B-Cell Precursor Acute Lymphoblastic Leukemia. *Int. J. Mol. Sci,* 23 (22), 14359.

Role of Gal-1 and Gal-3 in cancer (tumor invasion and metastasis)

Gal-3



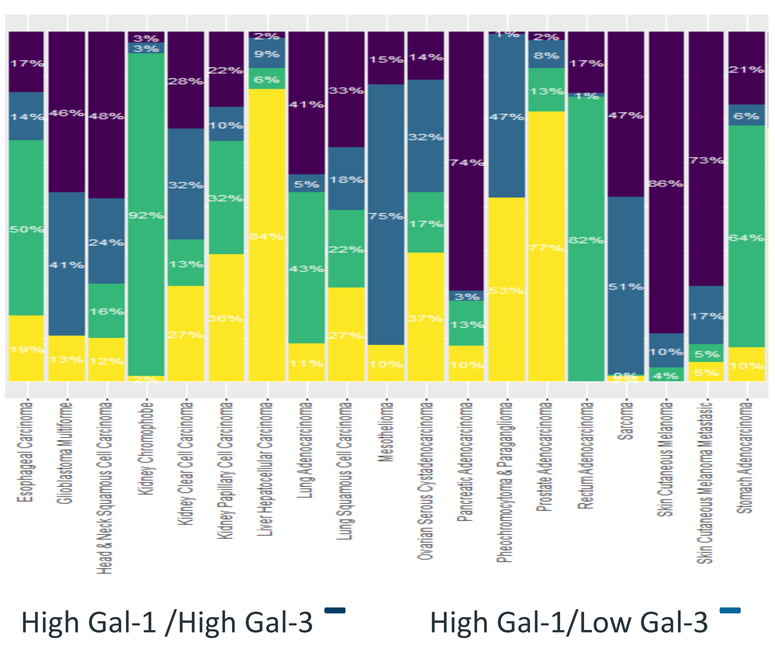
Gal-1



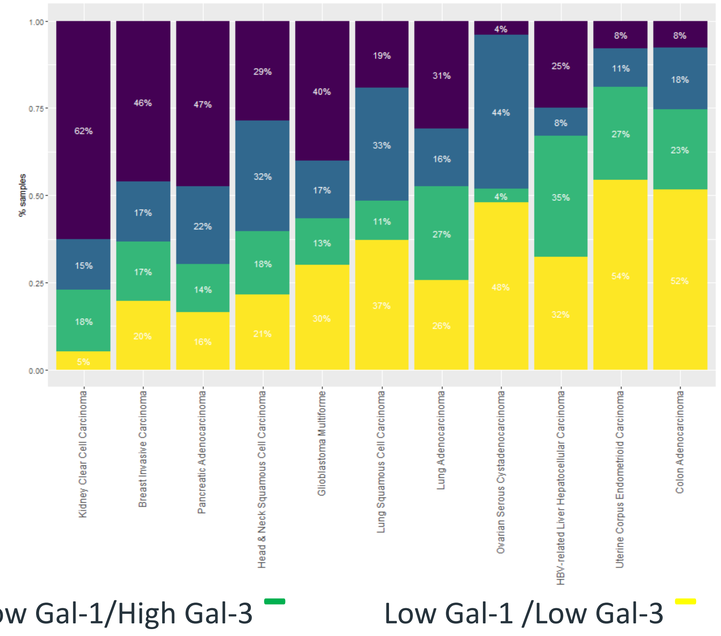
Reconstructive analysis showing Gal-3 (Figure 1, above and left) and Gal-1 (Figure 2, above and right) regulate various pathways in numerous cell types associated tumour invasion and metastasis. Snapshot of overlapping (also highlighted in yellow in the above pathway maps) and divergent pathways between the Gal-1 and Gal-3 in Table 1 (below)

Gal-1 divergent	Gal-3 divergent	Gal-1 and Gal-3 overlapping
RelA (pancreatic cells)	Platelet Glycoprotein 4	Integrins
Fibronectin/Laminin (Cancer cell to fibroblast interactions)	Mucins	MEK-ERK
H-Ras	Endothelial Cytokines	Rho-GTPase

Cancers with high Gal-1 and Gal-3 RNA and protein expression



High Gal-1 /High Gal-3 — High Gal-1/Low Gal-3



Low Gal-1/High Gal-3 — Low Gal-1 /Low Gal-3

Analysis of cohort samples for cancers with the highest RNA (Figure 3, above) and protein (Figure 4, above and right) expression of both Gal-1 and Gal-3.

