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Survey

Vascular galectins: Regulators of tumor progression and targets for cancer therapy

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ABSTRACT

Galectins are a family of carbohydrate binding proteins with a broad range of cytokine and growth factor-like functions in multiple steps of cancer progression. They contribute to tumor cell transformation, promote tumor angiogenesis, hamper the anti-tumor immune response, and facilitate tumor metastasis. Consequently, galectins are considered as multifunctional targets for cancer therapy. Interestingly, many of the functions related to tumor progression can be linked to galectins expressed by endothelial cells in the tumor vascular bed. Since the tumor vasculature is an easily accessible target for cancer therapy, understanding how galectins in the tumor endothelium influence cancer progression is important for the translational development of galectin-targeting therapies.

Contents

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1. The galectin family

The term galectins-previously referred to as β-galactoside-binding proteins – was coined in 1994 by Barondes et al. to define a family of lectins that share binding affinity for β-galactosides and that display significant sequence homology in their carbohydrate-binding domain [1,2]. In the following two decades, the protein family has expanded to 15 members that, with a few exceptions [3], meet the two galectin-defining requirements, i.e. beta-galactoside affinity and a conserved carbohydrate recognition domain (CRD). The CRD is the main functional domain of galectins. It is composed of approximately 130 amino acids forming two beta-sheets that fold in a beta-sandwich which is slightly bent. The outer or convex side of this sandwich is made out of 5 anti-parallel strands (F1–F5) while the inner or concave side contains 6 anti-parallel strands (S1–S6) (Fig. 1A). Carbohydrate binding occurs at the concave side in a groove formed by the curved shape of the sandwich. The core binding site for beta-galactoside containing disaccharides like lactose consists of conserved amino acids in strands S4–S6. However, the binding groove extends to strands S1–S3 which allows binding of more extended oligosaccharides with different affinities [4–6]. Such complex glycans are common and over the years several endogenous glycoproteins and glycopeptides have been identified as ligand for specific galectin CRDs, including extracellular matrix components, cell surface receptors, and adhesion molecules [7–11].

The increasing number of family members has allowed classification of galectins based on the number and organization of CRDs (Fig. 1B). At present, three subgroups are distinguished: (1) prototype galectins that consist of a single CRD which can dimerize, (2) tandem repeat galectins in which two CRDs are covalently bound by a linker peptide, and (3) chimeric galectins that contain an N-terminal tail of short amino acid repeats fused to the CRD [5,6]. Interestingly, several galectins can also assemble into non-covalently bound higher order oligomers [6,9,12–14]. This di- and multimerization is an important functional feature as it allows multivalent carbohydrate binding by which galectins can modulate the spatial organization and retention of glycoproteins at the cell surface [14–16]. In addition, it enables galectins to facilitate both intercellular interactions as well as interactions between cells and their environment. Galectins also engage in protein–protein interactions to mediate functions independent of carbohydrate binding. This type of binding mainly occurs intracellularly and further adds to the functional diversity of galectins [17,18].

2. Galectin expression in the endothelium

The expression of galectins has been frequently reported in endothelial cells of different sources and origin and appears to be confined to four family members, i.e. galectin-1, galectin-3, galectin-8, and galectin-9 [10,19–31]. Low mRNA levels of galectin-2, -4, and -12 have also been detected in cultured endothelial cells but expression at the protein level is still unresolved [32]. Endothelial galectins are found throughout the cell, i.e. in the nucleus, the cytoplasm and at the cell membrane [20,23,26,27,30,32–39] suggesting that they exert diverse functions in endothelial cell biology (Fig. 2A). This diversity is further increased by transcriptional and posttranslational modifications, including phosphorylation, proteolytic processing and mRNA splicing. For example, the two tandem-repeat galectins, i.e. galectin-8 and galectin-9, have been found to be subjective to extensive mRNA splicing [10,28–31,40]. At least two galectin-8 mRNA variants have been identified in cultured human endothelial cells [32]. Two bands reactive with anti-galectin-8 antibody have also been reported by Cueni et al. in lymphatic as well as in blood vessel derived human endothelial cells [10]. Delgado et al. reported the presence of 3 isoforms of galectin-8 in bovine aortic endothelial cells [30]. Regarding galectin-9 splicing, Spitzenberger et al. identified 3 mRNA transcripts which corroborates with other

