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REVIEW

Glycans and galectins in prostate cancer biology, angiogenesis and metastasis

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Prostate cancer is the second most common cause of cancer and the sixth leading cause of cancer death among men worldwide. While localized prostate cancer can be cured, advanced and metastatic prostate cancer remains a significant therapeutic challenge. Malignant transformation is associated with important modifications of the cellular glycosylation profile, and it is postulated that these changes have a considerable relevance for tumor biology. Metastasis is a multiphasic process that encompasses angiogenesis, the spread of tumor cells and their growth at distant sites from the primary tumor location. Recognition of glycoconjugates by galectins, among other lectins, plays a fundamental role in the metastatic spread, tumor immune escape and the neovascularization process. Particularly in prostate cancer, both carbohydrates and galectins have been implicated in many cellular processes such as proliferation, apoptosis, migration and invasion. However, a limited number of studies assessed their potential implications in the induction of metastasis in prostate cancer patients or in animal models. Moreover, the role of galectin–glycan interactions in vivo still remains poorly understood; concerted effort should thus be made in order to shed some light on this question. This review summarizes current evidence on both the expression and role of glycans and galectins in prostate cancer, particularly turning our attention to the angiogenic and metastatic processes.

Keywords: angiogenesis and metastasis / carbohydrate / galectin / glycan / prostate tumor

Introduction

Prostate cancer (PCa) is the second most common cancer in men and is a major cause of mortality in the world (Jemal et al. 2011). Approximately 15–20% of prostate cancer patients develop a metastatic process. PCa biopsies obtained from patients are subjected to histologic analysis, which in turn allows its classification into different Gleason scores (Gleason 1988). Cancers with a higher Gleason score are more aggressive and are associated to a poor prognosis. Early diagnosis of this disease is a key determinant of the efficiency of current therapies. Such treatments include surgery and radiotherapy but these are only effective in cases of localized PCa. Although androgen ablation is advisable in cases of metastasis (Denmeade and Isaacs 2002), metastatic PCa is practically incurable because tumor progression is still possible with the selection of those tumor cells whose growth is resistant to castration, giving place to metastatic castration- resistant PCa (mCRPC). Since 2004, docetaxel-based chemotherapy associated with prednisone or estramustine is considered a first-line standard therapy for mCRPC, which beneficial effects have been clinically demonstrated (Petrylak et al. 2004; Tannock et al. 2004). Unfortunately, clinical treatment with docetaxel leads to a variable number of side effects including drug resistance (Miller 2001; Geney et al. 2002; Petrylak 2005). It is therefore essential to identify novel therapeutic approaches to target growth and metastasis of PCa cells. Importantly, the latter should be regarded as a multistep process that includes migration, invasion and angiogenesis. This review compiles our current knowledge of glycans and galectins in PCa biology (Figure 1), and particularly focuses on their effect on the angiogenic and metastatic properties of PCa tumor cells.

Glycan remodeling in prostate cancer

Along their way through the secretory pathway, proteins and lipids are commonly glycosylated, and the resulting glycoconjugates are either secreted or openly exposed at the cell membrane, where they play a key role as sensors to maintain normal body homeostasis (Rabinovich and Toscano et al. 2009). These posttranslational modifications occur in the lumen of the endoplasmic reticulum and the Golgi apparatus as a consequence of the synchronized action of both glycosyltransferases and glycosidases. The expression and activity of these enzymes determine what is collectively known as the cellular glycome—historically considered as a mere cell decoration. However, recent advances in the methodologies used for N- and O-linked glycan analysis broadened our knowledge of the role of glycans in cellular biology (Mariño et al. 2010), and it is today accepted that the intrinsic diversity of the glycome encodes information

