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REVIEW

The oncofetal Thomsen–Friedenreich carbohydrate antigen in cancer progression

Lu-Gang Yu

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Abstract The oncofetal Thomsen–Friedenreich carbohydrate antigen (Galβ1-3GalNAcα1-Ser/Thr TF or T antigen) is a pan-carcinoma antigen highly expressed by about 90% of all human carcinomas. Its broad expression and high specificity in cancer have attracted many investigations into its potential use in cancer diagnosis and immunotherapy. Over the past few years increasing evidence suggests that the increased TF occurrence in cancer cells may be functionally important in cancer progression by allowing increased interaction/communication of the cells with endogenous carbohydrate-binding proteins (lectins), particularly the members of the galactoside-binding galectin family. This review focuses on the recent progress in understanding of the regulation and functional significance of increased TF occurrence in cancer progression and metastasis.

Keywords TF antigen · Cancer metastasis · Glycosylation · Adhesion · Galectins

Introduction

Changes in cellular glycosylation are commonly seen in all types of human cancers [1–3] and many of these changes result in exposure of tumour-associated carbohydrate structures [4–6]. Amongst the commonest glycosylation changes are the increased occurrence of GalNAcα1-Ser/Thr (Tn antigen), Neu5Acα2-6GalNAc (sialyl-Tn antigen) and Galβ1-3GalNAcα1-Ser/Thr (TF or T antigen).

The disaccharide Galβ1-3GalNAcα1-Ser/Thr, also known as the Thomsen–Friedenreich (TF or T) antigen, is the core 1 structure of *O*-linked mucin type glycans. In normal epithelium, the Galβ1-3GalNAcα1-Ser/Thr structure is concealed by sialic acids, sulphates or by addition of other sugar chains to form branched and complex *O*-glycans. In cancer and pre-cancerous conditions such as ulcerative colitis, unsubstituted Galβ1-3GalNAc occurs [5] in about 90% of all human cancers [6, 7] including colon [5, 8–10], breast [11–13], bladder [14, 15], prostate [16, 17], liver [18], ovary [19] and stomach [20, 21]. In many of these cases, the increased TF occurrence correlates with cancer progression and metastasis [22, 23]. For example, TF expression is four to six times higher in invasive than in non-invasive bladder cancer [15, 24]. In colon cancer patients, TF positive primary tumours have a nearly four-fold increased risk for liver metastasis compared to TF-negative tumours [25].

The broad expression and high specificity of TF expression in cancer have led to many investigations into its potential use in cancer diagnosis [4, 7, 12] and cancer immunotherapy [26, 29–33]. All humans have naturally occurring antibodies against TF that occur after weaning and are probably induced by their own intestinal flora, which contains many strains of bacteria that express TF [6, 27]. The expression of the naturally-occurring anti-TF antibodies is seen to be significantly reduced in the sera of gastric cancer patients [28]. TF vaccination using purified or synthetic TF, or TF-conjugated with immunogenic carriers shows high-titre anti-TF antibody induction in patients with colorectal [29], ovarian [30, 31], breast [31] and prostate cancers [32]. TF vaccination has demonstrated

L.-G. Yu (✉)
The Henry Wellcome Laboratory of Molecular and Cellular Gastroenterology, School of Clinical Science,
University of Liverpool,
Liverpool L69 3BX, UK
e-mail: lgyu@liverpool.ac.uk

induction of complement-mediated cytotoxicity of tumour cells in several clinical trials [30, 33, 34] and prolonged disease-free survival in breast and ovarian cancer patients [31, 33, 35].

