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REVIEW

The emerging role of galectins in high-fatality cancers

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Abstract Although we witnessed considerable progress in the prevention and treatment of cancer during the past few decades, a number of cancers remain difficult to treat. The main reasons for this are a lack of effective biomarkers necessary for an early detection and inefficient treatments for cancer that are diagnosed at late stages of the disease. Because of their alarmin-like properties and their protumorigenic role during cancer progression, members of the galectin family are uniquely positioned to provide information that could be used for the exploration of possible avenues for the treatment of high fatality cancer (HFC). A rapid overview of studies that examined the expressions and functions of galectins in cancer cells reveals that they play a central role in at least three major features that characterize HFCs: (1) induction of systemic and local immunosuppression, (2) chemoresistance of cancer cells, and (3) increased invasive behavior. Defining the galectinome in HFCs will also lead to a better understanding of tumor heterogeneity while providing critical information that could improve the accuracy of biomarker panels for a more personalized treatment of HFCs. In this review, we discuss the relevance of the galectinome in HFC and its possible contribution to providing potential solutions.

Keywords Galectins · High fatality cancer · Biomarker · Galectinome

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Abbreviations

HFC	High fatality cancer
TNBC	Triple-negative breast cancer
HGSC	High grade serous ovarian carcinoma
CRD	Carbohydrate-recognition domains
NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
HCC	Hepatocellular carcinoma
MPM	Malignant pleural mesothelioma
AML	Acute myeloid leukemia

Introduction on high fatality cancer

The definition of high fatality cancer (HFC) remains unclear and is often debated. For many, it is related to cancers for which a diagnosis can be a death sentence. In practice, and for the purpose of this review, HFCs are defined as cancers for which the five-year survival rate after diagnosis is below 25–30% (Fig. 1). They compose most of what is sometimes called "high mortality cancers", which include cancers with survival rates of less than 50%, as defined by the National Cancer Institute in President Obama's High Mortality Cancer Bill of 2013. Of course, these rates will vary according to both intrinsic (e.g., genetic) and extrinsic factors (e.g., lifestyle, environmental factors). Yet, HFCs can be arbitrarily classified into two broad categories: those in which little progress has been made (i.e., pancreatic, liver, non-small cell lung cancer, mesothelioma, gastric and glioblastoma), and high fatality subtypes ("bad" cancers among the "good", i.e., triple negative breast cancer (TNBC), high grade serous ovarian cancer (HGSC), acute myeloid leukemia (AML), or castrate resistant prostate cancer). The former category often refers to cancers that remain relatively rare. For example, there are approximately less than 2–5 gallbladder cancer