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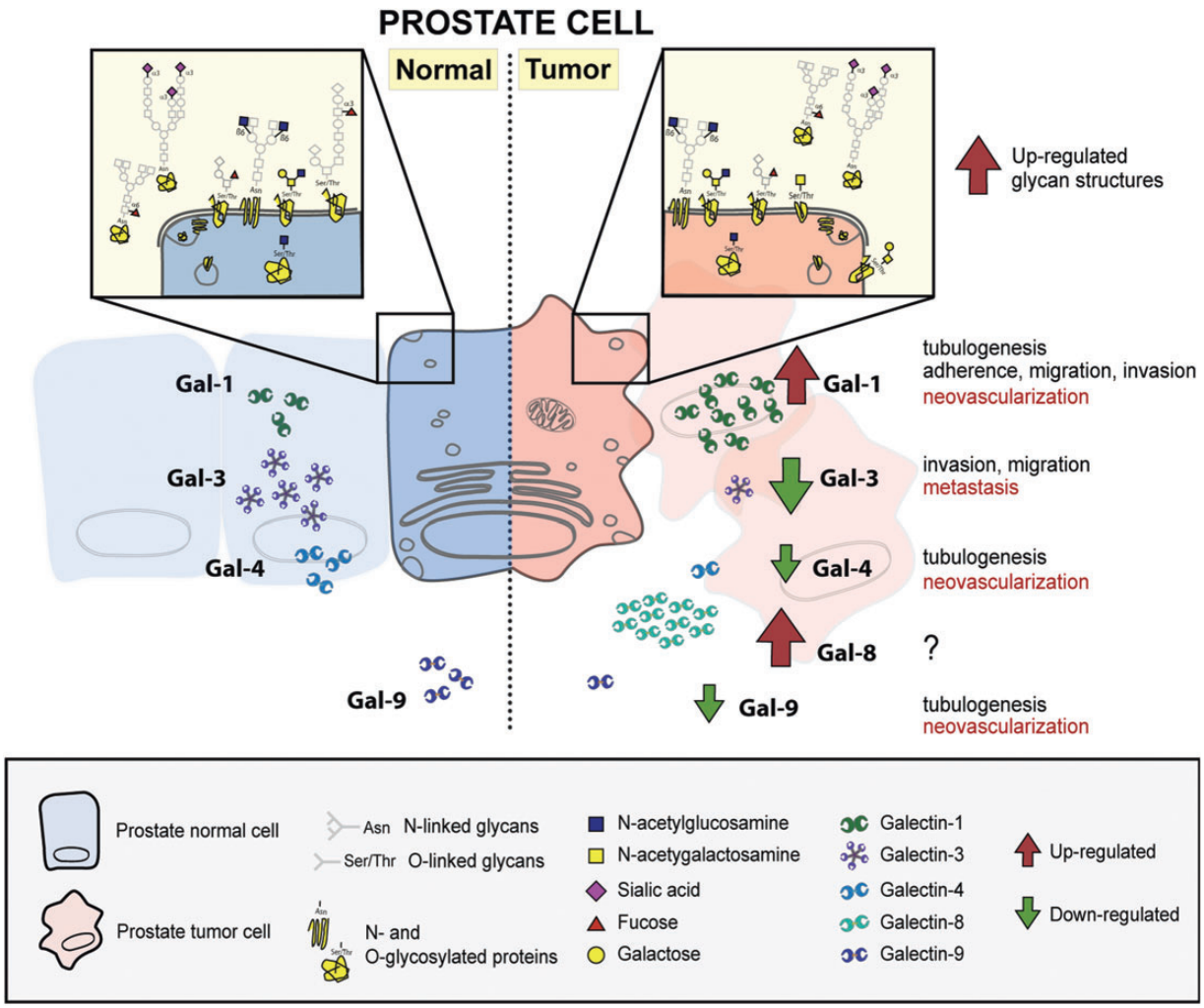

Fig. 1. Schematic representation of the described changes in galectin and glycan expression in prostate tumor versus prostate normal cells. Illustration depicts known qualitative and quantitative modifications in glycan (upper side) and galectin expression (lower side) comparing tumor (on the right) to normal prostate cells (on the left). Such modifications are described in the context of the biological processes that play a role in this disease (in vitro assays (black) or in vivo assays (red)).

which adds to the one introduced by the genome and the proteome.