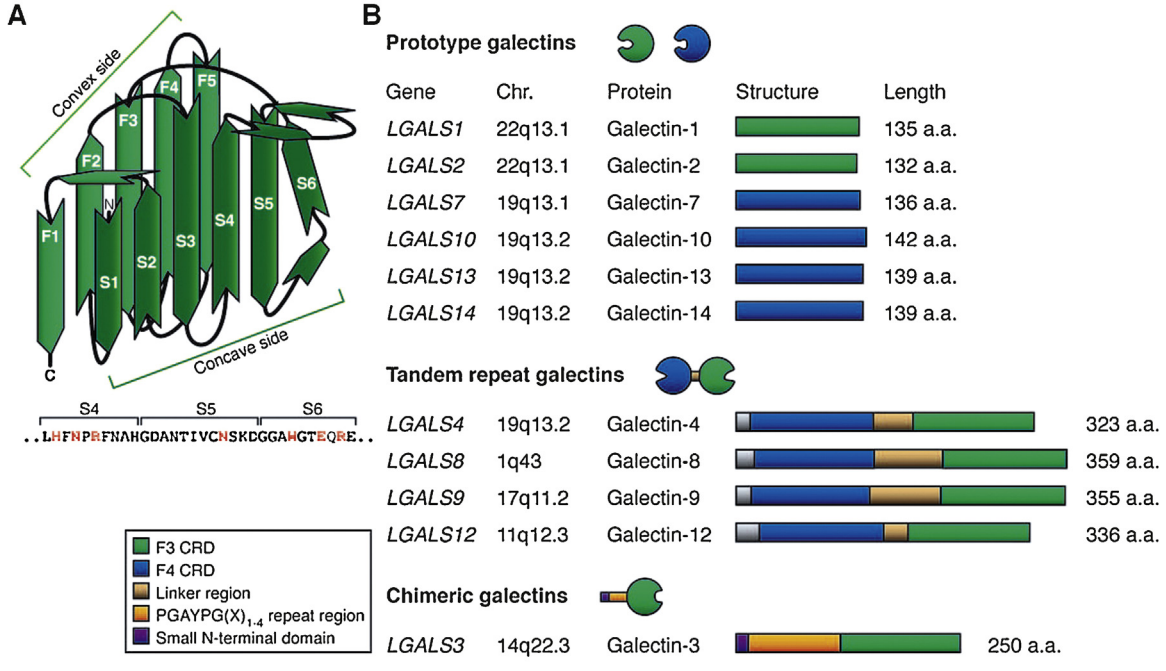

Fig. 1. The carbohydrate recognition domain and galectin classification. (A) Simplified cartoon of the conserved galectin carbohydrate recognition domain based on the crystal structure of galectin-1. The CRD is formed by two beta-sheets that are slightly bent resulting in a concave and convex side. The convex side consists of 5 anti-parallel strands (F1–F5) and the concave side of 6 anti-parallel strands (S1–S6). Carbohydrate binding occurs at the concave side and involves several conserved amino acids located in S4–S6 (shown for galectin-1 in the sequence below). (B) Classification of galectins in three subgroups, i.e. prototype, tandem repeat, and chimera, based on the protein structure and number of CRDs. For the tandem repeat galectins only the full length protein is shown. For several of these galectins alternative splicing has been reported which mainly affects the length of the linker region between the two CRDs.

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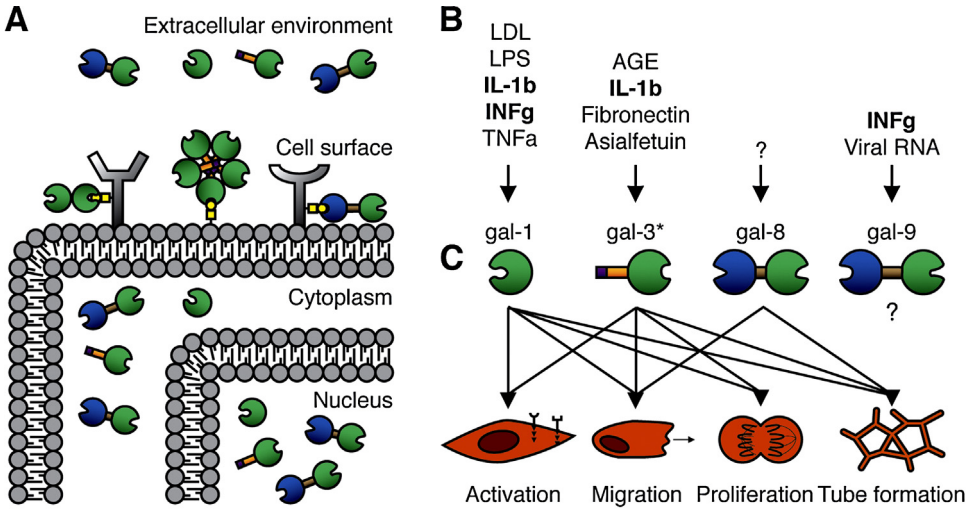

Fig. 2. Localization, regulation, and function of endothelial galectins. Schematic representation of the location, regulation and function of endothelial galectins. (A) Endothelial galectins, i.e. galectin-1, -3, -8, and -9, are found in the nucleus, the cytoplasm, and at the cell surface. Since galectins do not contain trans-membrane domains, binding at the cell surface is mainly mediated via carbohydrate groups on glycoproteins or glycolipids. (B) List of compounds that have been reported to induce galectin expression in endothelial cells. Compounds that activate multiple galectins are shown in bold. (C) Link between galectins and four key steps of the angiogenesis cascade. Except for galectin-9, for which no data are available, all galectins stimulate multiple endothelial cell functions during angiogenesis.

reports [29,32]. Apart from the full length transcript containing all exons (gal-9FL), the additional transcripts either lack exon 5 (gal-9Δ5) or exons 5 and 6 (gal-9Δ5/6) which encode for the linker domain. Endothelial expression of gal-9FL and gal-9Δ5 was also reported by Imaizumi et al. although they did not detect gal-9Δ5/6 [31,41,42]. The functional relevance of this extensive splicing is still not fully understood. The linker domains of tandem repeat galectins have been suggested to regulate the potency of ligand binding [14,43] and the susceptibility to proteolysis [44]. Consequently, splicing might influence protein stability or carbohydrate binding. In addition, splicing might affect the cellular localization of the protein by allowing or preventing secretion of specific isoforms [45–47].

3. Regulation of endothelial galectin expression

Several triggers have been identified that can affect galectin expression in different cell types. This includes interactions with other cells or extracellular proteins, changing flow dynamics, metabolic stress conditions like hypoxia, and cytokine stimulation [48–56]. Many of these triggers are also involved in regulating endothelial galectin expression (Fig. 2B). Baum and others have shown that endothelial galectin-1 expression can be induced by different stimuli, including low density lipoproteins (LDL), lipopolysaccharides (LPS), and a mixture of cytokines including IL-1beta, IFNgamma, and TNFalpha [57–59]. IL-1beta also induces endothelial galectin-3 expression [60] as do fibronectin [61] and advanced glycation end products (AGEs) [62,63]. These findings suggest that endothelial activation conditions dictate the expression profile of galectins. Indeed, galectin-1 has been identified as an early marker of endothelial cell activation in vitro [23,32]. In addition, endothelial cell activation is accompanied by an increased surface expression of galectin-1 [32,57,58,64]. Alterations in surface expression of endothelial galectin-3 have also been reported. Glinskii et al. found increased surface galectin-3 in human bone marrow derived endothelial cells exposed to asialofetuin, a glycoprotein containing multiple LacNAc epitopes [49]. Increased cytoplasmic and surface galectin-3 expression was also observed after adhesion and transmigration of neutrophils in response to IL-8 [37].

Reports on triggers that regulate galectin-8 and galectin-9 expression or localization in endothelial cells are scarce. A decrease in galectin-8 and galectin-9 mRNA expression was observed comparing quiescent to high serum activated endothelial cells [23,32]. Interestingly, total protein levels did not appear to change considerably while surface expression of galectin-8 and galectin-9 levels slightly increased, similar as for galectin-1 [32]. Recently, Alam et al. showed that IFNgamma induces galectin-9 expression in endothelial cells [39]. In agreement with other reports [31,42] the authors also showed that IFNgamma stimulates membrane translocation of galectin-9. The expression regulation was shown to be under control of HDAC3 and appeared to depend on a physical interaction of HDAC with both PI3K and IRF3 independent of the deacetylase activity of HDAC [39]. Another trigger for galectin-9 expression regulation in endothelial cells is viral infection [41,65,66] which was suggested to involve signaling via the TLR3-PI3K-IRF3 signaling axis [41].

