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Review

Galectin expression in cancer diagnosis and prognosis: A systematic review ☆

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ABSTRACT

Galectins are a family of proteins that bind to specific glycans thereby deciphering the information captured within the glycome. In the last two decades, several galectin family members have emerged as versatile modulators of tumor progression. This has initiated the development and preclinical assessment of galectin-targeting compounds. With the first compounds now entering clinical trials it is pivotal to gain insight in the diagnostic and prognostic value of galectins in cancer as this will allow a more rational selection of the patients that might benefit most from galectin-targeted therapies. Here, we present a systematic review of galectin expression in human cancer patients. Malignant transformation is frequently associated with altered galectin expression, most notably of galectin-1 and galectin-3. In most cancers, increased galectin-1 expression is associated with poor prognosis while elevated galectin-9 expression is emerging as a marker of favorable disease outcome. The prognostic value of galectin-3 appears to be tumor type dependent and the other galectins require further investigation. Regarding the latter, additional studies using larger patient cohorts are essential to fully unravel the diagnostic and prognostic value of galectin expression. Furthermore, to better compare different findings, consensus should be reached on how to assess galectin expression, not only with regard to localization within the tissue and within cellular compartments but also regarding alternative splicing and genomic variations. Finally, linking galectin expression and function to aberrant glycosylation in cancer cells will improve our understanding of how these versatile proteins can be exploited for diagnostic, prognostic and even therapeutic purposes in cancer patients.

Contents

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1. Introduction

Galectins are part of the lectin superfamily and they exert their main biological functions by interacting with specific glycoconjugates, i.e. carbohydrate structures linked to proteins, peptides and lipids. This way, galectins decipher the information encoded by the glycosylation machinery and translate this information into cellular functions. The interactions between galectins and glycoconjugates are mediated via a conserved carbohydrate recognition domain (CRD) of approximately 14 kD which shows binding affinity – albeit not exclusively – for β-galactosides [1,2]. Based on structural features, galectins can be classified into three subgroups, i.e. prototype galectins, tandem repeat galectins and chimeric galectins [3](Fig. 1A). An important feature of galectins is their ability to homodimerize and oligomerize which increases the glycan binding valency and allows galectins to simultaneously interact with multiple glycoconjugates [4,5]. As a result, galectins can mediate homo- and heterotypic interactions between cells, facilitate the binding of cells to extracellular matrix components and modulate signaling pathways and cellular behavior by e.g. receptor clustering [6,7](Fig. 1B).

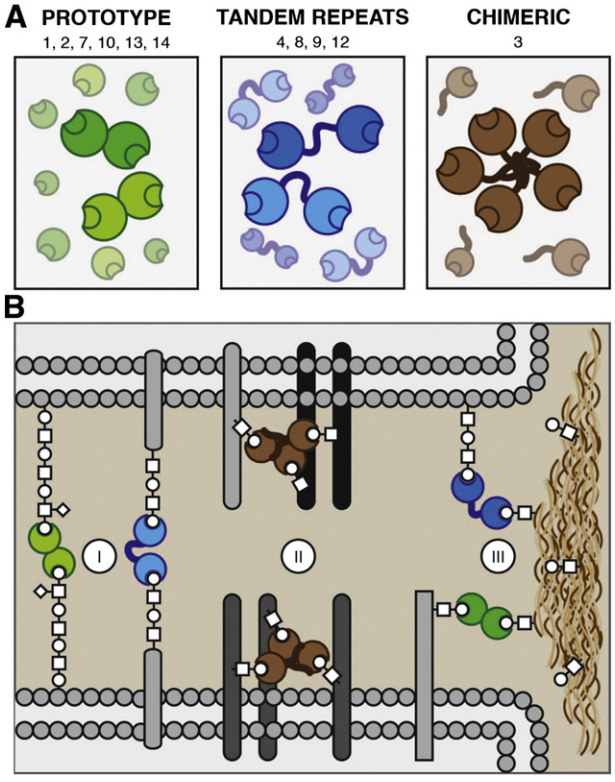

Fig. 1. The human galectin family and galectin function. A) The human galectin family consists of 11 members that are characterized by the presence of a conserved carbohydrate recognition domain. Based on the structural organization of these domain the galectins are divided of three subgroups. Prototype galectins consist of a single domain which can homodimerize. Tandem repeat galectins have two domains which are connected by a flexible linker, the length of which can vary due to alternative splicing. Chimeric galectins consist of a single domain fused to a N-terminal 'tail' of short stretches of proline, tyrosine and glycine-rich tandem repeats. B) Schematic overview of the most common extracellular functions of galectins. Dimerization and multimerization allows galectins to simultaneously bind multiple glycoconjugates. This way galectins can (I) mediate homo- and heterotypic cell-cell interactions, (II) stimulate or prolong signaling by clustering of cell-surface receptors, and (III) mediate cell-extracellular matrix interactions.