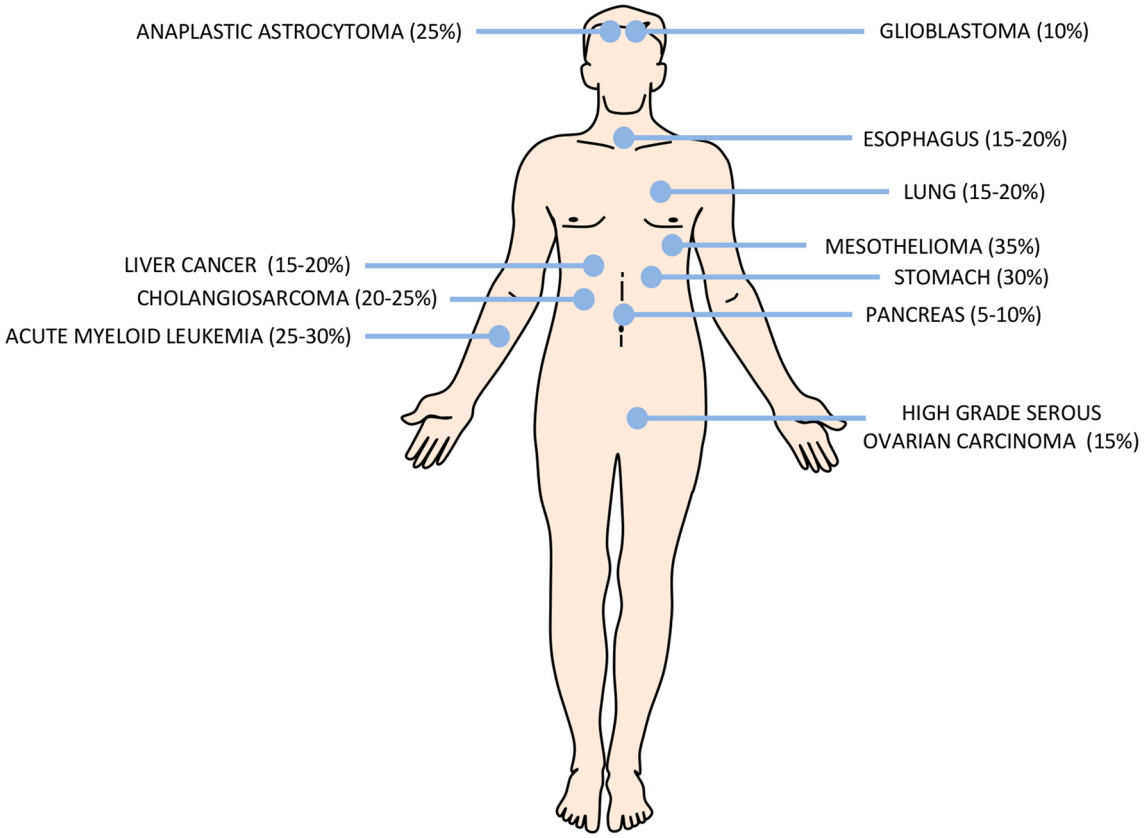

Fig. 1 High fatality cancer (HFCs) according to body location. Illustration of the major HFCs and the percentages indicate the approximative 5-year survival rate according to the 2017 annual report of the American Cancer Society (http://www.cancer.org)

cases per 100,000 persons, making it the 20th most frequent cancer in the world (http://www.wcrf.org). Unfortunately, others, such as lung cancer (30–50 cases per 100,000 persons) and breast cancer (more than 100 cases per 100,000 persons in more developed countries), are more frequent and largely responsible for high mortality rates. Clearly, there is an urgent need to develop new biomarkers that can be used to identify people at risk and to develop treatment with greater efficacy.

Galectins

Galectins are multifunctional proteins that belong to the animal lectin family. All galectins share similar binding affinities to β-galactosides and display high amino acid sequence homology among their carbohydrate-recognition domains (CRDs) [1]. In mammals, 19 different members of this family have been identified, with 13 of them being expressed in humans (galectin-5, -6, -11, -15, -16, -19, and -20 are not found in humans). Galectins are divided into three sub-groups according to their structure: prototypic galectins containing one CRD (Gal-1, -2, -5, -7, -10, -11, -13, -14, -15, -16, -17, -19, and -20), tandem-repeat galectins containing two covalently linked CRDs (Gal-4, -6, -8, -9 and -12) and chimera-type galectins containing multiple CRDs linked by their amino-terminal domain (Gal-3). While these proteins perform homeostatic functions inside normal cells, under pathological or stress conditions, galectins are released either passively from dead cells or actively via non-classical secretion pathways. Once released into the extracellular milieu, they bind to repeating units of high density N- and O-glycans on the peptide backbone of membrane receptors via their CRD. This ability of galectins to promote the packing of glycosylated receptors into an ordered cross-linked lattice at the cell surface is facilitated by their inherent multivalency. Such cross-linking of glycosylated receptors triggers signals that are critical for the regulation of cell fate.

Galectins as potential therapeutic targets in HFC?

While the main reasons for the high mortality rates for HFCs are linked to a late diagnosis, other factors that contribute to their aggressiveness include an elevated growth rate, sequestration from the immune system, lack of effective treatments,