Altogether, current observations suggest that endothelial cell activation stimulates galectin expression and induces translocation of galectins to the endothelial cell surface. Apart from galectin-9, the signaling cascades and mechanisms that underlie these effects are still largely unresolved. Consequently, it is not known whether the endothelial galectin expression is under control of similar signaling pathways. The observation that single cytokines such as IFNgamma or IL-beta1 can simultaneously modulate the expression of multiple galectins suggests some common regulatory pathways but the proof for this still has to be provided.

4. Involvement of galectins in endothelial cell function and angiogenesis

The observation that the expression of galectins is increased during endothelial cell activation suggests that galectins are involved in different steps of the angiogenesis cascade. In line with this, galectins have been shown to augment signaling pathways that lead to endothelial cell activation. For example, Hsieh et al. showed that galectin-1 interacts with neuropilin-1 thereby promoting signaling via VEGF receptor-2 [67]. It has also been shown that galectin-1 enhances H-Ras signaling in endothelial cells [26]. Galectin-3 was shown to stimulate the pro-angiogenic activity of VEGF and bFGF via clustering of ITGalphaV/beta3 as well

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as by augmenting the membrane retention of VEGF receptor 2 [68]. The latter was also suggested as the mechanism by which galectin-1 and galectin-3 enhance pro-angiogenic signaling via VEGF receptors 1 and 2 [69]. Thus, galectins are already involved in the first phase of angiogenesis, which further supports the observation that increased galectin expression is an early marker of endothelial cell activation [23,32].

Next to a role in angiogenic signaling, endothelial galectins are also involved in endothelial cell functions following cell activation (Figs. 2C and 3). Thus far, the effects of galectins on angiogenesis have been mainly studied by comparing endothelial cell function in the presence or absence of a specific recombinant galectin. It has been shown that exogenous application of galectin-1 stimulates endothelial cell proliferation, migration and tube formation in vitro [26,67,69,70] as well as angiogenesis in vivo [26]. These effects appear to be concentration dependent as higher concentrations can reduce endothelial function [26] and even induce apoptosis [71]. Angiostimulatory activities have also been attributed to galectin-3 [69,72–76]. Markowska and co-workers showed that galectin-3 induces a concentration dependent angiogenic response in vivo using the mouse corneal micropocket assay [73] while Nangia-Makker et al. showed that galectin-3 acts as a chemo-attractant for endothelial cells [74,77] thereby stimulating in vivo vascularization [74]. More recently the same group provided evidence that the angiogenic activity of galectin-3 is confined to a specific matrix metalloproteinase processed form of the protein [78,79]. Interestingly, Yang et al. identified aminopeptidase-N as a binding partner for galectin-3 on endothelial cells [38]. They showed that galectin-3 was no longer capable of inducing endothelial invasion and tube formation following knockdown of aminopeptidase-N [38]. The authors suggested that aminopeptidase-N might also be involved in proteolytic processing of galectin-3.

Besides galectin-1 and galectin-3, there are also reports showing angiostimulatory activity of galectin-8. Delgado et al. showed that galectin-8 stimulates in vitro migration and capillary network formation while in vivo angiogenesis was induced as assessed by the matrigel plug assay [30]. On the other hand, galectin-8 did not affect endothelial tube formation when cells were grown on fibronectin [10] nor did it affect cell adhesion to vitronectin [80]. The latter was explained by the fact that binding of cells to vitronectin is mainly mediated via ITGaVb3 which does not interact with galectin-8 [80]. Instead, galectin-8 appears to mainly interact with ITGa6b1, ITGa3b1 [80] which is in agreement with Carcamo et al. who identified ITGa3 and ITGb1 next to ITGa1 and ITGa5 as integrins that mediate Jurkat T cell adhesion to