Galectins also engage in direct protein-protein interactions, thereby influencing cell signaling, cell-cycle progression, apoptosis and even pre-mRNA splicing [8,9]. In line with this functional diversity, galectin dysfunction or altered expression has frequently been associated with disease, including cancer [10–12]. In the last two decades it has been shown that galectins contribute to many hallmarks of cancer [13], including sustained proliferative signaling, resistance to cell death signals, evasion of immune surveillance, induction of angiogenesis, and activation of the metastatic potential [2,9,14–16]. Consequently, efforts are being made to develop galectin-targeting compounds, ranging from competing carbohydrate ligands to small non-carbohydrate binding molecules and blocking antibodies [2,17]. Several of these compounds have been shown to possess anti-tumor activity *in vitro* as well as to hamper tumor progression in pre-clinical cancer models *in vivo* [18–23]. Currently, several clinical trials with different galectin-targeting agents are ongoing (Table 1). This marks the coming of age of galectin-based cancer therapies which is further exemplified by different patent applications for galectin inhibitors [24]. However, to successfully implement such inhibitors in future therapies it is pivotal to identify the patients that are likely to benefit most from these agents, i.e. patients in which galectins are associated with disease outcome. To facilitate this, we performed a systematic review of studies that reported on galectin expression in human cancer patients. We evaluated the diagnostic and prognostic value of galectin expression in tumor tissues as well as of circulating galectins. This not only resulted in a timely overview of the current knowledge but also identified the areas that require further investigation. This will help ongoing efforts that aim to implement galectin-targeted therapies in the clinic for the treatment of cancer patients.

2. Galectin expression in cancerous vs. normal tissues

Over 200 original studies were identified that reported on galectin expression in cancer patients, covering most tissues and cancer types (Fig. 2A). The median number of patients was 73 (range 4–2978) and 83 studies included 100 or more patients. The majority of the studies, i.e. >70%, focused on galectin-1 and galectin-3 while tumors of the digestive tract and the reproductive system were the best studied cancer types, accounting for a little over 50% (Fig. 2B + C). To get more insight in the involvement of galectins in cancer biology we first evaluated the studies that compared the expression of galectins in healthy and malignant tissues. Out of the 144 studies in which this comparison was performed, no change in galectin expression was reported only 23 times. In the majority of studies, alterations in expression were reported as discussed in the following paragraphs (Table 2).

2.1. Galectin-1

Galectin-1 expression is frequently reported to be increased in tumor tissues as compared to normal or benign tissues. Especially in tumors of the reproductive system there is ample evidence that malignant transformation is accompanied by elevated galectin-1 levels. Interestingly, the increase is often observed in the tumor stroma [25–28] a feature which is also reported in tumors of the digestive tract, including colon [29], liver [30] and pancreas [31–34] as well as in several lymphoid malignancies [35,36]. Apart from the reproductive system,

Table 1
Registered clinical trials with galectin-targeted therapy.

NCT Number*	Phase	Cancer type	Galectin targeting drug	Status
NCT01723813	I/II	Metastatic melanoma	GM-CT-01 (gal-1/-3)	Recruiting
NCT01724320	I	Solid tumors	OTX008 (gal-1)	Unknown
NCT02117362	I	Metastatic melanoma	GR-MD-02 (gal-1/-3)	Recruiting
NCT00054977	I	Colorectal, lung, breast, head&neck, prostate	GR-MD-02 (gal-1/-3)	Completed
NCT00386516	II	Gallbladder, bile duct	GR-MD-02 (gal-1/-3)	Terminated
NCT00110721	II	Colorectal	GR-MD-02 (gal-1/-3)	Terminated
NCT00388700	II	Colorectal	GR-MD-02 (gal-1/-3)	Terminated

* Data retrieved from www.clinicaltrials.gov.

digestive tract and lymphoid tissue, elevated galectin-1 expression levels in cancer cells, stroma or both have also been reported in myeloproliferative neoplasms [37] and in tumors of the respiratory and urinary system [38–44] as well as in thyroid cancer [45–47] and skin cancer [48,49]. Thus far, only three studies described a decrease in galectin-1 expression in malignant tissue compared to normal tissue, i.e. in head and neck squamous cell cancer [50], uterine cancer [51] and bladder cancer [52]. However, these findings contradict with several other studies in these cancer types [38,39,41,53–56] and are most likely related to differences in patient population, tumor subtype or methodology. Altogether, increased galectin-1 expression appears to be a common phenomenon in most cancer types although differences do exist in the specific localization within the different tumor types.

2.2. Galectin-2

Reports on altered galectin-2 expression in cancerous vs. normal tissue are scarce. Cada et al. reported on reduced expression in basal cell carcinoma of the skin as compared to normal skin [48]. An extensive study on galectin-2 expression in numerous cancerous tissues and their normal counterparts was performed by Saal et al. [57]. Using semi-quantitative analysis of gal-2 mRNA expression they observed a reduction in colon cancer and an increase in thyroid cancer. No changes were observed in stomach, lung, kidney or bladder cancer [57]. Subsequent immunohistochemical staining showed no changes in pancreatic, colon, skin or kidney cancer while galectin-2 levels were elevated in ovarian cancer as well as in the stroma of lung and bladder cancer but decreased in liver and breast cancer. While informative, the number of samples per group was too small for conclusive observations and additional studies are required using larger patient groups.