therapeutic resistance, metastasis, tumor microenvironment, dormancy and heterogeneity of the tumor. Because galectins have been shown to modulate most if not all these processes and can thus play a crucial role at different stages of cancer progression, their potential as therapeutic targets in HFC is high. The revived interest in designing new and effective immunotherapies for cancer treatment has further placed the galectin under the projector. This is largely due to recent studies showing that almost all secreted galectins share the ability to build an immunosuppressive microenvironment that helps tumor cells escape cancer-killing immune cells [2]. Such immunosuppressive activity represents a major obstacle to cancer treatment and slows down the pace of progress in cancer immunotherapy, a promising avenue for the treatment of aggressive cancers for which there are limited treatment options. This immunosuppressive function of galectins has been well-described during pregnancy, in which placental galectins have been shown to be essential for establishing immune tolerance that protects the fetus from an aggressive maternal allogeneic response [3, 4]. Such new paradigm attracts the interest of many researchers involved in the development of novel immunotherapies that target immune checkpoints, a valuable strategy for the treatment of HFC, most notably for those harboring an immune phenotype. The role of galectins in controlling immunological homeostasis explains that they are often considered alarmin-like proteins, a family of structurally unrelated proteins that are released from intracellular compartments in the milieu in response to stress signals or cell damage [5, 6]. However, the role of galectins in cancer is by far not limited to their immunomodulatory role. There is a large amount of literature establishing galectins as a group of proteins that induce resistance to drug-induced cell death or promote metastasis by facilitating cell-to-cell and cell-to-matrix adhesion. In the section below, we briefly review some of the key findings and recent advances illustrating the emergence of galectins as potential therapeutic targets in HFC.

Pancreatic cancer

Pancreatic ductal adenocarcinoma is the preeminent subtype of pancreatic cancer. The 5-year survival is less than 10% in the USA and the overall survival after being diagnosed varies between 3 and 6 months if no treatment is given (http://www.cancer.org). The main reason for pancreatic cancer having a poor prognosis is the late stage at which the disease is discovered. It is an asymptomatic disease that comes with an early metastasis and recurrence risk, as well as chemoresistance and radioresistance problems. At present, most of the studies on the role of galectins in pancreatic cancer have focused on gal-1 and gal-3. The role of gal-1 in pancreatic cancer has been mostly linked to its immunomodulatory properties and the potential for targeting extracellular gal-1 to restore the immunological barrier to cancer has been relatively well-documented, making gal-1 a strong candidate for pancreatic cancer therapy [7]. Gal-3, like gal-1, is also expressed at abnormally high levels in human pancreatic tumor tissue [8, 9]. The role of gal-3 in pancreatic cancer, however, is not linked to its extracellular form but to its ability to modulate intracellular signaling events by increasing Ras activity, thereby stimulating growth and invasive behavior of pancreatic cancer cells [10]. Such a role of gal-3 in pancreatic cell migration and invasion has also been reported by Kobayashi et al. [11]. The ability of gal-3 to modulate key signaling pathways, including the Akt pathway, also increases the resistance of pancreatic cancer cells to chemotherapy-induced apoptosis [12]. Two recent studies have shown, however, that galectins may not always be protumorigenic in pancreatic cancer. Van Die and colleagues recently reported that gal-4, which is absent in healthy pancreatic tissue but expressed at high levels in pancreatic cancer cells, has tumor suppressive functions [13, 14]. The authors showed that de novo expression of gal-4 interferes with the Wnt/β-catenin pathway and inhibits the invasive behavior of human pancreatic cancer cell lines and primary pancreatic ductal adenocarcinoma cells. However, although there are indications suggesting that galectins are important for pancreatic cancer progression, clearly, additional knowledge of their expressions and functions in pancreatic cancer cells is deeply needed, especially for the less well-known galectins.

Lung cancer

Because lung cancer is the deadliest form of cancer in terms of the number of victims worldwide [15–17], there has been considerable research on the role of galectins in lung cancer. There are two main subtypes of lung cancer; 85% are non-small cell lung cancer (NSCLC) and 15% are small cell lung cancer (SCLC), and they are associated with a 5-year overall survival rate of approximately 15 and 7%, respectively [15, 18]. The SCLC form is the more aggressive subtype, with an estimated life expectancy of 7 months if no treatment is given [18, 19]. The advanced stage at which it is diagnosed, the lack of an efficient early diagnosis technique, the rapid metastasis formation and the molecular complexity of this disease are the major factors that make SCLC an HFC [18]. These factors are also an obstacle to the survival of NSCLC patients, for whom the median survival is between 8 and 10 months [20–22]. Similarly to pancreatic cancer and other cancers, most of the research on galectins in lung cancer has focused on gal-1 and gal-3. Again, the role of gal-1 in modulating the antitumoral response and suppressing cancer-killing immune cells is well-documented [23–25]. This is not, however, the only role of gal-1 in lung cancer, as a number of studies have shown that it also promotes