Figure 5 (right) Violin plots of Gal-1 and Gal-3 RNA expression patterns from Pancreatic Adenocarcinoma cohort samples

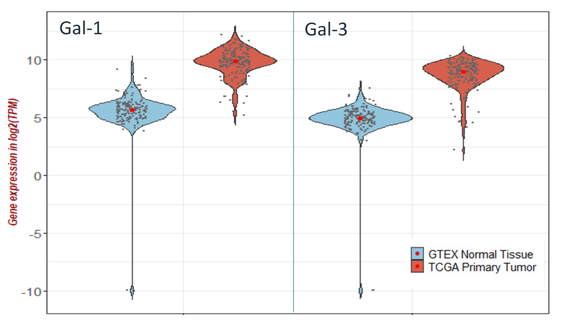
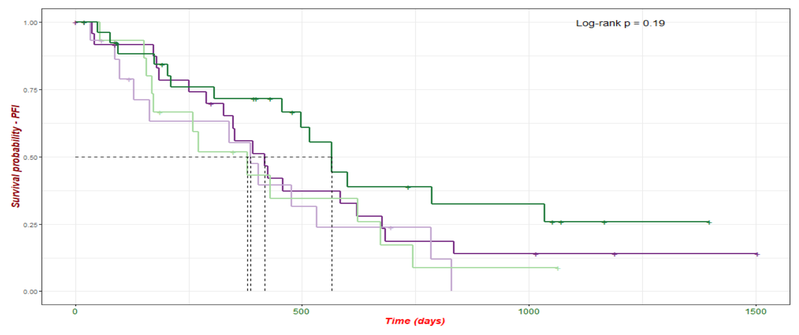
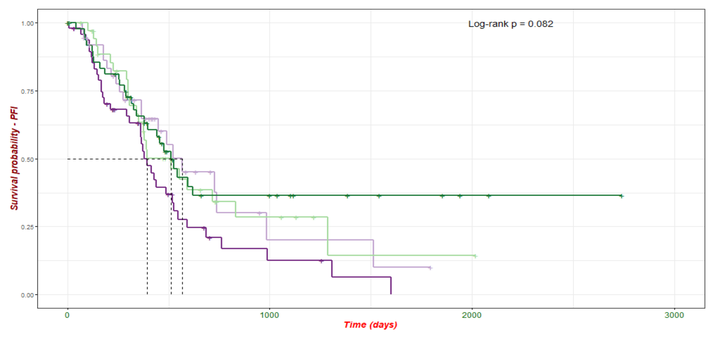


Table 2. High Gal-1 and Gal-3 RNA and Protein expressing cancers

1. Pancreatic Adenocarcinoma
2. Head & Neck Squamous Cell Carcinoma
3. Glioblastoma Multiforme

Survival correlates with Gal-1 and Gal-3 protein and RNA expression in Pancreatic Cancer





High Gal-1 /High Gal-3 — High Gal-1/Low Gal-3 — Low Gal-1/High Gal-3 — Low Gal-1 /Low Gal-3

Regarding the high/low categorization. the within-cancer median expression was used as a threshold to categorize samples, and a Log-rank test was performed, which reports a p-value (stated in each plot). Both survival plots are currently not statistically significant due to the relatively low number of samples in each cohort ≤50 for RNA and ≤27 for protein

Figure 6 (above and left) Pancreatic Adenocarcinoma survival rates were higher in patients with low Galectin-1 and Galectin-3 protein expression (dark green line) compared to high Gal-1 and Gal-3 expression (dark purple line). This observation was replicated when correlating with RNA expression profiles, Figure 7 (above and right)

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