2.3. Galectin-3

Together with galectin-1, galectin-3 is one of the most extensively studied galectins in cancer. Compared to galectin-1, the alterations in galectin-3 expression appear more heterogeneous. In general, in most tumors of the digestive tract and urinary system the expression appears to increase, comparable as described for galectin-1. The same holds true for thyroid cancer in which malignant transformation is clearly associated with increased galectin-3 expression [58–61]. On the other hand, in tumors of the reproductive system galectin-3 expression appears to be predominantly decreased which is opposite from galectin-1. Especially in prostate cancer there is ample evidence showing decreased expression in tumor tissue as compared to normal tissue. Of note, part of this decrease appears to be related to proteolytic cleavage of galectin-3 by metalloproteinases-2 and -9 which hampers recognition by monoclonal antibodies [62]. For other tumor types the results are more variable with studies reporting either increased or decreased expression, e.g. tumors of the respiratory system, brain cancers and skin cancers. In the latter two, this heterogeneity can be largely explained by the differences in tumor subtypes. For example, in skin tumors, basal and squamous cell carcinomas are associated with a decrease in galectin-3 expression [48,63–65] while melanomas are characterized by increased expression [49,65–68]. Similarly, galectin-3 expression regulation varies amongst different types of hematological malignancies. In anaplastic large cell lymphoma [69], chronic myeloid leukemia [70] and other myeloproliferative neoplasms [37] galectin-3 expression is increased, while it is decreased in chronic lymphocytic leukemia [71]. In addition, an increase of galectin-3 expression is often observed in only a subset of patients, as is the case for diffuse large B cell lymphoma [36,72,73] and cutaneous T cell lymphoma [74]. In brain cancer, the differences in galectin-3 expression have even been suggested to provide a tool to distinguish between tumors of different origin [75,76].

Contradicting changes in expression have also been linked to the cellular localization of galectin-3. For example, in colon cancer it was reported that, compared to normal tissue, nuclear expression decreased while cytoplasmic levels increased [29,77]. A similar observation was made in tongue squamous cell carcinomas [78] while in lung cancer patients differences in cytoplasmic and nuclear galectin-3 staining were observed between squamous cell carcinoma and adenocarcinoma [79]. Galectin-3 expression was consistently observed in T cell acute lymphoblastic leukemia. However, in a majority of cases galectin-3 expression was restricted to stromal cells [80]. Together with the observation that changes in galectin-1 are often restricted to the tumor stroma, these findings show the importance of distinguishing between differences in localization of galectin expression, not only when comparing normal with malignant tissues but also when different cancer subtypes are evaluated.

2.4. Galectin-4

Similar as for galectin-2, only limited information is available regarding galectin-4 expression in normal versus tumor tissues. The only cancer type that is clearly associated with a change in expression is colon cancer. Several studies reported that in malignant colon tissue galectin-4 expression is reduced as compared to normal tissue [81–83]. Reduced expression was also described for prostate cancer [84] and skin cancer [48] while increased expression was found in cancer of the pancreas [85], liver [86], ovary [87] and bladder [41]. However, these are all single study observations and additional research is required to obtain a better picture of galectin-4 expression in normal and malignant tissues.

2.5. Galectin-7

Information regarding altered galectin-7 expression between normal and tumor types is also mostly limited to single reports, similar as for galectin-2 and galectin-4. In skin [48,88], cervix [89] and stomach cancer [90], the expression appears to decrease while an increase was reported in esophagus [91], breast [92], thyroid [93], pharynx and larynx cancer [94] as well as in indolent lymphoproliferative disorders such as chronic lymphocytic leukemia, follicular lymphoma and mantle cell lymphoma [95]. In transitional cell carcinomas of the bladder conflicting results were found which might be related to the method of expression analysis, i.e. mRNA vs. protein [41,96]. In addition, some findings resemble the differences in galectin-3 expression with respect to cancer subtype and cellular localization. For example, in head and neck cancers, galectin-7 expression was not detected in basal cell