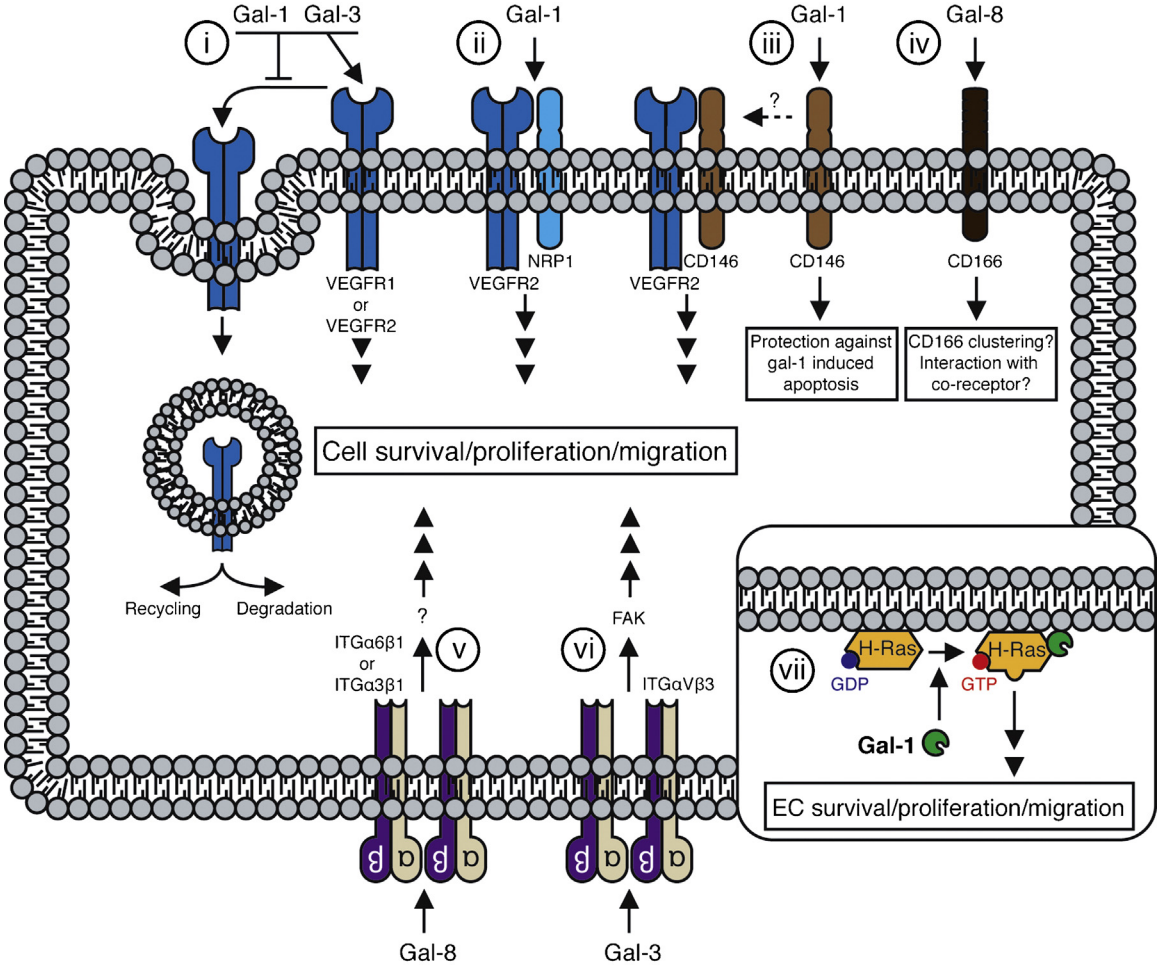

Fig. 3. Different activities of galectins in endothelial cell signaling. Galectin-1 and galectin-3 hamper the uptake of VEGF receptors-1 and -2 thereby stimulating/maintaining receptor signaling (i). Galectin-1 also enhances VEGF receptor-2 signaling by facilitating interaction with the neuropilin-1 (ii). In addition, galectin-1 binds to CD146 which protects EC from galectin-1 induced apoptosis (iii). Although speculative, the interaction between galectin-1 and CD146 might also underlie the interaction of CD146 with VEGF receptor-2 which also enhances pro-angiogenesis signaling. Galectin-8 was shown to bind CD166 but the exact effect of this interaction is unresolved (iv). It might enhance CD166 signaling through receptor clustering or facilitate interaction of CD166 with a yet unknown co-receptor. The same holds true for the described interaction between galectin-8 and different integrins (v). Finally, galectin-3 facilitates FAK signaling through integrin alphaV/beta3 (vi). The inset shows the role of galectin-1 in intracellular H-Ras signaling. Galectin-1 facilitates membrane anchorage of H-Ras-GTP thereby enhancing downstream signaling (vii).

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galectin-8 binding. Apparently, the interaction with galectin-8 is affected by the integrin expression level, the available heterodimers, or integrin glycosylation as suggested by Diskin et al. [81]. The effects of galectin-8 on angiogenesis are thus likely to depend on the type of extracellular matrix and the molecules involved in binding to the matrix components. At present, the role of exogenous galectin-9 in endothelial cell biology or angiogenesis has not been studied.

While the angiostimulatory effects of exogenously added galectins are well established, the role of endogenous galectin expression is somewhat ambiguous. Thus far, no apparent vascular phenotype has been observed in the available mice with a null mutation for any of the endothelial galectins, i.e. *Lgals-1*$^{-/-}$, *Lgals-3*$^{-/-}$, *Lgals-9*$^{-/-}$ mice [82–84]. However, recently we did report on a reversible fetal growth delay during pregnancy in *Lgals-1*$^{-/-}$ mice which could be linked to hampered placental vascularization [85]. In addition, knockdown of galectin-1 in zebrafish induced vascular abnormalities, indicative of impaired vascular guidance [23]. Knockdown of endogenous galectin-1 expression was also shown to hamper endothelial cell migration [26,67] and proliferation [23,26]. Impaired endothelial cell function has also been reported following knockdown of galectin-3 [68] and galectin-8 [30]. Thus, there is ample evidence that interfering with endogenous galectin expression interferes with endothelial cells function. However, since it has been shown that endothelial cells can compensate for the loss of endogenous galectin expression by uptake of exogenous galectin [26,86] the effects might depend on the efficiency of knockdown and the availability of galectins in the extracellular environment. Moreover it is still not clear whether individual galectins may play redundant, divergent or complementary roles fine-tuning the angiogenic phenotype. Experiments aimed at selectively ablating individual galectins in endothelial cells in vivo will contribute to address these issues.

5. Endothelial galectin expression in cancer

Based on their expression in the activated endothelium it has been anticipated that galectins are expressed in the tumor endothelium. Indeed, culturing endothelial cells in the presence of tumor conditioned medium affects the expression and localization of galectins [32,34,58]. In different animal models, tumor angiogenesis is also associated with increased galectin expression. Rysisch et al. found a more than 30-fold induction of galectin-3 mRNA expression in endothelial cells derived from mouse liver tumors as compared to endothelial cells from normal liver [24]. This was confirmed by Jia et al. in an orthotopic rat model of hepatocellular carcinoma which showed a 7-fold increase of galectin-3 protein expression in tumor endothelial cells compared to liver sinusoid endothelial cells [87]. Increased expression of galectins in tumor endothelial cells has also been reported in human cancer tissues. Clausse et al. observed in primary prostate cancer samples that the frequency of galectin-1 positive endothelial cells increased from 7% in not-tumor associated capillaries to 64% in tumor associated vessels [34]. Elevated endothelial galectin-1 expression has been described for other cancers as well, including squamous cell carcinoma [67], lung carcinoma [33], colon carcinoma [23,32], and prostate cancer [88]. On the other hand, endothelial galectin-1 staining was never observed in lymphomas of the central nervous system [89]. In these tumors, endothelial galectin-3 expression was a prognostic factor for shorter survival [89]. Galectin-3 expression has also been reported in tumor vasculature of other tumor types including head and neck and lung cancer [33], hepatocellular carcinoma, colon carcinoma [32], and glioma [90,91]. In the latter, expression appeared to decrease with increasing malignancy [90,92]. Reports on the expression of galectin-8 and galectin-9 in tumor blood vessels are scarce. Comparable levels of nuclear galectin-8 staining were observed in the endothelium of both normal colon and colon carcinoma [32]. Similar observations were described by Delgado et al. who compared endothelial galectin-8 expression in normal tissues from breast and prostate with malignant tissues [30].

Altogether, it appears that for most tumors the activated endothelium displays increased expression of at least galectin-1 and galectin-3. However, this might vary between tumor types and/or between the stages of a specific cancer. For the other two galectins the current literature is too limited to link expression to endothelial activation. Further studies are required to get more insight in the expression of different galectins in the tumor endothelium. In addition, it should be established whether alterations in the endothelial expression of specific galectins is correlated with cancer progression and/or patient survival.