The mechanism of increased TF occurrence in cancer

Despite the unequivocal demonstrations of the wide TF expression in various carcinomas, the mechanism of increased TF occurrence in cancer is still not fully understood. In O-linked mucin-type glycans, the core 1 Galβ1-3GalNAc-structure is the precursor for the branched core 2 structure and is synthesised by addition of galactose (Gal) from UDP-Gal to GalNAcα-Ser/Thr (Tn antigen) catalysed by core 1 β1,3 Gal-transferase. Both core 1 and core 2 structures are further modified or extended into complex *O*-glycans in normal epithelium. It is now known that a single gene—core 1 β1,3 Gal-transferase (also known as T-synthase) is responsible for the transfer of Gal from UDP-Gal to GalNAcα1-Ser/Thr [36, 37]. This single gene core 1 β1,3 Gal-transferase seems very different from the classical multigene families of glycosyltransferases that usually encode several enzymes with related structures and functions [38]. Although it is attractive to think that the increased TF occurrence seen in cancer might be due to increased expression of the core 1 β1,3 Gal-transferase, earlier investigations have revealed similar glycosyltransferase activities for the biosynthesis of Tn, sialyl-Tn and TF carbohydrates in normal and colorectal cancer tissues [39]. This implies that alteration of the core 1 β1,3 Gal-transferase gene expression *perse* may not be, at least in the case of colorectal cancer, the main determinant accountable for the increased TF occurrence in cancer cells.

Since sugars are added individually and sequentially in the Golgi apparatus, alteration of the relative activities of the glycosyl-transferases responsible for the biosynthesis of complex *O*-glycans will affect the structures of the *O*-glycans eventually appeared on the cell surface. In normal epithelial cells, the formation of core 1 (TF) carbohydrate structure after addition of Gal to the initial GalNAc by the core 1 β1,3 Gal-transferase is quickly converted to the core 2 structure by the addition of *N*-acetylglucosamine to the GalNAc residue catalysed by core 2 β1,6-GlcNAc-transferase. In breast cancer tissues, the expression of core 2 β1,6-GlcNAc-transferase is found to be significantly reduced [40, 41] and this reduced expression of core 2 β1,6-GlcNAc-transferase would cause a reduced conversion rate from core 1 to core 2 structures and an overall increased TF appearance. Moreover, as some TF structures are concealed by *O*-sulphate esters in the normal colonic epithelium [42], the reduced expression of carbohydrate sulphotransferase seen in colon cancer [43] could also contribute to increased TF occurrence.

The enhanced availability of the nucleotide sugar substrate UDP-galactose for the core 1 β1,3 Gal-transferase could also contribute to an increased biosynthesis and expression of TF. UDP-galactose is synthesised and normally located in the cytosol and is transported into Golgi apparatus for carbohydrate biosynthesis by the UDP-Gal transporter which is located in the Golgi membrane. In human colon cancer tissues the expression of UDP-Gal transporter is on average 3.6-fold greater than that in non-malignant mucosa [44]. This enhanced availability of UDP-Gal substrate for core 1 β1,3 Gal-transferase in cancer would favour an increased TF biosynthesis.

Another possible determinant of the increased TF expression in cancer is the acidification status of the Golgi apparatus. It is revealed recently that the media/trans-Golgi pH (pH ≥6.75) in a high proportional population of human breast (MCF-7) and colon (HT29 and SW48) cancer cells is higher than that in non-cancerous control cells (pH 5.9–6.5) [45]. Further more the Golgi pH in the subpopulation of TF-expressing MCF-7 cells is 0.3 pH units higher than in the subpopulation of non-TF-expressing MCF-7 cells [45]. A 0.2 pH unit increase of the Golgi pH by NH_4Cl or bafilomycin, inhibitors of Golgi H^+–K^+-ATPase responsible for acidification of intra-organelle vesicles [46], is sufficient to induce increased TF occurrence in non-cancerous green monkey kidney COS-7 cells [45].

The core 1 β1,3 Gal-transferase enzyme activity is also controlled by an ER-localized molecular chaperone Cosmc (Core 1 β1,3-Gal-T-specific molecular chaperone) that specifically promotes folding/stability of the core 1 β1,3 Gal-transferase [47]. In the absence of Cosmc, core 1 β1,3 Gal-transferase is targeted to proteasomes for degradation. This implies that any change of cellular Cosmc expression will affect the core 1 β1,3 Gal-transferase enzyme activity hence the expression of TF. Indeed, Cosmc mutation has been shown to be linked with increased Tn expression [49] and with the autoimmune disease Tn syndrome [48]. It is not yet known whether Cosmc expression is altered in cancer cells.