cancer progression by increasing the invasive behavior of lung cancer cells (Table 1). A protumorigenic role of gal-3 in lung cancer has also been attributed to intracellular gal-3 and its ability to modulate key signaling pathways, such as the β-catenin pathway [26]. However, while the roles of gal-1 and gal-3 in lung cancer generally mirror their roles in pancreatic cancer, this is certainly not the case for gal-4. Using biopsies collected from a cohort of more than 700 patients with lung adenocarcinoma, Hayashi and colleagues [27] showed that expression of intracellular gal-4 is inversely associated with clinicopathologic variables of disease progression. Such an anti-tumorigenic role of galectins in lung cancer is not unique to gal-4 as it has also been shown for gal-9 [28, 29], illustrating, again, their well-documented double-edged swords for their function [3]. Such opposing roles for galectins in HFC are also observed in stomach cancer. Again, while gal-1 is generally associated with tumor progression of stomach cancer, gal-7 and gal-9 express anti-tumorigenic properties [23, 25].

Brain cancer

The most common type of brain cancer diagnosed, glioblastoma multiforme, is also the most aggressive [30, 31]. The incidence of this grade IV astrocytoma is approximately 3 per 100,000 persons. Glioblastoma multiforme displays a median survival of 14.6 months [31, 32]. Another type of brain tumor with a low survival rate is anaplastic astrocytoma, a grade III astrocytoma with a 5-year survival rate of approximately 10% for people older than 55-years of age. An important restriction for the treatment of brain cancers is the blood–brain barrier, which restricts the passage of drugs. The heterogeneity of the disease and the higher proportion of recurrence or therapy resistance are among the reasons leading to this unfavorable prognosis [30, 33]. In this case, the role of galectins is unequivocal since most, if not all, studies on gal-1, -3, and -8 have reported these galectins as having a protumorigenic role (Table 1). The role of gal-1 secreted by glioma cancer cells in inhibiting infiltration of myeloid-derived suppressor cells confirms the importance of this galectin in controlling the anti-cancer immune response [34]. The ability of gal-1 and gal-3 to promote the migration and invasion of cancer cells is also a central theme in studies aimed at defining the role of galectins in brain cancer. There is, however, much to be learned about the role of galectins in brain cancer since all but one study have focused almost exclusively on gal-1 and gal-3.

Liver cancer

Liver cancer has the second highest mortality rate worldwide. Hepatocellular carcinoma (HCC) is the most common malignant hepatic disease [35]. The 5-year overall survival is approximately 10–20% but increases to 70% after a surgery [36–39]. Liver transplantation and other resection surgeries are effective procedures for this disease, but the late stage at which it is diagnosed, limited availability of organ donation, problem of recurrence and other associated liver dysfunctions are important obstacles to the successful therapy of HCC [36, 40]. What is unique to liver cancer is the dominant roles of gal-1 and gal-3 in conferring resistance of cancer cells to cell death induced by either antibodies or chemotherapeutic drugs (Table 1). A fair amount of studies on galectins in liver cancer have focused on gal-3 and its role in migration and invasion [41–43]. A number of studies have also focused on gal-9, which seems to have an anti-proliferative effect on hepatocarcinoma and cholangiocarcinoma cells [44–46].

Other HFCs

Very few studies have examined the role of galectins in other HFCs, including gallbladder cancer, a relatively rare (a global incidence of 2.2 per 100,000) [125, 126] but deadly disease. The 5-year overall survival rate of gallbladder cancer does not exceed 5% and it is associated with an average survival of 6 months [127]. Surprisingly, to our knowledge, there is only one study published on the roles of gal-1 and gal-3, the most commonly studied galectins in cancer. Yang et al. [128] have shown that an increased expression of gal-3 was associated with a decreased overall survival of patients with gallbladder adenocarcinoma. However, a recent study by a group in Japan has shown that gal-9 suppresses the growth of cancer cells and their resistance to apoptosis [129]. Such an antitumoral role of gal-9 has also been found in gastric cancer [130], the fourth most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide, with an incidence rate that varies greatly (from 2 to 3 in Egypt, and up to 65.9 in men and 25.9 in women in Korea) [131, 132]. On average, people diagnosed with stomach cancer have a 25% chance of living at least 5 years after their diagnosis. In contrast, the protumorigenic role of gal-1 and gal-3 in promoting invasive behavior and a resistance to drug-induced apoptosis in gastric cancer is relatively well-documented (Table 1). Preliminary reports have been published on the expressions of gal-4, gal-7 and gal-8 in gastric cancer [121, 133, 134]. However, functional data are lacking with regards to their role in tumor progression. On the other hand, a number of studies are now focusing on high mortality ("bad") subtypes of cancer that have a relatively high 5-year survival rate. This is the case, for example, for high grade serous ovarian carcinoma (HGSC), which has a 5-year survival rate of less than 15% while the overall survival rate of ovarian cancer is approximately 46%, in the US (http://www.cancer.org). Recent studies have shown that gal-3 and gal-7 may confer epithelial ovarian cancer cells