6. Contribution of endothelial galectins to tumor progression

In recent years it has become evident that several galectins are involved in different steps of tumor progression [93–95]. This occurs already at the level of tumor cell transformation via interactions with oncogenes like HRAS and KRAS [96,97]. Galectins have also been implicated in cell-cycle control and regulation of apoptosis [98,99]. Next to these direct effects, galectins indirectly contribute to tumor progression by facilitating tumor immune escape and tumor metastasis as well as by promoting tumor angiogenesis. In fact, there is compelling evidence that the indirect tumor promoting effects are partly mediated by galectins in the tumor vasculature, more specifically, by galectins expressed in the cells that line the luminal side of blood vessels, i.e. endothelial cells [100].

6.1. Tumor angiogenesis

Given their function in endothelial cell biology and the increased expression in the tumor endothelium it can be anticipated that galectins are directly involved in tumor angiogenesis. Using knockout mice it was shown that lack of host galectin-1 hampers tumor growth due to inadequate tumor angiogenesis [23]. Later studies showed that this effect was tumor type independent since tumor angiogenesis was decreased in different tumor models [26]. Moreover, the latter study also revealed that an increased expression and secretion of galectin-1 by the tumor cells could compensate for the loss of endothelial galectin-1 expression [26]. This observation allows the conclusion that galectin-1 can be considered an angiogenic growth factor. This is in agreement with the previously described angiostimulatory activity of galectin-1. Indeed, several recent studies show that knockdown of galectin-1 expression in tumor cells impairs tumor angiogenesis resulting in hampered tumor growth [56,70,88,101]. Croci et al. presented evidence that tumor derived galectin-1 served as direct link between hypoxia and tumor angiogenesis through binding to N- but not O-glycans on endothelial cells. They found that hypoxia induces the expression and secretion of galectin-1 by Kaposi's sarcoma cells via NFkB, independent of HIF1α or HIF2α. The subsequent angiostimulatory effects could be blocked by silencing the synthesis of galectin-1-binding glycans on endothelial cells [56].

Similar to galectin-1, tumor derived galectin-3 is also associated to tumor angiogenesis. As described previously, proteolytic processing of galectin-3 yields a more angiopotent galectin-3 variant. Using tumor cells expressing a protease resistant galectin-3 variant Nangia-Makker et al. observed significantly hampered tumor growth which was linked to reduce tumor angiogenesis [78]. Interestingly, Wu et al. had previously shown that increased

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galectin-1 expression in tumor cells induces MMP-2 and MMP-9 expression [102]. While the authors linked this to increased invasiveness of the tumor cells [102] it is tempting to speculate that this might also indirectly lead to increased angiogenesis via cleavage of galectin-3 to the more angiogenic variant. This way, galectin-1 could promote angiogenesis via galectin-3. On the other hand, when galectin-3 null mice were crossed with two mouse models of human intestinal cancer, i.e. the Apc(Min) and Apc(1638N) lines, neither tumor initiation nor tumor progression were affected. The vascular density was also comparable in all tumors [103]. The same was true for PyMT transgenic animals – a genetic model of primary mammary gland tumors – crossed with galectin-3 null mice [103]. These data suggest that galectin-3 is not involved in tumor angiogenesis. However, the observed discrepancies might be related to the type of model, i.e. spontaneously arising tumors in null mice vs. grafted tumors in null mice. Since the growth rate and aggressiveness of grafted tumors is usually higher, growth limiting effects of impaired angiogenesis become more obvious. In addition, the spontaneous tumor models do not allow analysis of the indirect angiostimulatory effects of tumor-derived galectins since the tumor cells are also galectin-deficient. To gain better insight in the role of galectins in tumor angiogenesis experiments in conditional knock out models or cell type specific knock out models are required. This also holds true for studies on galectin-8 and galectin-9 for which currently no data on their contribution to tumor angiogenesis are available.

6.2. Galectins in tumor immunity

Apart from their role in tumor angiogenesis, galectins are also widely recognized for their role in the immune system, most notably as modulators of tumor immune escape (for excellent reviews of the different galectins see [3,8,28,40,93,104–106]). Galectins, particularly galectin-1, contribute to create an immunosuppressive tumor microenvironment by blunting tumor-specific T-cell responses, instructing dendritic cells to become tolerogenic and expanding the regulatory T-cell compartment [107–111]. In recent years it has become evident that part of this modulatory effect might involve galectins expressed on tumor endothelium [100]. For example, endothelial galectin-1 can inhibit lymphocyte recruitment under flow conditions [112]. Furthermore, Perillo et al. showed that galectin-1 expressed on the surface of endothelial cells promotes apoptosis of adhering and transmigrating activated T-cells in a time and concentration dependent manner [59]. In a later study, the same group showed that endothelial galectin-1 also inhibits trans-endothelial migration of T-cells, independent of the apoptotic activity [58]. It was suggested that galectin-1 enhances CD43 clustering thereby interfering with the redistribution and signaling via CD43 which is required for proper migration [58]. Since expression of galectin-3 and galectin-9 on the vascular endothelium has also been described to induce T-cell apoptosis [43,113,114] it is tempting to speculate that the increased expression of these galectins in the activated tumor endothelium may contribute to tumor-immune escape. On the other hand, intracellular galectin-3 can protect T-cells against apoptosis [115] while extracellular galectin-3 promotes T-cell apoptosis, suggesting notable differences in the extracellular and intracellular activities of this protein [114]. Moreover, galectin-3 has been shown to contribute to T-cell anergy. Multivalent interactions between galectin-3 and N-glycans on CD8+ T-cells caused impaired IFNγ secretion and decreased mobility of T-cell receptors in tumor-specific CD8+ T-cells, suggesting that galectin-3 may contribute to T-cell anergy when cells migrate across the endothelium [116]. In addition, cell surface glycosylation has been shown to regulate the susceptibility of helper T-cell subpopulations (Th1, Th2 and Th17 cells) to galectin-1-induced apoptosis [43,117]. More recent data show that interactions of galectin-9 with protein disulfide isomerase on the surface of T-cells can even enhance T-cell migration [118]. Thus, increased endothelial expression of galectins might also modulate survival, activation, differentiation and anergy of intravasating inflammatory cells. In line with this, enhanced adhesion of eosinophils to galectin-9-expressing HUVEC has been observed [42,65]. Similar observations were reported for galectin-3 [60] which has also been shown to facilitate neutrophil adhesion to endothelial cells [119]. While these data show that endothelial galectins can modulate the immune response, they also illustrate that this regulation is complex and that there are many determinants that influence the overall effects, including the expression of galectins in tumor cells or stromal cells, including tumor-associated fibroblasts [120]. All these variables might explain conflicting observations regarding the role of galectins in tumor-associated immunity or angiogenesis [23,26,103,107,121]. While in some models galectin-induced immunosuppression prevails over angiogenesis [107], in other models the major target of galectin blockade is the tumor-associated vasculature [23,56]. Nevertheless, the current view indicates that increased expression of some members of the galectin family, particularly galectin-1, contributes to create an immuno-suppressive environment which sustains tumor progression. Whether a cross-talk exists between the immunosuppressive and pro-angiogenesis phenotypes of tumors remains to be elucidated.