Thus the molecular mechanisms that lead to increased TF occurrence in cancer are complex and possibly represent a combination of alterations in several steps of the *O*-glycosylation biosynthesis machinery.

The potential role of TF antigen in cancer cell proliferation

Uncontrolled cell growth is a key feature in tumour development. A number of studies have indicated that the increased occurrence of cell surface TF structures may play

an active role in tumour cell growth by allowing increased interaction of the cells with exogenous/endogenous carbohydrate binding lectins. Stimulation of human colonic cancer cell proliferation has been shown with dietary TF-binding lectins from peanut (*Arachis hypogea*) [50, 51], Amaranth (*Amaranthus caudatus*) [52], as well as with anti-TF monoclonal antibodies [54] *in vitro*. In contrast, the TF-binding lectins from common edible mushroom *Agaricus bisporus* [53, 54] and jackfruit *Artocarpus integrifolia* [52], which unlike peanut lectin, can also bind to sialylated TF structures, inhibit proliferation of epithelial cancer cells in a reversible and non-cytotoxic fashion. As many dietary lectins are tightly globular proteins that are highly resistance to heat and digestion [55] and can be detected in active form in faeces [51], the presence of dietary TF-binding lectins in foods is possible to be of considerable relevance in the functional relationship between diet and gastro-intestinal epithelial cell proliferation hence for the development of gastro-intestinal cancer. As a proof of concept, it has been demonstrated that people who express TF antigen in their rectal mucosae have a 40% increase in rectal mitotic index after 7 days daily ingestion of peanuts [56].

As TF disaccharide is a potential ligand of the endogenous galactoside-binding galectins, similar interactions between TF and members of the endogenous galectins are likely to occur and these interactions may affect the growth rate of tumour cells. Galectins are a family of 15 (to date) galactoside-binding mammalian proteins that are expressed intracellularly and extracelularly by many types of cells including epithelial and immune cells [57]. Galectin expressions are altered in various types of tumours including colon, breast, lung, pancreatic, head and neck and cervical cancers compared with their normal counterparts [57–59]. The functional significance of cell-associated galectins in cancer development has been the focuses of many studies [57] and cancer-associated galectins are now known to be important regulators of cancer cell proliferation, signalling, adhesion, invasion and metastasis [57, 60, 61]. The expression and role of circulating galectins in cancer is however less known and the only circulating galectin has been investigated to date is galectin-3 which shows up to five-fold increased expression in the sera of patients with breast, gastrointestinal, lung [62] and melanoma [63] than in healthy people. This increased concentration of circulating galectin-3 is associated with increased risk for metastasis [62]. Although poly *N*-acetyl-lactosamine (polylacNAc) and *N*-acetyl-lactosamine are the strongest binding ligands for galectins, many other galactose-terminated carbohydrate structures including TF antigen are also recognized by galectins [64–69]. Galectin-1 [64, 65, 68, 69] and -3 [66, 67, 70], the only two galectins have been studied for their interaction with TF to date, show significant binding, either directly or indirectly, to TF disaccharides. Galectin-1-mediated hemagglutination has been reported to be even better inhibited by TF-containing glycoproteins such as IgA1 than by *N*-acetyllactosamine [68].