Table 1 Functional effects of galectins in HFCs

Cancer type	Subtypes	Galectins	Effect	References
Liver	Hepatocellular carcinoma	Gal-1	↑ Tumor progression	[47–54]
			Contribute to resistance to antibody-mediated killing of cancer cells	[55]
			Contribute to Sorafenib and Cisplatin chemoresistance	[49, 56]
		Gal-3	↑ Tumor progression	[41–43, 57–62]
		Gal-4	↑ Tumor progression	[63]
		Gal-9	Interact with Tim-3 to promote degeneration of T cells	[64]
			↓ Tumor progression	[44, 65]
			Gal-9 expression correlates with recurrence of cancer	[66]
	Cholangiocarcinoma	Gal-1	↑ Tumor progression	[67]
		Gal-3	↑ Anti-apoptosis capacities of cancer cells	[68]
			Contribute to the chemoresistance	
			Involved in the preneoplasic and neoplasic transformation	[67]
		Gal-9	↓ Tumor progression	[45]
	General	Gal-9	Gal-9 induced lymphocyte apoptosis and tumor cell immune escape	[46]
Brain	Glioblastomas	Gal-1	↑ Tumor progression	[28, 34, 69–72]
			Contribute to the chemoresistance	[29]
			Reduces motility	[73]
		Gal-3	↑ Tumor progression	[71]
			Enhances the adhesion of homotypic tumor cell	[74]
		Gal-8	↑ Tumor progression	[71]
	Astrocytomas	Gal-1	↑ Tumor progression	[71, 72]
		Gal-3	↑ Tumor progression	[71, 75]
		Gal-8	↑ Tumor progression	[71]
	General	Gal-1	↑ tumor progression	[76, 77]
			Silencing of tumor-derived gal-1 increased survival	[34]
		Gal-3	↑ Tumor progression	[78, 79]
Ovaries	Serous high grade	Gal-3	↓ Cellular proliferation of Clear Carcinoma cancer cells	[80]
			Contribute to the chemoresistance to CDDP	
		Gal-7	↑ Tumor progression	[81, 82]
Breast	Triple negative	Gal-3	↑ Tumor progression	[83]
		Gal-7	↑ Tumor progression	[158]
Pancreatic	Undefined	Gal-1	↑ Tumor progression and tumor evasion	[7, 84–91]
		Gal-3	↑ Tumor progression and chemoresistance	[10, 12, 89, 92, 93]
		Gal-4	↓ The tumors progression	[13, 14]
Lung	Undefined	Gal-1	↑ Tumor progression, chemoresistance and tumor evasion	[23, 24, 94–98]
		Gal-3	↑ Tumor progression and chemoresistance	[26, 99–106]
		Gal-4	↑ Tumor progression	[27]
		Gal-9	↓ Tumor progression	[107, 108]
Oesophagus	Undefined	Gal-3	Nuclear gal-3 inversely correlates with vascular invasion	[109]
			↑ Tumor progression	
			↑ Chemoresistance to Gefitinib treatment	[110]
		Gal-7	↑ Tumor progression	[111]
Stomach	Undefined	Gal-1	↑ Tumor progression	[112, 113]
		Gal-3	↑ Tumor progression	[114–119]
			↓ Metastasis formation	[120]
			Contribute to the chemotherapy resistance of cancer cells	[119]
		Gal-7	↓ Tumor progression	[121]
		Gal-9	↓ Tumor progression	[122–124]

with resistance to drug-induced apoptosis [80–82]. This field of research is likely to rapidly progress as we are now to able to refine the classification of cancer subtypes and identify novel aggressive molecular subtypes with the help of comparative transcriptome analysis of large cohort of patients.

