Review paper

The complexity of tumour angiogenesis based on recently described molecules

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Tumour angiogenesis is a crucial factor associated with tumour growth, progression, and metastasis. The whole process is the result of an interaction between a wide range of different molecules, influencing each other. Herein we summarize novel discoveries related to the less known angiogenic molecules such as galectins, pentraxin-3, Ral-interacting protein of 76 kDa (RLIP76), long non-coding RNAs (lncRNAs), B7-H3, and delta-like ligand-4 (DLL-4) and their role in the process of tumour angiogenesis. These molecules influence the most important molecular pathways involved in the formation of blood vessels in cancer, including the vascular endothelial growth factor (VEGF)-vascular endothelial growth factor receptor interaction (VEGFR), HIF1-α activation, or PI3K/Akt/mTOR and JAK-STAT signalling pathways. Increased expression of galectins, RLIP76, and B7H3 has been proven in several malignancies. Pentraxin-3, which appears to inhibit tumour angiogenesis, shows reduced expression in tumour tissues. Anti-angiogenic treatment based mainly on VEGF inhibition has proved to be of limited effectiveness, leading to the development of drug resistance. The newly discovered molecules are of great interest as a potential source of new anti-cancer therapies. Their role as targets for new drugs and as prognostic markers in neoplasms is discussed in this review.

Key words: angiogenesis, carcinogenesis, galectins.

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Introduction

Angiogenesis is recognized to play a crucial role in tumour growth, progression, and metastasis [1]. It is widely described that tumours cannot grow beyond 2 mm^3 without an adequate supply of nutrients and oxygen via a proper vascular system [2]. Many molecular pathways are directly related to angiogenesis, but only some of them have been extensively studied and described so far [3]. The main role in this process is attributed to angiogenic molecules such as vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), or the platelet-derived growth factor family, but also phenomena such as hypoxia, immune cell activity, or changes in the tumour microenvironment [3]. Progressive knowledge about the extensive role of angiogenesis in cancer has inspired scientists to seek therapies based on inhibiting the growth of the new vessels [4]. However, therapies based mainly on the inhibition of key molecules such as VEGF have proven to be of limited effectiveness, leading to the development of drug resistance [5–7]. This emphasizes the need for further research, to improve anti-angiogenic therapies in the future. Recently, many new molecules that influence the formation of new vessels have been discovered, proving the complexity of this process. In this review, we summarize the latest reports about less known molecules involved in angiogenesis.

Galectins

Galectins, a family of lectins that bind βgalactosides, are generally well-known due to their role in cell-to-extracellular matrix interactions [8]. They contain one or more evolutionarily conserved carbohydrate-recognition domains (CRDs) – sequences that are responsible for binding to carbohydrates [9]. Recently, a lot of attention has been paid to galectins due to their freshly described multidirectional activity in facilitating the development of malignant tumours [10]. Extracellularly localized galectins interact with the cell-surface and extracellular matrix, while these localized intracellularly influence cytoplasmic and nuclear signalling pathways [8]. Moreover, some of them – such as galectin-3 – are present both at the cell surface and inside the cytoplasm, and may be secreted into biological fluids like serum and urine [11]. The galectin-glycan interaction plays an important role in physiological and pathological processes including angiogenesis, regulation of immune response, metastasis, and apoptosis [12–15]. Many of the functions related to angiogenesis such as endothelial cells (EC) activation, proliferation, adhesion, migration, tube formation, and sprouting may be assigned to galectins highly expressed in endothelial cells, such as galectin –1, –3, –8, and –9 [16].

Galectin-1 (gal-1) is the first described human galectin, and one of the best-studied members of this family. Among many other functions, gal-1 plays a key role in stimulating tumour angiogenesis by inducing endothelial cell proliferation and migration, mirroring the effects of VEGF [17]. Gal-1 has the ability to bind N-glycans complex on vascular endothelial growth factor receptor 2 (VEGFR2), which results in increased phosphorylation and activation of kinases Akt and Erk1/2, mimicking the phosphorylation pattern following VEGF-VEGFR interaction [17]. Moreover, gal-1 can act as an independent pro-angiogenic growth factor, indirectly inducing pro-angiogenic signalling by stimulating VEGFR2 clustering or increasing receptor membrane retention. In addition, in murine models, Gal-1 was found to be increasingly secreted by tumours resistant to anti-VEGF agents [16, 17]. A study by van Beijnum *et al.* [18] revealed that inhibition of gal-1 by specific antibodies inhibits sprouting angiogenesis both *in vitro* and *in vivo*.