Galectins, particularly galectin-1 and -3, have been demonstrated to regulate the growth of several types of cancers [71]. Recombinant galectin-3 stimulates proliferation of human lung fibroblast IMR-90 [72] and hepatic stellate cells [73] *in vitro*. Down regulation of galectin-3 expression by antisense technique in human breast carcinoma MDA-MB-435 cells leads to significant suppression of the tumour growth in soft agar and in nude mice [74]. Recombinant galectin-1 promotes proliferation of MA-10 Leydig tumour cells [75] and rat hepatic stellate cells [73] at low concentrations but shows inhibition of cell proliferation at higher concentrations (>20 ug/ml) on trophoblast tumour cells [69] and (>12.5 ug/ml) on neuroblastoma [76]. In all those proliferation studies on galectins, however, the galectin binding ligands are not characterized hence the level of involvement of the TF structure in these galectin-mediated effects on cell growth remains to be determined.

The involvement of TF antigen in metastasis

Cancer metastasis from primary to secondary tumour site is a multi-step process involving various cell–cell and cell–matrix interactions. These include angiogenesis, detachment of the cancer cells from the primary tumour site and intra-vasation through the extracellular matrix into the blood, adhesion of the circulating cancer cells to blood vessel endothelium, tumour embolus formation, extravasation of the cancer cells through the blood vessel and growth at the secondary tumour sites. This metastasis cascade stems from dysregulation of the normal cell–cell and cell–matrix interactions. Over the past few years increasing evidence suggests that the increased occurrence of TF on cancer cell surface may be actively involved in promoting several key cell–cell interactions in metastasis by allowing increased interaction of the cells with neighbouring/adjacent carbohydrate-binding lectins, particularly the members of the galectin family.

The role of TF in cancer cell adhesion to endothelium

The adhesion of circulating cancer cells to the microvascular endothelium of a target organ is an essential rate-limiting step in cancer metastasis. Our current knowledge of the molecular mechanism of cancer cell adhesion to endothelium is largely derived from the leukocyte adhesion process. Leukocyte recruitment into the site of inflammation involves sequential events of rolling, adhesion and transmigration across the vascular wall with rolling as the rate-limiting step required for stable leukocyte adhesion to

endothelium [70]. Leukocyte rolling is largely mediated via the interaction of Lewis-related carbohydrate structures, such as sialyl-Lewis^a (Neu5Ac2-3Galβ1-4[Fucα1-4]GlcNAc) and sialyl-Lewis^X (Neu5Ac2-3Galβ1-4[Fucα1-3]GlcNAc), with E- and L-selectins expressed on endothelium and leukocytes [78]. Although similar interactions between cancer-associated Lewis-related carbohydrate structures and selectins also occur in the adhesion process of circulating cancer cells to blood vessel endothelium [77, 80, 81], there is evidence that cancer cell adhesion to endothelium is not always consistent with the leukocyte adhesion model [79]. For example, anti-selectin antibodies could not prevent the adhesion of melanoma A375M [82] and metastatic breast carcinoma MDA-MB-435 cells [83] to endothelial cells under shear flow conditions. Several human cancer cell lines including human colon (DLD-1, HT29 and HCT8), breast (MCF-7) and bladder (TT24) cells, although strongly expressing sialyl-Lewis$^{a/x}$ structures, do not show leukocyte-like rolling or adhesion to venular endothelium after injection into the superior mesenteric artery in rabbits at physiological blood flow rates while human neutrophils injected under the same conditions roll and adhere well [84]. It seems very likely that the interaction between selectins and Lewis-carbohydrate structures may represent one of several key molecular interactions that control the adhesion of cancer cells to endothelium.