Galectins as biomarkers in HFCs

Currently, considerable efforts are being dedicated to the development of predictive biomarkers for the early detection of HFC and for the initiation of treatment in the early stages of progression before metastasis. The benefit of early detection using imaging procedures, routine clinical exams, cytology screening, or blood tests has been well-established for several cancers, including breast, colon, prostate and cervical cancers. Biomarkers are also used to assess disease susceptibility and risk, grading severity of the disease, the determination of an optimal treatment or predicting outcomes to a specific treatment. They are at the center of precision medicine, which requires better stratification of patients. Ideally, they are used as companion tests in harmony with a given therapeutic drug. A case in point is testing for HER-2 expression, which classifies patients with breast cancer into two categories: responders and non-responders to targeted therapy with Trastuzumab (Herceptin). This immunohistochemistry test detects the expression of HER-2 membrane proteins at the surface of epithelial breast cancer cells. Although the "Her-2 test", which was approved in 1998, has survived numerous obstacles linked to reproducibility and quantification, the general view is that measurements of plasma biomarkers by ELISA testing are better suited not only because of the ease and its relatively non-invasive nature but also because this assay is more quantifiable and reproducible. Not surprisingly, given the soluble nature of galectins and their release outside of cells, plasma levels of galectins are now commonly used as a predictive biomarker in many diseases. The best-known galectin plasma biomarker is probably gal-13, also known as PP-13, which is specifically expressed in placental tissues where it plays a central role in maternal–fetal immune tolerance [135]. Its potential as a biomarker alone or in combination with other biomarkers for detecting pre-eclampsia in the first trimester has been well-documented and tested clinically [136–138]. Another good example is plasmatic gal-3, which is commonly used as a biomarker in patients with various vascular diseases, thereby helping in the prognosis of these patients [139]. Measurements of plasma galectin-3 were approved by the US Food and Drug Administration in 2011 as helping in the prognosis of patients with heart failure. Abnormally high levels of galectins have also been reported in many other diseases, including colorectal cancer [140], acute intracerebral hemorrhage [141], pulmonary arterial hypertension [142], prediabetes and diabetes [143, 144], systemic lupus erythematosus [145] and viral infections [146]. Galectin levels have also been shown to be elevated in patients with HFCs such as pancreatic cancer [147]. Clearly, levels of galectins in plasma samples and other liquid biopsies can be used for prognostic purposes. However, given their dual role in cancer, it is logical to believe that plasma levels of a given galectin may not necessarily correlate with the cancer's aggressiveness. This is well-illustrated in malignant pleural mesothelioma (MPM), the most frequent type of mesothelioma, which has a median survival time of approximately 12 months after diagnosis [148]. Gal-3 concentrations in pleural fluids are significantly lower in MPM than in lung adenocarcinoma. Gal-3 can thus be used to differentiate MPM from lung adenocarcinoma and as a negative marker to exclude a diagnosis of MPM [149, 150]. This is in contrast to gal-1. In this case, high concentrations of gal-1 in pleural fluids correlates with a lower overall survival [151], which is consistent with its well-documented role in creating an immunosuppressive tumor microenvironment [152]. Whether other galectins are present in pleural effusion or other liquid biopsies (including cerebrospinal fluids, which contains several biomarkers for different forms of brain cancer) remains unknown. The potential of using galectins in liquid biopsies as a predictive tool in cancer patients, however, is a rapidly evolving field of research investigation, and there are reasons to believe that they may be useful, alone or in combination, for prognostic purposes or for predicting responses to treatment. A good example is the combination of galectins and MUC-1 as potential biomarkers for metastatic breast cancer [153], reinforcing the association between galectins and MUC-1, a highly glycosylated cell surface receptor expressed on the surface of cancer cells [154, 155].