In tumor biology in particular, it has been shown that the glycosylation profile of tumor cells is dramatically altered throughout disease progression because of changes in either the expression levels or activity of glycosyltransferases and glycosidases (Brockhausen 1999; Dube and Bertozzi 2005; Packer et al. 2008). These modifications have been associated with enhanced malignancy and could exert a profound impact on the modulation of tumor biological properties (Hauselmann and Borsig 2014). It is therefore important to elucidate the intricate pathways in which glycans are involved.

Tumor is a complex tissue that comprises tumor cells *per se* and a surrounding stroma. In the case of PCa, both tumor and stromal cells have been reported to undergo changes in the glycosylation pathway. In fact, certain types of glycosylations have been shown to strongly correlate with disease progression, as estimated by the Gleason score. Data from tissue microarrays derived from radical prostatectomies have reported that β-(1,6)-branched *N*-glycans are frequently overexpressed in PCa (Lange et al. 2012). Also, similarly to other types of cancer, PCa cells often bear the Tn antigen (GalNAc-*O*-Ser/Thr) on their surfaces, which has been proposed as a target for immunotherapy (Slovin et al. 2003). To date, the role of this particular glycosylation in PCa biology is still unknown.

Given their glandular origin, prostatic cells have a secretory nature. The secretome of PCa cells is also differently glycosylated from that of normal prostatic cells. As shown by HPLC and MALDI-MS analysis of PCa patients' sera, both core fucosylation and α-(2,3)-sialylation were increased when compared with sera from benign prostatic hyperplasia patients (Ohyama et al. 2004; Saldova et al. 2011; Mechref et al. 2012). In particular, aberrant glycoforms of the prostate-specific antigen (PSA)—the tumor marker currently used for PCa diagnosis and recurrence survey—have been reported, although evidence is often contradictory, mainly because the amount of serum PSA is too low for its assessment (Gilgunn et al. 2013). There is however consensus of opinion suggesting that sugar chains found on PCa-derived PSA are β-*N*-acetylgalactosaminated, α-(1,2)-fucosylated and α-(2,3)-sialylated (Peracaula et al. 2003; Fukushima et al. 2010).

The influence of these particular modifications in PCa progression remains inconclusive.

Furthermore, several nuclear and cytoplasmic proteins are attached with an O-linked β-*N*-acetylglucosamine (O-GlcNAc) onto serine or threonine residues, so-called O-GlcNAcylation. This modification is essential for several fundamental cellular processes such as cellular proliferation, invasion and angiogenesis, and is frequently dysregulated in human diseases, including cancer. Clinicopathological data of PCa patients has shown that high intracellular O-GlcNAcylation levels are positively correlated with higher Gleason scores and negatively correlated with overall patient survival (Kamigaito et al. 2014), and further in vitro studies associate O-GlcNAcylation with enhanced PCa cells proliferation, invasion and angiogenesis (Lynch et al. 2012; Liu et al. 2014).

Although the role of these modifications is overall poorly understood, many of these changes have been reported to directly affect tumor growth, neovascularization, invasion, migration and metastasis, as well as mechanisms including detachment from basement membrane, camouflage against immunosurveillance and protection from several pro-apoptotic stimuli. It is believed that glycan–lectin interactions play a key role in the initial reversible phase in which primary cell–cell recognition occurs. Consequently, the adhesive properties of cancer cells are strongly influenced by glycan modifications. For instance, core-3-*O*-glycan-synthase suppresses tumor formation and metastasis by regulating the integrin complex function (Lee et al. 2009). PCa cells usually metastasize to the bone, and this process is generally facilitated by increased expression levels of fucosyltransferases (FTs) (Barthel et al. 2008; Yin et al. 2010). FT6 in particular has been shown to enable PCa metastasis by enhancing cell binding to endothelial E-selectin (Li et al. 2013). Glycosylation can also confer PCa cells protection from apoptosis. It has been reported that core-2-*O*-glycan-expressing PCa cells show enhanced resistance to natural killer cells cytotoxicity (Okamoto et al. 2013).