Over the past few years, Glinsky et al. have reported that the interaction of cancer-associated TF with endothelial-associated galectin-3 or with cancer associated-galectin-3 is crucial in breast and prostate cancer cell adhesion to endothelium and in homotypic cancer cell–cell aggregation at the cancer–endothelium adhesion sites [66, 67]. They have demonstrated that highly metastatic breast carcinoma MDA-MB-435 cells which express high levels of both TF and galectin-3 show significantly increased adhesion to endothelial monolayer when compared with the non-metastatic counterpart MDA-MB-468 cells which express less TF antigen *in vitro* [83]. MDA-MB-435 cells demonstrate increased homotypic cell–cell aggregation and increased adhesion and intravascular retention within the microvessels of transplanted lung allografts under sheer flow conditions in nude mice compared with the non-metastatic MDA-MB-468 cells [83]. Initial attachment of the cancer cells to endothelial monolayer causes rapid clustering of endothelial-associated galectin-3 at the cancer-endothelium contacts whist the cancer-associated galectin-3 is accumulated at the homotypic cancer–cancer cell contacts [83, 85]. Introduction of a TF antigen-binding peptide (HGRFILPWWYAFSPS), or a synthetic TF antigen-mimicking peptide (lactulosyl-l-leucine) or TF antigen-expressing glycoproteins [66, 67] significantly inhibits rolling and stable adhesion of MDA-MB-435 cells to endothelial monolayer under static [56, 57] and flow conditions [86]. Furthermore, intravenous co-inoculation of breast and prostate cancer cells with antibodies against either TF or galectin-3 shows over 90% inhibition of the formation of the cancer cell deposits in mouse lung and bones [87, 88]. These studies suggest that metastatic cancer cell adhesion to target organ microvessels and homotypic cancer cell aggregation at the cancer-endothelium adhesion sites are regulated by the interaction of cancer-associated TF antigen with endothelial- and cancer-associated galectin-3. This is consistent with the discovery that exposure of the cell surface TF antigen by sialidase pre-treatment of mouse Colon26 cells results in a higher frequency in liver metastases in syngeneic Balb/c mice, an effect which could be effectively prevented by co-application of an anti-TF antibody (A78-G/A7), but not a control antibody [89]. It seems also consistent with a suggested role of cancer-associated galectin-3 in stabilization of epithelial cancer-endothelial interaction networks revealed in an *in vitro* three-dimensional co-culture model [90].

The nature of the TF expressing glycoproteins in cancer

Although increased TF occurrence has been shown to be a common feature of human carcinoma, there has been relatively little study of the cell membrane proteins which carry the TF antigen. Amongst the few proteins known to express unsubstituted TF antigen are the high molecular weight splicing variant of the cell surface adhesion molecule CD44 (v6) [91] and the transmembrane mucin protein MUC1 [92]. Interestingly, increased expression of both CD44v6 [93, 94] and MUC1 [95, 96] occur in association with cancer invasion and metastasis [97].

CD44v6 is a splicing variant produced by alternative splicing of the CD44 gene. CD44v6 is expressed in a subset of epithelia in non-malignant tissues [98] but is intensely expressed in a majority of squamous cell carcinomas and adenocarcinomas of different origins and has been implicated in tumourigenesis, tumour cell invasion and metastasis [94, 99]. Transfection of splice variant CD44 isoforms containing CD44v6 (isoforms v4-7 and v6-7) confers metastatic potential on cells of a nonmetastatic rat tumour cell line in a syngeneic rat tumour model [100], whilst antisense inhibition of CD44v6 expression in human colon cancer HT29 cells before intrasplenic injection of the cells into nude mice results in marked reduction in liver metastasis compared with animals inoculated with control HT29 cells [101].

MUC1 is a large and heavily glycosylated transmembrane mucin protein expressed on the apical surface of most normal secretory epithelia [102]. MUC1 expression is increased up to 10 fold in many epithelial cancers [103] and this increased MUC1 expression is associated with high metastatic potential and poor prognosis [95, 96]. Cancer-associated MUC1 shows reduced expression of complex *O*-

glycans and increased expression of short oligosaccharides such as Tn, sialyl-Tn and TF [104]. Immunohistochemistry analysis using A78-G/A7 anti-TF antibody, which binds to TF antigen irrespective of its protein carriers [105], and BW835 anti-TF antibody, which binds specifically to the TF disaccharide within the MUC1 tandem repeat region [106], have revealed MUC1 molecules as the predominate carriers of TF antigen in gastric and colorectal adenocarcinomas [92, 107]. TF expression on MUC1 (BW835 antibody immunoreactivity) correlates with the presence of lymph node metastases and an unfavourable prognosis in patients with gastric cancer [21] and with increased pTNM staging, histologic grading and lower survival probability in patients with colorectal carcinoma [10].