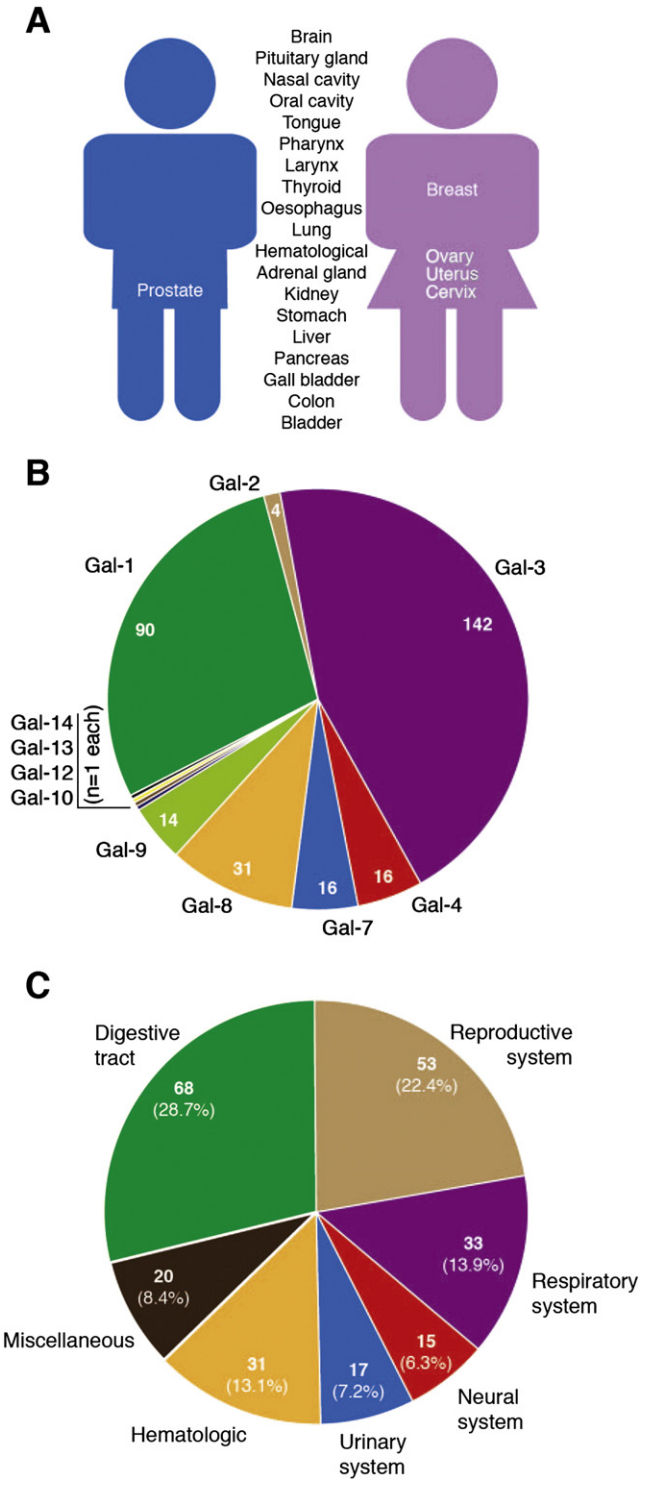

Fig. 2. Characteristics of the studies included in the systematic review. A) List of tissues in which the expression of one or more galectins has been evaluated in cancer patients. B) Pie chart showing the number of studies that analyzed the expression of a specific galectin in cancer patients. C) Pie chart showing the distribution of studies over the different organ and tissue systems (see Table 2 for specific tissues/organs included in each category).

carcinomas while expression was observed in squamous cell carcinomas [94]. Furthermore, in esophageal cancer, the cellular localization of galectin-7 was found to change from strictly nuclear in normal tissues to nuclear and cytoplasmic in malignant tissue [91]. These observation further exemplify that galectin localization might be used to distinguish between histological subtypes.

2.6. Galectin-8

Compared to normal tissues, galectin-8 expression appears to be increased in breast cancer [97], larynx cancer [98,99] and a subset of cutaneous T cell lymphomas [74], and decreased in skin cancer [48,97] as well as in several cancers of the digestive tract including pancreas, liver and colon [97,100]. In the latter it was reported that the protein localization shifted from the nucleus to the cytoplasm in malignant cells [97,100]. For prostate cancer and tumors of the urinary and respiratory system, conflicting results have been reported, but in general, the expression in these malignant tissues appears to be comparable to normal tissues [84,97,101,102]. Overall, the number of studies is limited and in some studies the sample size was small. So, more conclusive evidence awaits additional studies in larger patient groups. A complicating factor is the fact that the galectin-8 mRNA transcript is subject to extensive splicing which results in the generation of different galectin-8 isoforms [103]. Thus far, no antibodies have been described that can distinguish between these isoforms which limits immunohistochemical analyses to the evaluation of only the total galectin-8 expression level.

2.7. Galectin-9

Similar as for galectin-8, extensive splicing of galectin-9 mRNA transcripts has been described. This complicates the interpretation of studies in which no distinction between these splice variants has been made. For example, in gastric cancer it has been described that mRNA levels decrease [104] while protein levels increase [105] when comparing cancer tissue with normal mucosa. While this might be caused by differences between patient populations it could just as well reflect a switch in isoform expression. The difficulty to properly assess galectin-9 isoform expression might also underlie the low number of studies that compare expression between cancerous and normal tissues. Most of the studied cancer tissues display a decreased expression [48,84,106,107] with the exception of oral cancer [108], pancreatic cancer [109] and Hodgkin lymphoma [110]. The lack of studies documenting the expression of galectin-9 in hematological malignancies is surprising considering its well documented role in immunity and inflammation [111]. Similar as for galectin-8, additional studies are required to get a more comprehensive picture of galectin-9 expression in malignant transformation.