Carbohydrates are abundant components on the cell membrane in the form of glycoconjugates. It is now clear that glycosylation is not only an inert decoration of the cell surface but an efficient way for the cells to sense and communicate with neighboring cells and their environment. The decoding of the information represented by all these altered glycan structures needs the intervention of players able to do it. In this regard, lectins consist of a heterogenous family of proteins with carbohydrate-binding domains that are responsible of quantitatively and qualitatively decrypting the endogenous glycome, and play a key role in tumor biology by sensing the aberrant glycan profile and consequently signaling differently when compared with physiological conditions. For instance, *O*-glycosylation has been reported to regulate susceptibility of LNCaP cells—widely used as a human PCa cell model—to cell death induced by the β-galactoside-binding lectin galectin-1. In this regard, preventing the elongation of polylactosamine structures in the *O*-glycosylation pathway renders tumor cells resistant to galectin-1-induced apoptosis (Valenzuela et al. 2007). Also, Zhuo and colleagues showed in colon tumors that β1-integrin has elevated levels of α2,6-sialylation, which prevents galectin-3 binding and consequently protects tumor cells from galectin-3-induced apoptosis (Zhuo et al. 2008). Taken altogether, these results showed that the glycan profile and galectin expression levels could affect cancer cell behavior.

Additionally, lectin expression is also frequently dysregulated in cancer (Rabinovich and Croci 2012). This review focuses on the role of galectins, a particular family of lectins, which comprise a 15-member family with the ability to recognize the disaccharide *N*-acetyllactosamine [Galβ(1–4)-GlcNAc]. Inside the cell, galectins regulate different molecular processes, including mRNA assembly, signal transduction and gene expression. At the extracellular level, galectins are involved in adhesion, migration and intercellular communication (Compagno et al. 2014). Recognition of glycoconjugates by galectins plays a fundamental role in tumor immune escape, neovascularization processes and metastatic spreading. The general biochemical and functional properties of galectins have been described elsewhere (Liu and Rabinovich 2005; van Kooyk and Rabinovich 2008; Laderach et al. 2010; Di Lella et al. 2011). In addition, galectins, more precisely galectins (Gals)-1 and -3, have been also reported to play a central role in the angiogenic cascade not related to PCa (Nangia-Makker et al. 2000; Thijssen et al. 2006; Markowska et al. 2011; Croci et al. 2012, 2014; D'Haene et al. 2013). Hence, this review deals with the role of these evolutionary conserved carbohydrate-binding proteins only in PCa progression with particular focus on their impact during tumor neovascularization and metastasis.

Galectins in prostate cancer

It is well known that progression towards advanced stages in cancer implies different principles. First, cancerous tissues are comprised by heterogeneous subpopulations of cells with different angiogenic, invasive and migratory properties, which in turn allow some of them to disseminate into circulation. Second, the journey to the distal site poses a selection process to be overcome. Finally, the success of the metastatic cells depends upon their ability to interact and utilize the "soil" provided in their new microenvironment. One central factor in the first phase of metastasis is hypoxia, which alters the cellular glucose metabolism, increasing the chance of survival in the nutrient starved tumor mass, and at the same time turns on cellular programs associated with embryogenesis (epithelial-to-mesenchymal shift), wound healing (remodeling of the extracellular matrix, ECM) and new blood vessel formation (Pienta and Loberg 2005). Thus, malignant cells acquire several properties that enable their dissociation from the primary tumor, the degradation of the ECM, the invasion of surrounding tissues, the adhesion to blood vessels and, finally, their ability to metastasize to new distant organs. Several research groups focused their studies to elucidate the role of galectins in tumor progression.

With regard to PCa, our group recently reported a particular pattern of expression of galectins, as evidenced both in human PCa cell lines and, more importantly, in PCa patient samples (Laderach et al. 2013). In the early stages of the disease, Gals-1, -3 and -8 are strongly expressed, whereas Gals-4, -9 and -12 are also expressed but at lower levels. As the disease progresses towards more aggressive stages, Gal-1 is the only family member that evidences an up-regulated expression. In contrast, Gals-3, -4, -9 and -12 gradually decrease their expression levels

as the disease progresses; Gal-3 expression is even lost in advanced stages. In contrast to other members, Gal-8 is expressed at moderate yet constant levels throughout all the stages of the disease. These data delineate a "galectin-specific signature" characterized by selective up- or downregulation of galectins during PCa progression (Compagno et al. 2013).