Galectin-3-TF/MUC1 interaction in cancer cell adhesion to endothelium

Recently, we have revealed that MUC1 is a natural ligand for endogenous galectin-3 in human colon cancer cells and that the MUC1-galectin-3 interaction is largely mediated via binding of galectin-3 to TF on MUC1 [70]. We have found that recombinant galectin-3 at the concentrations similar to those found in the sera of patients with metastatic breast or colon cancer induces significant increase of human breast (ZR-75-1) and colon (HT29-5F7) cancer cell adhesion to human umbilical vein endothelial cell (HUVEC) monolayer *in vitro*. A similar effect of recombinant galectin-3 is also seen in human breast HBL-100 MUC1-positive transfectants (HCA1.7+) that express MUC1 bearing predominantly unsubstituted TF antigen, but not in MUC1-negative revertants (HCA1.7−). Galectin-3-mediated adhesion of HCA1.7+ cells to HUVEC is reduced by pre-treatment of the cells with Endo-*N*-acetylgalactosaminidase (*O*-glyconase), which is highly specific for liberating unsubstituted TF from serine or threonine residues [108]. Furthermore, MUC1-positive transfectants (MDE9.2+) that express MUC1 bearing predominantly sialylated-TF structure only demonstrate an adhesive response to recombinant galectin-3 after pre-treatment of the cells with sialidase to reveal TF [70]. These results suggest that galectin-3-MUC1 interaction, via unsubstituted TF on MUC1, promotes cancer cell adhesion to endothelium. It is highly likely therefore that an increased interaction between circulating galectin-3 and cancer-associated MUC1 via TF may represent a critical step in cancer cell adhesion to endothelium hence the spread of circulating cancer cells to secondary tumour sites. In support to this hypothesis the presence of a sialylated short-chain MUC1 glycoform is seen to be associated with a better prognosis in patients with breast cancer [109] and intravenous inoculation of an anti-TF antibody (JAA-F11) with breast tumour MDA-MB-435 cells shows almost completely blockage of the metastatic deposits of the tumour cells in the mouse lungs [87].

The discoveries that the cell surface MUC1 lost focal circumferential staining in recombinant galectin-3 treated cells and that the MUC1 is absent at the epithelial–endothelial contacts [70] have led us to propose a model of galectin-3-TF/MUC1-mediated cancer cell adhesion (Fig. 1). In this model, the massive size of MUC1 (often ten times bigger than typical cell surface adhesion molecules, [103, 110]) on the surface of cancer cells shields the smaller cell adhesion molecules (or ligands to adhesion molecules) and this "shield effect" of MUC1 prohibits interaction of the circulating cancer cells with blood vessel endothelium. Binding of circulating galectin-3 to TF on cancer-associated MUC1, both of which, *i.e.* TF and MUC1, are over-expressed in cancer cells, causes re-distribution of MUC1 on cell surface and the exposure of the smaller cell adhesion molecules (or ligands) thus allowing interaction of the cancer cells with endothelium. The cell adhesion molecules involved in galectin-3-MUC1-mediated cell adhesion likely include E-selectin and CD44H as the presence of antibodies against either CD44H or E-selectin abolishes galectin-3-induced cell adhesion [70]. This model is in keeping with the earlier proposal of MUC1 primarily as an anti-adhesion molecule on the cell surface [111]. MUC1 polarization induced by a cross-linking anti-MUC1 antibody in human breast cancer cells causes adherence of these cells to extracellular matrix proteins *in vitro* [112]. Down-regulation of MUC1 expression by antisense oligonucleotide increases E-cadherin-mediated cell–cell aggregation of breast cancer cells [113]. This model is also in keeping with a recent report showing that reversed apical polarization of MUC1 in a subgroup of breast cancer patients