6.3. Metastasis

The role of endothelial galectins in tumor metastasis is more obvious and appears to be mainly mediated through the regulation of heterotypic cell–cell interactions [122]. Glinsky et al. showed that galectin-1 and galectin-3 accumulates at the site where breast tumor cells (MDA-MB-435) interact with endothelial cells. [123,124]. Galectin-1 was shown to accumulate in the tumor cells while galectin-3 accumulates in the endothelial cells [123,124]. The heterotypic interaction involves the Thomsen-Friedenreich antigen which was shown to induce galectin-3 expression in endothelial cells [49,50,125] and suggested to increase cancer cell adhesion to the endothelium [126]. Krishnan et al. found that the adhesion of B16F10 cells to endothelial cells involves binding of galectin-3 to poly N-acetyllactosamine present on lysosomal-associated membrane protein 1 (LAMP1) [20]. Previously, it had been shown that carcinoma cells that express more sialyl Lewis X structures at the termini of poly-N-acetyllactosaminyl side chains have increased metastatic potential [127,128]. Furthermore, LAMP-1 is known to translocate to the membrane of metastatic melanoma cells [129,130] and it was suggested that (lung) endothelial galectin-3 might serve as an anchor for circulating tumor cells presenting LAMP1 on their surface [20,129,130]. Besides a role of endothelial galectin-3 in tumor metastasis, Clausse et al. showed that increasing the galectin-1 expression in endothelial cells augments adhesion of prostate cancer cells (PC-1) [34]. Thus, galectins can mediate heterotypic interactions between tumor cells and endothelial cells which can facilitate tumor metastasis [100,104]. In fact, the preference of some tumor cells to metastasize to specific tissues might be influenced by their prevalence to bind to galectins which show elevated expression in the endothelium of these tissues [33,131].

7. Targeting endothelial galectins for cancer therapy

As described above, galectins in the tumor endothelium appear to contribute to tumor progression on multiple levels, i.e. tumor angiogenesis, tumor immune escape and tumor metastasis. Interestingly, the tumor endothelium is an attractive target for

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therapy. It allows direct and tumor type independent drug delivery without the need to determine the location of the tumor. Furthermore, the target cells, i.e. the endothelial cells, are less likely to acquire a drug resistant phenotype [132]. Despite these advantages and the development of several angiostatic agents that have reached the clinic [133], most current angiostatic approaches only give moderate effects [134,135]. Thus, novel endothelial specific targets are required to develop better treatment modalities. Endothelial galectins might serve as such target molecules since tumor activated endothelial cells show increased surface expression of galectins. Furthermore, Cederfur et al. observed that the galectins that bind most serum glycoproteins were galectin-1, -3, -8, and -9 [136], i.e. the galectins that are expressed on the surface of endothelial cells. This might me exploited to target drugs to the tumor microenvironment. Moreover, endothelial galectins contribute to multiple steps of tumor progression. This increases their therapeutic potential and has consequently raised an interest in targeting these galectins for therapeutic applications. Several different strategies have been used to target galectins in the endothelium, including blocking antibodies, competing glycans, or protein inhibitors (Fig. 4). These approaches mainly aim to interfere with the three main functions of endothelial galectins in tumor progression, i.e. angiogenesis, immuno-editing, and metastasis.

7.1. Inhibition of angiogenesis

It has been shown that a polyclonal anti-galectin-1 antibody can inhibit the migration of endothelial cells plated on gelatin [23]. The same antibody also hampers angiogenesis in the in vivo chorioallantoic membrane assay [23]. A similar but more indirect effect of antibody treatment was described by Delgado et al. As already described, these authors identified CD166 as an endothelial binding partner for galectin-8. Subsequent experiments showed that anti-CD166 antibodies inhibit the induction of endothelial cell migration and tube formation by galectin-8 [30]. All these experiments suggest that blocking endothelial galectins or galectin-binding proteins with antibodies can interfere with angiogenesis. On the other hand, Fukushi et al. found that antibodies targeting galectin-3 did not interfere with endothelial cell migration on either matrigel, fibronectin, or type I collagen [36]. In addition, Rabinovich et al. showed that anti-galectin-1 or anti-galectin-3 antibodies can even counteract the angiostatic activity of galectin targeting compounds [22]. Apparently the effects of antibodies depend on the context and type of assay in which they are used. This is further exemplified by the observation that galectin-3 antibodies can be inhibited the induction of endothelial cell tube formation on matrigel [74]. Moreover, Yan et al. showed that anti-galectin-3 antibodies can partially prevent an angiogenic response in ischemic rat brain [72]. Thus, in pathologies where galectin-3 is secreted to induce endothelial activity, antibody-based therapy might be beneficial. Interestingly, Croci et al. found that an anti-galectin-1-specific monoclonal antibody prevents hypoxia-driven angiogenesis in vivo and tumorigenesis in a model op Kaposi's sarcoma [56]. Further experiments should reveal whether the activity of antibodies also depends on the site where they bind galectins since blocking the carbohydrate-binding site might induce other effects compared to blocking the site involved in di- or multimerization of galectins.