Galectin-1 in PCa

In a pioneer publication that studied galectins in PCa, Gal-1 expression levels were assessed in 100 human prostate carcinoma samples and showed that this lectin was expressed by endothelial cells from capillaries infiltrating the tumor tissue in 64% of the cases (Clausse et al. 1999). In contrast, endothelial cells in the adjacent non-tumoral stroma expressed Gal-1 in very few cases (7/100). The investigators complemented these observations by performing in vitro assays with PCa human cell lines. The incubation of human umbilical vein endothelial cells with conditioned media from PC-3 or DU-145 prostate carcinoma cells—both human PCa cellular models—led to a significant increase of Gal-1 expression at the protein level. PC-3-conditioned medium also improved the adhesion capacity of PC-3 cells to endothelial cells, and secreted Gal-1 was shown as principal inducer of this phenotype as an anti-Gal-1 antiserum abolished this modulation and recombinant Gal-1 also induced increased adhesion values in a dose-dependent fashion (Clausse et al. 1999). Moreover, preferential Gal-1 expression in tumor-associated endothelial cells could both enhance tumor cell ability to interact with the endothelium as well as provide defense against the host immune system (He and Baum 2006) and T-cell transendothelial migration (Clausse et al. 1999). Similarly, Gal-1 was detected on the surface of LNCaP cells, apparently contributing to the adhesive properties of these cells to ECM components such as laminin and fibronectin (Ellerhorst, Nguyen, et al. 1999). Of note, contrary to previous observations in breast cancer and leukemia, hardly any human PCa cell line showed Gal-1 binding, thus conferring them resistance to Gal-1-induced apoptosis. This supports a tissue-specific pro-apoptotic effect of this lectin (Valenzuela et al. 2007).

Finally, we have added some evidence on the role of Gal-1 in PCa neovascularization. In fact, Gal-1 appeared as the most expressed and closely regulated galectin in the PCa microenvironment. Gal-1 silencing in tumor cells prevents the initiation of the neovascularization process. More importantly, this inhibition was obtained without alteration of other classic pro-angiogenic or anti-angiogenic mediators present in the tumor microenvironment. The role of Gal-1 in neovascularization seems to be tissue specific, as Gal-1 expression correlates with blood vessel markers in advanced PCa but not in human breast cancer (Laderach et al. 2013). Additional studies are required to further address the role of Gal-1 in PCa progression.

Galectin-3 in PCa

Gal-3 is one of the most investigated galectins in PCa. Its implication in the metastatic process and angiogenesis has been assessed using both in vitro and in vivo approaches. In patients, we and others reported that reduced Gal-3 protein expression is associated with disease progression in PCa (Ellerhorst, Troncoso, et al. 1999; Merseburger et al. 2008; Wang et al. 2009; Knapp et al. 2013; Laderach et al. 2013). Moreover, Gal-3 downregulation appears to be involved in PCa progression, since its expression levels decrease sequentially from benign prostate gland to the advanced castration-resistant PCa stage (Ellerhorst, Troncoso, et al. 1999). Of note, proteolytic cleavage of Gal-3 is one of the most important posttranslational modifications regulating its function (Saraswati et al. 2011). In PCa in particular, the cleavage of Gal-3 by matrix metalloproteinase (MMP) or PSA is plausibly involved in the loss of Gal-3 expression along the disease at least in the primary stages when this lectin is expressed. This issue is of great interest and should be further addressed in PCa patients. In fact, cleavage of Gal-3 by MMP was demonstrated to indirectly promote tumor progression by modulating angiogenesis. These observations, however, were made using breast cancer models (Nangia-Makker et al. 2010) and should be validated in PCa, since tissue-specific activities of lectins have already been reported. Moreover, phosphorylation of Gal-3 prevents PSA cleavage in vitro (Balan et al. 2012), but this observation has not been yet validated in PCa patients. Nevertheless, the extent to which Gal-3 cleavage could shape PCa biology remains controversial, since its loss of expression along PCa progression has been clearly demonstrated. In fact, by using prostatectomy samples, Ahmed et al. (2007) have shown that the *GAL3* promoter undergoes exhaustive methylation. In this regard, assessment of metastasis samples could prove useful and could in turn shed some light on the role of Gal-3 and its cleavage in PCa progression since reversion of its downregulation in metastatic lesions cannot be ruled out. Additional studies are thus required to see whether Gal-3 and its cleavage are essential along PCa progression. In this regard, assessment of circulating tumor cells or metastasis biopsies could prove helpful.