2.8. Galectin-10/-12/-13/-14

Of all known mammalian galectins, galectin-10, -12, -13 and -14 are the least well studied. To our knowledge, only one study compared the expression of galectin-12 between normal (benign hyperplasia) and malignant prostate tissue. It was described that galectin-12 expression gradually decreased with increasing stage [84]. Of note, despite the lack of studies including normal tissue, there have been reports that suggest a role for galectin-10, -13 and -14 in cancer biology [112,113]. These findings warrant further investigation of these galectins.

3. Galectin expression and prognosis.

Apart from comparing galectin expression between normal and malignant tissues, many studies explored the prognostic value of galectin expression in cancer. From these studies, it has become apparent that galectins can be linked to patient outcome. For example, there is ample evidence that increased galectin-1 expression is associated with poor overall survival (OS) and disease free survival (DFS), irrespective of the cancer type (Supplementary Table 1). The opposite picture is emerging for galectin-9, albeit that only a limited number of different tumor types have been evaluated. The prognostic value of galectin-3, which has been evaluated in numerous studies, is less clear and appears to depend on the type of cancer. For example, in colon cancer, brain cancer and acute myeloid leukemia, high galectin-3 expression is

Table 2
Galectin expression in tumor vs. normal tissue.

	gal-1	gal-2	gal-3	gal-4	gal-7	gal-8	gal-9	gal-12
Digestive tract								
Tongue	↓ [50] ↑ [55]		↓ [50,78] ↑ [204]					
Oral cavity	↓ [50] ↑ [39,53,54,205]		↓ [50,206]				↑ [108]	
Esophagus					↑ [91]			
Gastric		= [57]	= [207]		↓ [90] ↑ [57]	= [97]	↓ [104] ↑ [105]	
Pancreas	↑ [31–34,208,209]	= [57]	↑ [32,109,165,210–214] ↑ [215]	↑ [85]		↓ [97]	↑ [109]	
Gall bladder								
Liver	↑ [30,216,217]	↓ [57]	↑ [217,218]	↑ [86]		↓ [97]	↓ [107]	
Colon	↑ [29,219]	= [57] ↓ [57]	= [157,220] ↓ [29,77,220] ↑ [29,77,115,121,123,219]	↓ [81–83]	↑ [57]	↓ [97,100]		
Reproductive system								
Breast	↑ [19,28]	↓ [57]	↓ [133,201,221,222] ↑ [223]		↑ [92]	↑ [97]		
Ovarian	↑ [27,127,224]	↑ [57]	↓ [225–227] ↑ [137]	↑ [87]				
Uterus	= [228] ↓ [51] ↑ [56]		= [228] ↓ [56,229,230] ↑ [230]					
Cervix	↑ [26,231]		↓ [232]		↓ [89]		↓ [233]	
Prostate	= [234] ↑ [25,84,235]		↓ [62,84,166,234,236–240]	↓ [84]		= [84,97,102] ↑ [241]	↓ [84]	↓ [84]
Respiratory system								
Pharynx	↓ [50] ↑ [39,43]		↓ [50,206] ↑ [242]		↑ [94]	↑ [98]		
Larynx	↓ [50] ↑ [39]		↓ [50,206] ↑ [242,243]		↑ [94]	↓ [97] ↑ [98,99]		
Nasal cavity			↓ [206]					
Lung	↑ [40,42]	= [57] ↑ [57]	↑ [42]		= [57]	= [97,101] ↑ [244]		
Neural system								
Brain			↑ [75,76,119,176,245] ↓ [75,76]					
Pituitary gland			↑ [246]					
Urinary system								
Kidney	↑ [44]	= [57]	↓ [247] ↑ [44,248,249]		↑ [57]	= [97]		
Bladder	↑ [38,41] ↓ [52]	= [57]	↑ [38]	↑ [41]	= [57] ↓ [96] ↑ [41]	= [97] ↑ [41]		
Adrenal gland			↑ [250]					
Hematologic								
Lymphoid	= [71] ↑ [74,148,251]		= [36] ↑ [36,69,74,252] ↓ [71]			↑ [74]	↑ [110]	
Myeloid	↑ [37]		= [136] ↑ [37]		↑ [95]			
Miscellaneous								
Thyroid[a]	↑ [45–47]	↑ [57]	↑ [46,47,61,253–255]		↑ [57,93]			
Skin	↑ [48,49]	= [57] ↓ [48]	↓ [48,63–65,67,256] ↑ [49,65–68,256]	↓ [48]	↓ [48,88]	↓ [48,97]	= [49] ↓ [48,106]	

a) Only a selection of studies reporting on increased galectin-3 expression in malignant vs. normal/benign thyroid tissue is included. = Expression unaltered; ↑Expression increased; ↓ Expression decreased in cancerous tissue vs. normal/benign tissue.

associated with poor OS [114–116], while in gastric cancer high galectin-3 expression appears to be favorable [117,118]. For most other cancer types, only limited information is available and either no or conflicting associations have been reported. The latter is possibly related to differences in methodology which again illustrates the necessity to standardize the methods which are used to evaluate galectin expression in tumor tissues. Especially for the less well studied galectins, i.e. galectin-2, -4, -7, and -8, it is important to reach consensus on how the expression should be analyzed in future studies to allow proper comparison of findings.

