Galectin-1 as a therapeutic target in pancreatic cancer: the tumor stroma in the spotlight

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Treating pancreatic cancer is one of the great challenges in cancer research and identification of new strategies is a must, considering the poor efficiency of standard chemotherapy and current patients’ dismal prognosis. We have recently identified Galectin-1 as a master regulator driving pancreatic cancer progression in the Ela-myc model. Interestingly, Galectin-1 depletion in these tumors not only results in decreased tumor cell proliferation but also in a profound remodeling of the desmoplastic reaction, impairing angiogenesis, stroma activation and boosting the animal immune response. Intriguingly, our experimental data indicate that Galectin-1 regulates the Hedgehog signaling pathway, which may well be responsible for some of the effects driven by the lectin in pancreatic cancer. We herein discuss how Galectin-1 may remodel the tumor microenvironment in this pathology and highlight its potential as a therapeutic target.

Keywords: pancreatic cancer; Galectin-1; tumor microenvironment; desmoplasia; stroma; angiogenesis; immune surveillance; Hedgehog


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Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancers, accounting for the fourth cause of cancer related deaths in developed countries. Although incidence rates are not very high compared to many other neoplasias, its dismal prognosis (with a 5 year survival rate lower than 5% [1]) renders PDAC one of the outstanding issues for cancer research and oncologists, being considered as the second cause of cancer related death in US by 2030 [2]. Only around 20% of the cases show localized and small tumors that are subject to surgical resection. For most of the diagnosed patients, though, current therapies include chemotherapy administration mostly focused on tumor epithelial cells, which show, in general, a very modest benefit. Interestingly, recent data have demonstrated that PDAC resistance to conventional chemotherapy is due to its intrinsic abundant fibrotic stroma, rendering drug delivery very inefficient. Accordingly, targeting pancreatic tumor microenvironment has emerged as a promising novel therapy for this pathology [3-8]. The tumor microenvironment of PDAC is characterized by the presence of a very important desmoplastic reaction gathering around tumor cells a dense extracellular matrix as well as activated fibroblasts, blood vessels and immune and inflammatory cells. All these elements form a complex microenvironmental network that continuously signals to
tumor cells influencing their behavior, being critical for tumor development and progression.

Galectin-1 (Gal1) is a galactoside binding protein that is highly overexpressed in the pancreatic tumoral stroma[9]. In vitro experiments have shown that Gal1 is involved in pancreatic stellate cell activation [10,11], contributing to the immune escape [12] and favoring tumor invasion and migration [13,14]. Although in humans, Gal1 tumor levels faithfully correlate with PDA stage [15] and patient survival [16,17], previous studies were only descriptive and did not provide any insights about the mechanism of the in vivo Gal1 role during pancreatic tumor progression. In order to cover this gap, we have recently analyzed the effects of Gal1 depletion using a transgenic mice model that develops pancreatic tumors [18]. Interestingly, one of our major findings was that Gal1 depletion in Ela-myc mice results in tumor microenvironment remodeling (Figure 1), rendering an increase of the 20% in animal lifespan. Gal1-mediated changes in tumor stroma comprise induction of angiogenesis and fibroblasts activation, as well as contribution to the tumor immune privilege by reducing the amount of T cells and neutrophils (Figure 1). Besides, Gal1 also increases proliferation of tumor epithelial cells and is involved in the acinar-to-ductal metaplasia, a critical event linked to tumor initiation [19].

Gal1 effects observed on the tumor microenvironment in this pancreatic cancer model can be explained by several

Figure 1. Gal1 drives pancreatic cancer progression in the Ela-myc model. Gal1 is involved in pancreatic tumor progression by increasing tumor cell proliferation and remodeling the desmoplastic reaction including boosting stroma activation, stimulating angiogenesis and silencing of the immune response by inducing T-cell apoptosis and impairing neutrophil recruitment.
mechanisms. First, Gal1-induced angiogenesis in pancreatic cancer might be mediated by activation of H-Ras/Erk signaling that promotes endothelial cell proliferation and migration, as previously reported in other tumors [20,21]. Moreover, Croci et al. have recently described that Gal1 interaction with VEGFR2 results in receptor activation independently of VEGF and is sufficient to trigger pro-angiogenic signals [22]. Interestingly, targeting Gal1 turns out to render anti-VEGF refractory tumors into sensitive ones, highlighting the relevance of Gal1 as an anti-angiogenic therapy.

Regarding the reduction on T cell and neutrophil infiltrates observed upon Gal1 depletion in vivo, it has been reported that Gal1 interaction with TCR and other glycosylated cell membrane receptors triggers T cell apoptosis and hampers full T cell activation and proliferation [23-25]. Besides, in vitro studies have also revealed that Gal1 is able to impair neutrophil chemotaxis and migration via carbohydrate binding to CD43 and p38 activation [26, 27]. Remarkably, our evidence on the in vivo role of Gal1 in silencing the tumor immune attack in pancreatic cancer gives strength to the putative use of Gal1 inhibition for PDAC immunotherapy [28].