Apart from antibodies, several efforts have been made to block galectins with synthetic or naturally occurring carbohydrates. For example, a modified form of citrus pectin (MCP), a polysaccharide rich in galactose residues, can counteract the induction of endothelial tube formation by galectin-3 [74]. In addition, MCP prevents binding of galectin-3 to endothelial cells and inhibits the chemotactic activity of galectin-3 on these cells [77]. Rabinovich et al. designed synthetic lactulose amine derivates (SLA) that bind with different affinity to galectin-1 and galectin-3 and that selectively inhibited endothelial cell tube formation on matrigel [22]. Another synthetic carbohydrate, i.e. the disaccharide thiodigalactoside (TDG), has also been shown to inhibit galectin-1 induced tube formation [70]. In addition, TDG treatment of tumor bearing mice reduced the number of tumor vessels as well as the vessel diameter. Consequently, tumor growth was impaired and

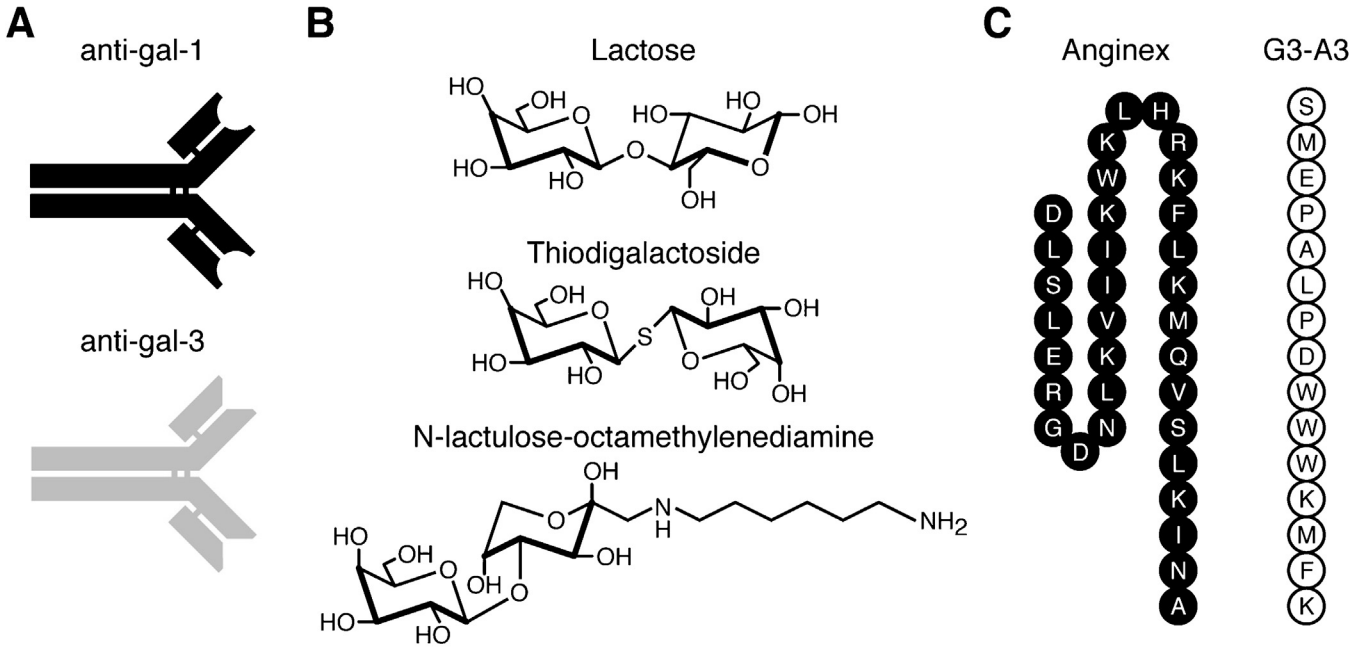

Fig. 4. Galectin-targeting molecules. Examples of molecules that have been used to block galectins and interfere with their activity in angiogenesis. Three main groups can be distinguished, i.e. antibodies (A), carbohydrates (B), and peptides (C). For the carbohydrate inhibitor modified citrus pectin no unique structure is available but it is rich in galactose residues and consists mainly of linear homogalacturonanic acid. The structure of N-lactulose-octamethylenediamine is illustrative for the SLAs reported by Rabinovich et al. [22]. The peptide G3-A3 is one of the validated galectin-3-binding peptides identified by Zou et al. using phage display [150].

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further experiments in immune-compromised mice confirmed that this anti-tumor effect was indeed partly caused by inhibition of angiogenesis [70]. A more recent study suggested that TDG also inhibits the angiostimulatory activity of galectin-8 [30]. This is agreement with the fact that TDG has been shown to bind multiple galectins, including galectin-8 [137]. Thus, TDG might be considered as a broad-spectrum angiostatic compound that can simultaneously block the angiogenic activity of different endothelial galectins.

A third group of angiostatic galectin inhibitors consist of proteins and peptides. For example, a 22 kDa galectin-3 fragment (galectin-3C) has been developed which consists of only the carbohydrate recognition domain. This fragment can antagonize the angiogenic activity of full length galectin-3 [73]. While endothelial cell viability is not affected by gal-3C the protein inhibits tube formation of HUVEC on matrigel. Galectin-3C treatment also hampers growth of human multiple myeloma cells in a xenograft mouse model although the effects on angiogenesis were not further assessed [138]. Comparable effects were observed in a xenograft mouse model of breast cancer [139]. These data suggest that dominant negative variants of galectins might be used as therapeutic agents. In the case of galectin-3C, the inhibitory effects are most likely caused by the lack to form multimers via the C-terminal tail, but direct modifications to the CRD that affect carbohydrate affinity or specificity might also be considered [140]. This is illustrated by the galectin-1 binding peptide anginex. This synthetic 33-mer peptide as well as it derivates inhibits endothelial cell function in vitro and tumor angiogenesis in vivo [141–144]. It was shown that the activity requires the presence of galectin-1 in the tumor endothelium [23]. In addition, anginex was found to inhibit membrane translocation of activated H-Ras which inhibits downstream signaling [26]. Recent data suggest that the carbohydrate affinity and specificity of galectin-1 are modified by anginex [145]. Apparently, this effect involves direct protein–protein interactions which can influence glycan-binding properties, a feature that might be further exploited for therapeutic applications.

Thus, galectin-targeted angiostatic therapy can be aimed at scavenging the secreted angiostimulatory galectins with antibodies – comparable to e.g. the anti-VEGF antibody bevacizumab – or it can aim to block the function of galectins on endothelial cells by interfering with carbohydrate binding. While the advantage of the former relies on the specificity of monoclonal antibodies for individual galectins, the advantage of the latter approach is that multivalent inhibitors could be developed that simultaneously block the function of multiple endothelial galectins.