It is also important to note that alterations in galectin expression are frequently associated with classical prognostic markers like tumor grade, stage and nodal status. For example, most studies in brain cancer describe a positive correlation between tumor grade and galectin-3 expression levels [75,119,120]. Also in colon cancer, galectin-3 expression often correlates with tumor stage in colon cancer [29,114,115,121–123] while galectin-1 appears to positively correlate with stage in e.g. gastric cancer [124–126], ovarian cancer [27,127] and chronic lymphocytic leukemia [128]. Finally, galectin-7 and galectin-9 are frequently negatively correlated with tumor stage, grade or nodal involvement. The latter is in

line with the observation that increased galectin-7 and -9 levels are generally associated with improved OS [89,105–107,129,130]. Altogether, these findings confirm the involvement of galectins in tumor progression and indicate that galectins could serve as therapeutic targets. On the other hand, the associations also suggest that galectins have only limited added value over classical prognostic parameters. Interestingly, the opposite has been shown in several studies in which galectins were identified as independent prognostic factors for disease outcome. For example, in early stage bladder cancer, reduced galectin-3 and galectin-8 expression were found to be independent predictors of tumor recurrence [131,132]. Reduced galectin-3 expression was also identified as a predictor of tumor recurrence in breast cancer patients [133] while reduced galectin-9 was an independent predictive factor for distant metastasis [134]. In early stage non-small cell lung cancer, galectin-1 and a specific galectin-9 isoform were independent prognostic factors for OS [129]. In cervical cancer, galectin-1 was identified as an independent prognostic factor for local recurrence and disease specific survival (DSS) while galectin-7 was described as an independent prognostic factor for OS [89,130] as well as for DSS and distant metastasis free survival [130]. Elevated galectin-1 expression was also an independent prognostic factor for DFS in renal cancer [135] and galectin-3 expression was an independent prognostic factor for OS in acute myeloid leukemia [136]. All these findings clearly indicate that galectins can have additional prognostic value. However, it is also apparent that this differs between different tumor (sub)types. For example, in ovarian cancer neither galectin-1 nor galectin-3 appear to serve as independent prognostic factors [27,137,138] while both galectins have been reported as independent prognostic factor in e.g. head & neck cancers [78,139–142]. This tumor type specificity is further illustrated by observations in gastric cancer in which galectin-1 was identified as an independent prognostic factor only in the intestinal type and not in the diffuse type [124]. Finally, galectin-3 expression was reported to be significantly different between small cell and non-small cell lung cancer [143]. Besides these differences between tumor subtypes, the prognostic value also appears to be related to tissue distribution within the tumor, e.g. stromal or epithelial [25,144,145], as well as to cellular localization, e.g. nuclear or cytoplasmic [67,78].

Overall, current literature suggests that galectins can serve as prognostic markers in different types of cancer. Galectins can even have additional value over classical histological parameters. However, comparison of different findings is complex due the plethora of approaches and methods that have been used to assess galectin expression. This has resulted in inconclusive and conflicting reports which make it difficult to draw definite conclusions and hampers the implementation of galectins for prognostic and therapeutic purposes.

4. Circulating galectins as diagnostic biomarkers

As evident from the previous paragraphs, cancerous tissue is frequently characterized by altered galectin expression. Since galectins are known to be secreted it has been anticipated that changes in the levels of circulating galectins might reveal the presence of malignant tissue. Indeed, in thyroid cancer, increased levels of circulating galectin-1 and galectin-3 have been reported [146,147], which corroborates with the observed increase in tissue expression. Also for other cancer types, the changes in circulating galectins are often in agreement with altered tissue expression, e.g. galectin-1 in lung cancer [40] and T cell lymphoma [148], galectin-3 in melanoma [149], bladder cancer [150] and colon cancer [151–154] as well as galectin-8 in breast cancer [151]. All these observations suggest that measuring circulating galectins could serve as diagnostic biomarkers (Table 3). However, in thyroid cancer, circulating galectin-3 appears in patients with both benign as malignant tumors [146,147] suggesting only limited diagnostic value in this cancer type. Thus, further research is warranted to fully determine the applicability of circulating galectins in cancer diagnosis. Of note, the levels of galectin-binding glycoproteins might also be of diagnostic value. For example, in colon cancer patients, Bresalier et al. detected a 10–30-fold increase in serum levels of a glycoprotein related to haptoglobin which binds galectin-3 [155]. Likewise, the amount of galectin-1-binding glycoproteins was significantly increased in breast cancer patients [156]. The galectin-3 binding protein LGALS3BP (Mac-2BP/90 K) is also frequently found to be elevated in sera of cancer patients [157–161]. The functional consequence of these interactions is poorly understood and warrants further investigation.