Additionally, Gal-3 can exert antitumor activities when present in the nucleus, whereas it can favor tumor progression when expressed in the cytoplasm (Califice et al. 2004). Several research teams found that a nuclear-to-cytoplasmic shift in Gal-3 expression correlated with disease progression (van den Brule et al. 2000; Ahmed et al. 2007); and more recently it was shown that the decreasing gradient of Gal-3 staining from benign to prostate cancer tissues correlates with biochemical recurrence (Knapp et al. 2013).

In vitro studies using PCa cell lines demonstrated that Gal-3 is necessary for cell migration and invasion, and activation of MMPs (MMP-2 and MMP-9); all of which facilitate metastatic events. Raz's group has carried out pioneering studies on the role of Gal-3 in PCa (Wang et al. 2009, 2013). In these studies, Raz and collaborators showed cell-cycle arrest induction at the G1 phase and cell growth impaired when Gal-3 is silenced by RNA interference strategies. This downregulation of Gal-3 expression also resulted in reduced tumor growth when cells were injected in the ventral prostate of nude mice. Considering these observations in PCa and others in different types of tumors, the authors postulated that Gal-3 expression is associated with the maintenance of the tumorigenic potential of cancer cells. However, some human PCa cell lines (e.g. 22Rv1) showed completely loss of Gal-3 expression and are still highly tumorigenic in nude mice (Compagno et al. 2007; Laderach et al. 2013). Nevertheless, why this galectin is silenced in advanced stages of PCa—at least in the primary tumor as shown in prostatectomies from PCa patients (Ellerhorst, Troncoso, et al. 1999; Merseburger et al. 2008; Knapp et al. 2013; Laderach

et al. 2013)—remains unanswered. It is possible that Gal-3 expression could revert in other tumor compartments, such as circulating tumor cells or metastatic bone lesions. This kind of samples are, however, very difficult to obtain but should be strongly considered to further define the role of this particular galectin in the progression of PCa since it is well demonstrated that Gal-3 is also implicated in the resistance to chemotherapeutic drugs (see for review Fukumori et al. 2007).

Hematogenous spread of PCa is an extremely complex process regulated at many levels and involving multiple rate-limiting steps (Roodman 2004). Recent results demonstrated that several critical steps in hematogenous cancer metastasis are regulated in part by β-galactoside-mediated interactions involving cancer-associated Thomsen–Friedenreich carbohydrate antigen (TF; Galβ1-3GalNAc disaccharide) and β-galactoside-binding lectin Gal-3 (Glinskii et al. 2014). During the extravasation step of the metastatic process, cancer cells bind to endothelial cells through protein–carbohydrate interactions and penetrate through the endothelium and basement membrane. The concept of using carbohydrate-based galectin inhibitors for targeting prostate cancer metastasis has been conceived by pioneering work from Raz's group (Pienta et al. 1995). In this study, modified citrus pectin (MCP) was the first inhibitor used to target Gal-3-binding properties to TF antigen. This compound has been shown to inhibit experimental metastasis in vivo in several animal models, particularly in the rat MAT-LyLu prostate carcinoma model. The oral administration of the MCP in drinking water inhibited spontaneous metastasis to the lungs when MAT-LyLu cells were injected into the hindlimb of syngenic Copenhagen rats demonstrating that Gal-3 binding to TF antigen influence PCa progression through metastatic stage (Pienta et al. 1995).