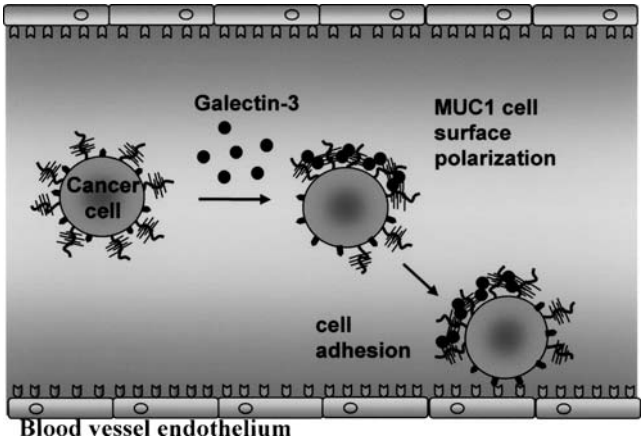

Fig. 1 A proposed model of galectin-3-TF/MUC1-mediated cancer cell adhesion to endothelium. Cancer-associated, TF-expressing MUC1 on the cell surface shields the smaller cell adhesion molecules (or ligands to adhesion molecules) and this "shield effect" prohibits interaction of circulating cancer cells with blood wall endothelium. Binding of circulating galectin-3 to TF/MUC1 causes re-distribution of MUC1 on the cell surface leading to exposure of the smaller cell adhesion molecules (or ligands) thus allowing epithelial–endothelial interaction (from [70] with modification)

is in correlation with higher lymphatic invasion, recurrence rate and lower overall survival than those patients with whole membrane MUC1 expression [114].

The role of TF expression in angiogenesis

Angiogenesis is a complex multi-step process comprising a series of cellular events that lead to neovascularization from existing blood vessels and is a key step in cancer metastasis. The potential involvement of TF-associated glycosylation in microvascular angiogenesis is implicated recently in a animal study in which core 1 β1,3 Gal-transferase double-knock out mice embryos develop normally for 9 days but, thereafter, larger hemorrhages occur in the brain and spinal cord and the embryos die within 14 days [115]. Biochemical and immunochemical analysis of the animal brains shows a chaotic microvascular network with distorted capillary lumens and defective association of endothelial cells with pericytes and extracellular matrix. Although at this stage we can only speculate on the molecular mechanisms involved, there might involve interactions of TF-related carbohydrate structures with endogenous galectins. Galectin-3, for example, is known to stimulate tube formation of HUVEC on Matrigel [116, 117]. Subcutaneous injection of galectin-3-expressing (11-9-1-4) or non-expressing (BT-549) human breast cancer cells into nude mice along with Matrigel shows nearly five-times higher capillary density in the tumours induced by galectin-3-expressing cells than by non-galectin-3-expressing cells [97]. Significantly lower amount of blood vessels is observed in galectin-1-null mice compared with wild-type mice [118].

Conclusion remarks

Although changes of cellular glycosylation have long been recognized as common features in cancer and pre-cancerours conditions, the possible contribution of these changes to cancer progression has remained poorly understood. Recent investigations suggest that the increased occurrence of the TF disaccharide in cancer, likely the consequence of alterations in several steps in the *O*-glycosylation biosynthesis machinery, promotes cancer cell progression and metastasis. This is at least partly due to increased interaction of the cells via TF with members of the endogenous galactoside-binding galectins. Further investigation into the molecular mechanisms that underlie the involvement of TF in cancer progression will increase our understanding of cancer development and could help in identification of novel therapeutic targets for cancer treatment. With the realization that about 1% of the genes in the human genome contribute to the production and modification of cellular glycoconjugates [38], understanding the functional importance of cellular glycosylation in the complexity of events regulating protein–protein and cell–cell interactions in disease conditions is likely to be one of the very promising but challenging research areas in biomedical science in the post-genomic era.

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