Table 3
Serum galectins.

gal-1	gal-2	gal-3	gal-4	gal-7[d]	gal-8	gal-9
Increased serum levels in patients with malignant cancer vs. benign/healthy						
Lung [40] Thyroid[a] [147] Glioma [185] Colon [154,151][e] Lymphoid [128,148,179]	Breast [151] Colon [151]	Breast [151,181] Colon [151–154,181,183][c] Thyroid[a] [146,147,162] Prostate [257] Pancreas [165,182] Bladder [150] Head&Neck [164] Melanoma [149] Lymphoid [258][f]	Colon [151,154,183][c]		Breast [151] Colon [151]	Colon [151][e]
Decreased serum levels in patients with malignant cancer vs. benign/healthy						
Breast [151] Colon [259] Ovarian [260]		Prostate[b] [166]				
Similar serum levels in patients with malignant cancer vs. benign/healthy						
Colon [151][e] Head&Neck [164]	Colon [154]	Pancreas [184] Bile duct [261] Thyroid [163] Non-Hodgkin's lymphoma [181] diffuse large B-cell lymphoma [252]	Breast [151]	Colon [154]		Breast [151]

[a] Elevated both in benign and malignant tumors.
[b] Down both in benign and malignant tumors.
[c] Simultaneous galectin-3/4 measurement.
[d] Saussez et al. could not detect galectin-7 in serum of HNSCC patients [164].
[e] Only elevated in metastatic colon cancer.
[f] Only in bone marrow serum, not in peripheral blood serum

While most findings suggest that the levels of circulating galectins and galectin ligands might be associated with the expression in malignant tissue, there are also reports in which the alterations in galectin serum levels conflict with the changes in tissue expression. For example, in a study in thyroid cancer patients there was no association between serum and tissue expression of galectin-3 [162] nor was circulating galectin-3 increased compared to healthy controls [163]. Likewise, galectin-7 was not detected in serum of thyroid cancer or head-and-neck cancer patients [147,164] despite reports of increased expression in malignant tissue. Also in breast cancer, colon cancer and chronic lymphocytic leukemia the changes in galectin expression are not necessarily reflected at the level of circulating galectins [71,128,151,154]. Apart from method-based differences [165,166], a possible explanation for these conflicting findings could be related to altered secretion of galectins. Galectins are secreted by a non-classical secretion pathway that is still poorly understood and protein modifications like proteolytic cleavage, splicing or phosphorylation are known to affect cellular localization and trafficking of galectins [167–171]. The abnormal activity of cellular pathways that regulate these processes in tumor cells is thus likely to cause mismatches between tissue expression and secretion. An additional explanation might involve changes in the composition of galectin-binding glycans within the tumor tissue. Proper glycosylation is pivotal for normal cell function [172] and it is well recognized that cancer cells are frequently characterized by an aberrant glycosylation machinery [173,174]. Thus, it can be anticipated that this affects the availability of glycoconjugates to which galectins bind. Indeed, studies that used labeled galectins for histochemical staining of cancerous tissues confirm changes in the galectin-permissive glycoprofile of cancer tissues [41,175–178]. Together with the altered secretion, this might result in either increased tissue accumulation or enhanced shedding of galectins which could underlie the observed discrepancies when linking tissue expression to galectin serum levels in some cancer types.

5. Circulating galectins as biomarkers of prognosis and therapeutic efficacy

Despite some discrepancies, there is ample evidence that circulating galectins can provide valuable patient information. This extends beyond diagnostic purposes as e.g. circulating galectin-1 levels correlate well with the clinical stage and other prognostic markers in Hodgkin lymphoma [179] and circulating galectin-3 was found to have prognostic value in stage III/IV melanoma patients [180]. In addition, there are reports linking altered galectin serum levels to metastatic disease. Iurisci et al. observed significant differences in circulating galectin-3 when comparing metastatic vs. nonmetastatic patients with either breast cancer or gastrointestinal cancer [181]. In HNSCC and pancreas cancer patients, galectin-3 levels also were found elevated in metastatic disease as compared to localized disease [164,182]. Likewise, galectin-1, galectin-9 as well as combined galectin-3/4 levels were found to differ between metastatic and non-metastatic colon cancer [151,183]. All these findings suggest that measuring serum galectins might be valuable to select patients that would benefit from a more aggressive therapeutic approach or from galectin-targeted therapy.

Serum galectins could also be useful to monitor therapeutic efficacy. Gaida et al. observed that galectin-3 levels in the serum of pancreatic cancer patients significantly dropped following surgery [184]. Also in colorectal cancer patients the levels of galectin-3 [181] as well as of galectin-1 and -4 [154] dropped following surgery. In HNSCC, both galectin-1 and -3 serum levels dropped following different types of treatment [164]. Whether the levels increase again in patients with recurrent disease is not known and requires further investigation. In addition, treatment does not always induce changes in serum galectin levels [185], suggesting tumor specific effects. Nevertheless, monitoring galectin levels in the circulation can provide useful patient information and additional research is needed to fully establish the value of circulating galectins as biomarkers in cancer patients.