Additionally, Gal-3 was implicated in PCa cell preferential adhesion to bone marrow endothelial cells (Lehr and Pienta 1998). TF antigen–Gal-3 interactions were shown to mediate several processes, including the adhesion of metastatic cells to the endothelium (Glinsky et al. 2001; Zou et al. 2005; Heimburg et al. 2006), the homotypic cancer cell aggregation at the sites of primary attachment to the endothelium (Glinsky et al. 2003; Zou et al. 2005), the in vivo formation of metastatic deposits in lungs and bones of experimental animals after intravenous inoculation (Glinskii et al. 2005; Heimburg et al. 2006), as well as clonogenic survival and growth of metastatic cancer cell lines (Glinsky et al. 2003, 2009; Johnson et al. 2007). Gal-3 is also expressed by the capillary endothelium and has been reported to play a major role in the docking of cancer cells by specifically interacting with the TF antigen present on their surface. Furthermore, tumor-secreted circulating Gal-3 indirectly promotes tumor–endothelial cell interactions by binding to tumor-associated TF antigen-expressing Mucin1 (MUC1). This Gal-3/MUC1 binding polarizes MUC1, which otherwise shields smaller cell adhesion molecules, allowing epithelial–endothelial interactions via ligands such as E-selectin and CD44H (Yu et al. 2007). The circulating Gal-3 also mediates homotypic adhesion of cancer cells by binding to the surface TF antigen (Zhao et al. 2010), although other interactions may be involved. Importantly, all these critical rate-limiting steps in tumor spreading could be efficiently inhibited using carbohydrate-based compounds, blocking galectins by mimicking essential structural features of their natural ligands (Glinsky et al. 1996, 2001, 2009; Nangia-Makker et al. 2002). Based on these observations, Guha and colleagues hypothesized that exogenous TF disaccharide (TFD) would block Gal-3-mediated homotypic aggregation and tumor cell–endothelial interactions in order to prevent metastasis. Furthermore, TFD would also block Gal-3-mediated T-cell apoptosis to facilitate an antitumor immune response. They reported that TFD100 (a TFD-containing glycopeptide of molecular mass 100 kDa isolated from *Gadus macrocephalus* and purified by high affinity to Gal-3) inhibited in vitro adhesion of androgen-insensitive PCa cell line PC-3 to endothelial cells; and also angiogenesis and prevented PC-3-induced metastasis in nude mice as a result of all these anti-PCa properties (Guha et al. 2013).

In the same way but based on the intracardiac injection of PC-3Luc cells, Glinskii et al. investigated the ability of Lac-L-Leu—a non-toxic carbohydrate based small-molecular-weight galectin inhibitor—to affect the establishment and development of PCa metastatic bone lesions (Glinskii et al. 2012). In this animal model which does not assess cell detachment from the primary tumor, it should be noted that the intravenous injection makes it a dissemination rather than a metastasis model. However, they found that daily treatment of experimental animals with Lac-L-Leu—without any addition of cytotoxic drugs—resulted in a 3-fold inhibition of PCa growth at bone sites. Mechanistically, Lac-L-Leu effects were associated with the inhibition of PCa cell adhesion to the bone marrow endothelium, their homotypic aggregation and transendothelial migration, as well as clonogenic survival and growth, suggesting that Lac-L-Leu as galectin inhibitors might affect both the establishment and the early development of PCa migration especially to bone (Glinskii et al. 2012).

Galectin-8 in PCa

Another important galectin in PCa is Gal-8, which was initially referred to as Prostate Cancer Tumor Antigen-1 because of its expression in neoplastic prostate cells and its absence in normal prostate tissue (Su et al. 1996). The overexpressed lectin might give these neoplasms some growth- and/or metastasis-related advantages due to its ability to modulate cell adhesion and cellular growth (Zick et al. 2004). Upon secretion, Gal-8 acts as a physiological modulator of cell adhesion. This lectin may regulate both positively or negatively cell adhesion, depending on the extracellular context. When immobilized onto a surface, Gal-8 can promote cell adhesion, spreading and migration by ligation to and clustering of a selective subset of cell surface integrin receptors. The binding of Gal-8 to integrins is sugar dependent (Hadari et al. 2000) and triggers integrin-mediated signaling cascades such as tyrosine phosphorylation of focal adhesion kinase and paxilin (Levy et al. 2001), which in term allows cytoskeletal reorganization (Levy et al. 2003). Soluble Gal-8, however, was shown to inhibit cell adhesion to ECM molecules such as fibronectin and laminin, possibly by masking the ligand-binding sites of integrin receptors and thereby preventing cell–matrix interactions. As a consequence, tumor growth and metastasis could be modulated by soluble Gal-8. In fact, Zick et al. showed that these processes are negatively regulated by soluble Gal-8 (Zick et al. 2004). Its ability to both positively and negatively regulate cell adhesion makes

Gal-8 a novel member of adhesion-modulating proteins, collectively known as ECM proteins.