Predictive value of intracellular galectins

Although most of the attention on galectins has historically focused on their extracellular functions, their intracellular patterns of expression are often significantly altered in cancers compared to normal cells. In cancer cells, they can be found almost anywhere, including in cytosolic, nuclear, and mitochondrial compartments, where they accomplish distinct and often contradictory functions [156]. Such distinct patterns of expression can be exploited for the development of biomarkers for risk prediction in cancer patients. A good example is galectin-8, a galectin known to shuttle between the nucleus and the cytosol in cancer cells [157]. Our recent studies showed that nuclear, but not cytosolic, gal-8 is associated with a good prognosis in patients diagnosed with TNBC, one of the most aggressive subtypes of breast cancer. TNBC patients with nuclear gal-8 have a significantly

better disease-free survival, metastasis, and overall survival [158]. This is in contrast to nuclear gal-1, which is rather associated with a poor prognosis. Interestingly, in TNBC patients who expressed both nuclear gal-1 and gal-8, the phenotype of nuclear gal-8 is clearly dominant. Indeed, despite having nuclear gal-1, the 5-year survival rate of TNBC patients expressing nuclear both gal-1 and gal-8 is 100% [158]. Such findings illustrate the importance of looking at the overall galectinome when examining the predictive values of galectins in patients with cancer. Such shuttling between intracellular compartments in cancer cells has also been well-documented for gal-3, which translocates to the nucleus to modulate β-catenin regulated transcriptional activity [159]. Although there are indications that nuclear gal-3 is expressed in pancreatic and gallbladder cancer cells, its potential as a predictive factor for these HFCs remains unknown [128, 160]. The potential of nuclear gal-3 as a predictive biomarker in HFC has, however, been reported for at least two other HFCs. These include lung and esophageal carcinomas [109, 161, 162].

Galectin inhibitors for the treatment of HFCs?

Because of their critical role in cancer, considerable efforts have been directed towards the development of carbohydrate-based inhibitors that would limit the binding of galectins to glycosylated residues on cell surface receptors. Up to now, however, most of these efforts have focused on targeting the glycan binding site of extracellular gal-1 and gal-3 using either modified mono- and disaccharides, synthetic glycodendrimers and modified complex glycans, and peptide inhibitors, such as Anginex [163–166]. Such inhibitors have shown great potential against HFCs. For example, a polysaccharide purified from the flower of Panax notoginseng has shown strong antiproliferative activity against pancreatic cancer cells in vitro by disrupting the interaction between Gal-3 and EGFR [167]. Despite decades of research, however, the progression in this field has been relatively slow. Achieving specificity and high affinity for these compounds, most notably considering our limited knowledge on less well-characterized galectins, is a true challenge. Consequently, the benefits of using these inhibitors for the treatment of cancer are currently shadowed by their putative off-target effects. More specific inhibitors are alternative strategies are thus urgently needed. The use of antisense- and short hairpin RNA-based strategies is one possibility. We and others have shown that such approach is an interesting option to inhibit the pro-tumoral activity of galectins, most notably in glioblastoma, pancreatic cancer and highly aggressive forms of lymphoid malignancies [12, 28, 93, 168–170]. Yet, another consideration to take into account in the design of inhibitors is the need to target intracellular galectins. This is not trivial as we found that accumulation of galectins occurs in several intracellular compartments and that their pro-tumoral role with depend on their intracellular localization [156]. A better understanding of the roles of intracellular galectins is thus needed to determine how galectins collaboratively modulate cancer progression from within the cells. This is especially important as it is increasingly clear that is the cellular context, as defined by the balance of intracellular and extracellular signaling events, that dictates whether galectins will spare the cancer cell or lead to its apoptotic demise.

Conclusions

The search for finding new and effective biomarkers and treatment options that would offer hope for patients with HFCs needs to be conducted using new approaches, given the distinct characteristics of HFCs. A rapid overview of studies that examined the expressions and functions of galectins in cancer cells reveals that they play a central role in at least three major features that characterize HFCs: (1) induction of systemic and local immunosuppression, (2) chemoresistance of cancer cells, and (3) increased invasive behavior. It is important to note, however, that galectins are not exclusively associated with increased aggressiveness. Many of them do have anti-tumorigenic functions and do inhibit cancer progression. Because we do find a relatively large and heterogeneous galectinome in cancer tissues, the use of galectins as therapeutic targets will need to be well-thought and ideally involved companion diagnostic testings. This is, especially true as most of the studies have focused on a limited number of galectins and we still know very little information about the less well-known galectins. Exploiting our knowledge on galectins to fight HFCs will thus require both the identification of the specific galectinome expressed in cancer tissues and the development of highly specific galectin inhibitors. Defining the galectinome in HFCs will also lead to a better understanding of tumor heterogeneity while providing critical information that could improve the accuracy of biomarker panels for a more personalized treatment of HFCs.

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