6. Conclusions and future perspectives

Since their recognition as a distinct protein family twenty years ago [1], galectins have emerged as versatile glycan-binding proteins that facilitate a wide range of cellular functions and biological processes. Consequently, deregulated galectin expression has often been associated with aberrant cellular behavior, most notably in cancer. Indeed, over 130 studies have described alterations in galectin expression when comparing malignant tissues with normal tissues. Furthermore, altered galectin expression is frequently associated with parameters of tumor progression like stage, grade and metastasis as well as with patient prognosis. This confirms the involvement of galectins in tumor progression and has identified galectins as potential therapeutic targets. This is supported by numerous preclinical studies in which galectin-targeted therapy, mostly aimed at galectin-1 and galectin-3, resulted in hampered tumor progression. This anti-cancer effect not only occurred at the level of tumor cell function, e.g. survival, growth and migration [81,100,186,187], but also involved modulation of tumor immune escape [19,21,188–190], tumor angiogenesis [18,21,190–192] and tumor metastasis [19,189,193–198]. Owing to its immune-modulatory function, galectin-9 has been shown to exert anti-cancer effects when administered as a recombinant protein in preclinical models of various hematological malignancies [111]. These findings exemplify the therapeutic potential of targeting galectins. It should be noted that several preclinical studies targeted galectins by interfering with gene expression, using either knockout models or knockdown strategies. Obviously, such approaches are currently not feasible to treat patients in a clinical setting. Nevertheless, promising results have been obtained using galectin-targeting antibodies, peptides, protein fragments and small carbohydrate ligands. Which of these will be most successful is difficult to foresee as each type of compound has different characteristics regarding specificity, stability, and tissue penetration. Furthermore, the therapeutic efficacy will depend on properties like galectin expression, protein turn-over and tissue distribution. As discussed here, it is still difficult to extract a clear picture of which galectins are involved in specific malignancies and which patients might benefit most from galectin-targeted therapy. Based on current literature, colon cancer patients might benefit from galectin-3 inhibitors as the levels of this galectin are frequently reported to be elevated in tumor tissue and serum and multiple studies have shown that the increased expression is associated with poor OS and DFS. Another eligible candidate for therapy appears to be galectin-1 in different tumor types, including lung, ovarian, gastric, head and neck, and possibly pancreas. For most other galectins and cancer types, the information is still too limited. For several cancer types only a single report is available or only a small number of patients has been evaluated. Furthermore, lack of consensus on how to assess galectin expression has resulted in a plethora of -sometimes conflicting- observations which make it difficult to compare findings. Reaching consensus on the parameters that should be determined when evaluating galectin expression presents an important step for the galectin research community. Adhering to the REMARK guidelines [199] (REporting recommendations for tumor MARKer prognostic studies) would be a first step in obtaining more consistent data that allow a better comparison of different studies. In addition, it is important to specify the localization of protein expression, both within the tissue, e.g. epithelial and/or stromal, as well as within different cellular compartments, i.e. membranous, cytoplasmic, nuclear. Furthermore, it will be valuable to distinguish between different splice variants and to include information on possible genomic variations [129,200]. For example, conflicting results have been reported regarding the prognostic value of galectin-3 in Caucasian and Asian women with breast cancer [133,201]. This might be related to a single nucleotide polymorphism (SNP) that affects the malignant activity of the protein [200,202]. Another SNP in galectin-3 was associated with the prognosis of NSCLC patients and their response to chemotherapy [203]. Further insights in the role and prevalence of such genomic variations is important to

better understand how galectin expression is linked to prognosis of cancer patients.

Finally, galectins act as cellular interpreters that translate the information held within the glycome into protein function and cellular activity [16]. Consequently, altered expression and function of galectins in cancerous tissues likely reflects changes in the glycosylation machinery. For example, it has recently been shown that altered VEGF-receptor glycosylation can cause galectin-1 mediated resistance to anti-VEGF cancer therapy [21]. Thus, a better understanding of aberrant glycosylation in cancer tissues could shed light on the specific activities of galectins in tumor progression. This will help to link altered galectin expression to diagnosis and prognosis. Foremost, it will facilitate the development of novel therapeutic strategies that interfere with the malignant galectin-glycan axis for the benefit of cancer patients.

7. Literature survey and data collection

Citations were managed using SENTE 6 (version 6.6.5, Third Street Software). Within SENTE, a library was generated following a search of the Pubmed database with the search string 'GALECTIN AND CANCER'. Within this library further searches were performed combining a specific 'GALECTIN' with 'PROGNOSIS', 'SERUM' and/or 'PATIENT'. From each study, the following information was retrieved (if available): galectin type, tumor type (including sub classification), number of patients, number of controls, mRNA/protein expression in patients vs. controls, the tissue and/or cellular localization of galectin expression and the association of galectin expression with clinical parameters including overall survival, disease free survival, stage, grade, metastasis, age, gender.

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Transparency Document

The Transparency document associated with this article can be found, in online version.

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Despite the thorough and systematic literature screening approach, it is possible that some relevant studies were missed. The authors apologize for these unintentional omissions.

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