Regarding vascularization, previous studies demonstrated that Gal-8 promotes endothelial cell migration and angiogenesis (Delgado et al. 2011). On the other hand, lymphatic endothelial cell functions are also modulated by this lectin by its interaction with podoplanin in a glycosylation-dependent manner, consequently promoting adhesion and spreading of these cells (Cueni and Detmar 2009). However and more importantly, all these data were not yet corroborated using animal models, especially in PCa. These studies could shed some light on the role of Gal-8 in PCa tumorigenesis and, hopefully, new therapeutic avenues could be developed by targeting this lectin.

Other Galectins in PCa

As regards the other members of the galectin family, there is evidence that silencing of either Gal-4 or -9 exerts a strong reduction of in vitro tubulogenesis and VEGF-induced blood vessel formation in Matrigel plug assays (Guha et al. 2013). To our knowledge, there are still no study exploring the role of other member of the galectin family in PCa biology.

Conclusions

Altogether, these results highlight a major role of the interactions between galectins and their corresponding glycosylated ligands in determining tumor-associated angiogenesis and the metastatic process in PCa. More than a decade ago, Van den Brule and colleagues had shown a link between galectin expression and PCa patient outcome (Clausse et al. 1999; van den Brule et al. 2000), these pioneer studies were recently confirmed by others (Knapp et al. 2013), suggesting also galectins as possible new therapeutic targets for advanced and incurable stages of this specific disease.

However, we are still far from completely understanding the role of tumor cell glycosylation in PCa progression. Further research should be carried out to gain a deeper understanding about how and when glycosylation modifications occur along PCa progression, and whether these modifications affect the clinical outcome of PCa patients. To date, several studies have detected altered glycosylation in cancer cells and tissues using lectin array-based strategies (Fry et al. 2012), lectin histochemistry-binding assays (Brooks and Hall 2012) or chromatography methods (Mariño et al. 2010). As recently highlighted by Dalziel et al., molecular and structural understanding of the mechanistic role that glycans play in various pathological processes could be helpful to define new therapeutic targets and pathways (Dalziel et al. 2014).

Galectin analyses reveal a highly regulated profile of expression throughout PCa progression. Gal-1 and -3 are the most studied members of this lectin family in PCa but little is understood in terms of their role in the evolution of the disease. This is mainly due to the limited number of PCa animal models available, especially of those that either reflect the entire metastatic cascade—rather than intravenous dissemination models or *in situ* metastasis microenvironment models—or consider the influence of the immune system (Chauchereau 2011; Grabowska et al. 2014). This last aspect is essential since galectins are major players in cancer immune evasion, endothelial cell activity and metastatic process (Thijssen et al. 2010; Rabinovich and Croci 2012). Since wild-type mice do not spontaneously develop PCa, cooperative endeavors are still required with a view to developing new PCa models using syngenic implantations of murine PCa cells in immune competent animals. This will in term allow the evaluation of the role and relevance of carbohydrate–galectin interactions in PCa progression, even in the context of metastatic spread, with a view to developing new therapeutic strategies by targeting these lectins.

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Conflict of interest

None declared.

Abbreviations

ECM, extracellular matrix; FTs, fucosyltransferases; Gals, galectins; MCP, modified citrus pectin; mCRPC, metastatic castration-resistant prostate cancer; MMP, matrix metalloprotease; MUC1, Mucin1; O-GlcNAc, O-linked β-*N*-acetylglucosamine; PCa, prostate cancer; PSA, prostate-specific antigen; TF, Thomsen–Friedenreich carbohydrate antigen, TFD; TF disaccharide.

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