On the other hand, our molecular analysis provides the first evidence that the Hedgehog (Hh) signaling pathway is one of the mechanisms responsible for Gal1 effects in tumor fibroblasts activation, bridging the lectin to one of the core signaling pathways in pancreatic cancer [29]. Hh signaling pathway is crucial in pancreas development and one of the best characterized mediators of the PDAC desmoplastic reaction [30-32]. Canonical Hh signaling pathway is characterized by ligand binding to the transmembrane protein patched (Ptc), which results in smoothened (Smo) derepression and allows Gli transcription factors to translocate into the nucleus, where they activate gene expression, including Gli1 and Ptc1 among others. Besides, a non-canonical mechanism has been described, where Gli target genes can be regulated by K-Ras and TGF-β, unconnected to the Ptc-Smo axis [33]. Indeed, it has been described that the canonical Hh pathway would be active in the stromal compartment, by responding in a paracrine manner to the Hh ligands expressed by tumor epithelial cells, whereas the non-canonical pathway would explain transcription of Gli target genes in the epithelial compartment. The relevance of Hh pathway in PDAC has been disclosed by several reports showing its role in tumor initiation, growth and metastasis [34-39]. Interestingly, in our work we have shown that Gal1 is able to regulate Gli target genes both in pancreatic epithelial cells and in fibroblasts, suggesting that Gal1 could be mediating the tumor/stroma crosstalk by modulating the Hh signaling pathway. Our data finding Gli1 levels to be also regulated by Gal1 in the epithelial compartment both in vitro and in vivo fits with the non-canonical mechanism [33]. Indeed, Nolan-Stevaux et al. described that K-Ras and TGF-β regulate Gli1 and Ptc1 in the epithelial compartment, linking their expression to cell survival and transformation. Considering that Gal1 can be regulated by TGF-β [40,41] and that Gal1 is able to increase K-Ras activation [42], our data might help to understand the molecular events linking TGF-β and K-Ras to Gli target gene activation in the Hh non-canonical signaling pathway. Moreover, it is also interesting to note that CXCL12/CXCR4 regulates Hh levels in pancreatic cancer cells [43] and that Gal1 induces CXCR4 expression [44], offering another possible way to explain Gal1 regulation of Hh activity. In addition to stroma activation, the Hh signaling pathway may be responsible, at least in part, for some of the other Gal1 driven effects that we observe in our in vivo pancreatic tumors such as pancreatic cell proliferation [37,45-47], angiogenesis [48,49], immune surveillance escape [50-52] and acinar-ductal metaplasia [37].

Altogether, our data finding that the multiple effects observed in tumor microenvironment after Gal1 depletion in pancreatic tumors results in increased animal survival would stand for considering targeting the stroma in this pathology. However, the state of the art regarding the role of the stroma in promoting pancreatic tumor progression and the role of the Hh signaling pathway as a master regulator of this dangerous desmplastic reaction have been shaken very recently with two important papers describing that stromal abolishment (either through depletion of tumor fibroblasts or by deleting Hh in the pancreas) leads to increased survival in K-Ras driven mice models of pancreatic cancer [53,54]. These data contradicts previous similar in vivo works in which targeting the stromal compartment resulted in an improvement on chemotherapy delivery and increased survival [3-5] and try to explain the big disappointments that the medical community has faced upon trying Hh inhibitors in clinical trials [55]. However, these studies should be taken with caution because the genetic strategies used lead to almost a complete disruption of the tissue surrounding the tumor mass. Still, we do understand any tissue, even in a neoplastic situation, as a delicate organized system, and we bet on therapies targeting the stroma against particular pro-tumoral signals, rather than completely abrogating the desmplastic reaction.

Thus, considering our preclinical data finding that targeting Gal1 in pancreatic cancer in vivo results in impaired tumor proliferation, stroma activation, angiogenesis and acinar-ductal metaplasia while it reinforces the anti-tumor immune response (Figure 1), and taking into account that: 1) Gal1 is not expressed in the normal pancreas, 2) Gal1 deficiency in mice does not
compromise viability and 3) a clear phenotype was already observed upon single loss of one allele of the lectin; we do believe that targeting Ga1 in pancreatic cancer could bring a breath of fresh air into this pathology and shed light on new approaches to surmount its dismal prognosis. Still, Ga1 multifunctionality and the complex repertoire of glycans present in tumor cells jeopardize optimistic speculations\(^{[56]}\) and render further future studies with Ga1 blocking strategies as an imperative need in pancreatic cancer research.

**Conflicting interests**

The authors have declared that no competing interests exist.

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