7.2. Targeting tumor immune escape

How different inhibitors affect the immuno-suppressive effects of endothelial galectins is less well studied. He et al. showed that an anti-galectin-1 antibody could block the inhibitory effect of endothelial galectin-1 on the transendothelial migration of T-cells [58]. This would favor a potentiation of anti-tumor responses. In line with this evidence, Ito et al. observed that blocking galectin-1 with TDG increased tumor infiltration of CD4+ and CD8+ lymphocytes in a mouse tumor model [146]. However, this appeared to be mainly related to inhibition of tumor derived galectin-1 since effect of TDG was lost when galectin-1 knockdown tumor cells were used [70]. Treatment of tumors in either galectin-1 wild type or null mice with anginex did not affect the anti-tumor immune response [23,26]. Moreover, interfering with galectin-3 might even hamper the adhesion of neutrophils and eosinophils to the endothelial cell layer [60,119]. Reduced eosinophil adhesion to endothelial cells was also observed when a specific prostaglandin, i.e. 15d-PGJ_2, was used to prevent the IFNgamma induced expression of galectin-9 [42]. These data illustrate the previously described complexity of immune-modulation by endothelial galectins and show that it will be difficult to predict how galectin-targeted therapy will affect the immune response at the tumor–vascular interface.

7.3. Prevention of metastasis

While the effects on immune-modulation appear inconclusive there is ample evidence that targeting endothelial galectins can prevent tumor metastasis. Like the inhibition of angiogenesis this can be achieved using antibodies, carbohydrates, or peptides. Already in 1994 Lotan et al. showed that an anti-galectin-1 antibody prevents the adhesion of large cell lymphoma cells to endothelial cell monolayers [33]. A similar effect was observed when adhesion of PC-1 prostate carcinoma cells to endothelial cells was assessed [34]. The adhesion of prostate cancer cells to bone marrow endothelial cells could also be blocked by anti-galectin-3 antibodies as well as by the previously described polysaccharide MCP [131]. The latter also prevented the galectin-3 mediated adhesion of rat prostate cancer cells or breast cancer cells to endothelial cells in vitro [77,147]. Furthermore, in vivo treatment with anti-galectin-3 antibodies or MCP can significantly reduce metastasis of tumor cells to the lungs [77,147,148]. Recently, mushroom derived polysaccharides were shown to prevent the adhesion of different tumor cells to endothelial cell monolayers. This appeared to be related to galectin-3 expression in the tumor cells and the polysaccharides did not affect endothelial cell viability [149]. That carbohydrate derived inhibitors do not have to be very complex was shown by Krishnan et al. who used lactose to prevent adhesion of B16F10 cells to galectin-3 expressed on the surface of mouse lung endothelial cells [20].

Zou et al. used phage display screening to identify galectin-3 binding peptides that might interfere binding of galectin-3 to the tumor-specific Thomsen-Friedenreich antigen. They identified high affinity peptides that specifically bound to the carbohydrate recognition domain of galectin-3 [150]. Furthermore, the peptides did not bind the carbohydrate recognition domain of other galectins and plant lectins. These peptides significantly inhibited rolling and stable heterotypic adhesion of breast carcinoma cells to endothelial cells [150]. This is in line with previous findings with a Thomsen-Friedenreich antigen peptide (P-30) or antigen mimetics [123–125,151].

Thus, blocking the binding of tumor derived carbohydrates to endothelial galectins provides a powerful opportunity to prevent tumor metastasis and several agents have been developed that exert this inhibitory effect. Future studies should focus on the clinical application of these agents for treatment of cancer patients.

7.4. Additional applications of targeting endothelial galectins

All the previous paragraphs illustrate the potential of interfering with endothelial galectins for therapeutic applications. However, the endothelial galectins are not only suitable as targets for therapy. Since activated endothelial cells express more galectins at their surface, galectin-binding proteins have also been used to target the tumor vasculature. This can be exploited to e.g. guide cytotoxic compounds specifically to the tumor. This is illustrated by Dings et al. who conjugated anginex to the chemotherapeutic agent 6-hydroxilpropylacylfulvene (HPAF). The conjugate was a more potent inhibitor of endothelial cell proliferation compared to anginex alone [152]. More importantly, in tumor experiments in vivo, the conjugate showed less toxicity compared to the unconjugated HPAF [152]. Anginex has also been used alone or in combination with the ITGaVb3 binding RGD-peptide to target liposomes to tumor vessels. The combination

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resulted in better liposome uptake by HUVEC and displayed strong anti-proliferative activity [153]. Additional loading of these dual targeting liposomes with e.g. MRI contrast agents could thus be used for simultaneous diagnosis and therapy of angiogenesis related pathologies as suggested by Brandwijk et al. [154,155]. Whether other galectin-binding molecules can also be used for such applications still needs to be resolved. However, the finding that tumor cells present carbohydrates at their surface that allows them to bind to endothelial galectins suggests that specific carbohydrates might be synthesized for such applications.

8. Conclusions and future perspectives

As shown in this review, galectins play versatile roles in many cells and tissue, including in the cells that line the vasculature, i.e. endothelial cells. Current literature indicates that endothelial cells express at least four galectins, i.e. galectin-1, -3, -8, and -9. These galectins are present in the nucleus, the cytoplasm and at the cell surface. Furthermore, the expression and localization is influenced by endothelial cell activation. Exogenous application of most endothelial galectins promotes endothelial cell function and angiogenesis. In addition, knockdown of endogenous galectin expression can hamper endothelial cell functions. Future studies should focus on unraveling the interplay between exogenous and endogenous galectin to get a better insight in their mutual or exclusive functions. In addition, it is still poorly understood which triggers and pathways control galectin expression and processing in endothelial cells. Especially regarding splicing of e.g. galectin-8 and galectin-9 little information is available and this certainly is a challenge for future research.

It is now also evident that tumor endothelial cells frequently display increased galectin expression. This can facilitate tumor progression on different levels including angiogenesis, immunosurveillance, and metastasis. It is pivotal to further unravel how endothelial galectins simultaneously regulate these processes and whether pathways or mechanisms are shared that depend on a single family member. Furthermore, different strategies have been developed to block endothelial galectins and to interfere with their tumor promoting activities. Apart from direct therapeutic applications, the endothelial galectins can also provide opportunities for diagnosis or targeted drug delivery. Thus far, most strategies have been mainly tested in a pre-clinical setting and future research should focus on translating these findings to the clinic. Furthermore, it will be important to study whether and when galectin expression has prognostic value in order to select those patients that will benefit most from galectin-targeted therapy. Increasing our understanding of the regulation and function of endothelial galectins in the normal and diseased vasculature can lead to the development of novel and more potent galectin inhibitors. Finally, the recognition of vascular galectins as multipotent regulators of tumor progression will open new diagnostic and therapeutic opportunities, not only for cancer but possibly for other pathologies characterized by aberrant angiogenesis.

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