In tumour vessels, Gal-1 expression was found to be increased in comparison to vessels in healthy tissue. Elevated gal-1 expression has been described in neoplastic cells of lung [19], prostate [20], oral cancer [21], and gliomas [22]. Recently, it was also described to be overexpressed in the tumour tissue of renal cell carcinoma [23]. High expression of gal-1 is associated with poor overall survival (OS) in hepatocellular carcinoma (HCC), colorectal, gastric, and pancreatic cancer. In these malignancies, gal-1 is up-regulated in both tumour-associated stromal cells and epithelial cells [24]. Moreover, gal-1 overexpression is associated with resistance to sorafenib (a tyrosine kinase inhibitor of, among others, VEGFR-2 and VEGFR-3), poor tumour control, and low response rate in HCC [25]. In gastric cancer, gal-1 is highly expressed by cancer-associated fibroblasts (CAFs), and it was shown to facilitate the interaction between CAFs and human umbilical vein endothelial cells, stimulating their proliferation, migration, and tube formation *in vitro* [26]. Similarly, in human multiple myeloma, gal-1 expression was shown to be regulated by hypoxia-inducible factor 1α (HIF-1α), and its suppression resulted in reduced angiogenesis and bone lesion formations *in vivo* in 2 different murine models [27]. Gal-1 secreted by human omental microvascular endothelial cells (HOMECs) in metastasized high-grade serous carcinoma (HGSC) of the ovary was proven to increase the number of microvessels in omental metastases, potentially via the MEK/ERK1/2 signalling pathway [28]. Moreover, in pancreatic ductal adenocarcinoma (PDA), gal-1 mediates the action of human pancreatic stellate cells (HPSCs), which encompass the stimulation of cancer proliferation, migration, and invasion. In PDA murine models, gal-1 knock-out diminished metastasis rates and prolonged survival [29].

These discoveries prompted research assessing the potential use of gal-1 inhibitors, targeting gal-1 contribution to angiogenesis, as a possible anti-cancer treatment option. One of the gal-1 inhibitors is an artificial, non-specific peptide, Anginex, which, among other properties, binds to gal-1, inhibits its function, and stops gal-1 uptake by EC [30]. Many clinical studies revealed the synergistic effect of Anginex treatment in combination with radiotherapy [31, 32] or chemotherapy [33]. Koonce *et al.* [34] used a non-peptidic galectin-1 inhibitor OTX008 in human head and neck squamous cell carcinoma (HNSCC) models, and its administration resulted in tumour vessel normalization and tumour reoxygenation, which may improve HNSCC susceptibility to radio- and chemotherapy. Another molecule that is promising for designing specific galectin antagonists is lactulose. Its derivatives showed the ability to bind galectin-1 and galectin-3 carbohydrate recognition domains [35]. Gal-1 can also be a target for specific, designed antibodies, used as therapeutic and diagnostic agents [18]. Finally, as was mentioned in the case of sorafenib resistance in HCC, gal-1 may be responsible for limited benefits of anti-VEGF treatment, and therefore, targeting gal-1 may improve the effectiveness of anti-VEGF therapies [17].

Galectin-3 (gal-3) is a unique member of the family of galectins. Structurally, gal-3 contains a proline- and glycine-rich N-terminal domain, enabling it to form oligomers. In addition, gal-3 may be localized in the cytoplasm, on the cell surface, or as a free form in biological fluids like serum [36]. Galectin-3 was also identified as a receptor for advanced glycosylation end products (AGE). However, gal-3 plays a receptor role not independently but rather in association with other AGE receptors [37]. Moreover, in the tumour microenvironment, it takes part in neo-vascularization by several molecular mechanisms, which include VEGFR2 retention and activation, integrin $\alpha V\beta 3$ activation and promotion of angiogenesis by the basic fibroblast growth factor (bFGF), VEGF, and neuron-glial antigen 2 (NG2) signalling pathways [38, 39]. In addition, under hypoxic conditions, gal-3 is released by neoplastic cells and increasingly binds to ECs, which activates the JAG1/Notch signalling pathway and triggers angiogenic sprouting [39]. The biological function of Gal-3 is highly dependent on its ability to multimerize and to bind to many glycoproteins. Gal-3 is involved in the process of formation of signalling platforms on the cellular membrane, that contain receptors of other molecules, including those that induce angiogenesis [40]. In this sense, Gal-3 is responsible for the amplification of the signal and acts as an important cofactor [41]. Gal-3 can promote vessel formation not only by direct interaction with EC but also indirectly, by stimulating macrophages and platelets to release VEGF [41].

The increased endothelial gal-3 expression has been reported in hepatic, pancreatic, oral, thyroid, bladder, and gastric carcinoma [42]. Recently, it was also found to be upregulated in clear cell, chromophobe, and papillary renal cell carcinomas [43]. However, increased expression of gal-3 is not universally observed in malignancies, as other studies described down-regulation of gal-3 in the tumour tissue of the breast, prostate, cervical, and endometrial carcinoma [42, 44]. Serum levels of gal-3 from patients with lung, thyroid, hepatocellular, prostate, bladder, breast, renal, gastrointestinal, and head and neck carcinomas were significantly elevated when compared to those in healthy individuals [11, 42]. Circulating galectin-3 plays an important role in metastasis and angiogenesis by mediating cancer cell-endothelial adhesion via interacting with mucins: MUC1 and MUC4. Gal-3 inhibitors were shown to

inhibit the development of lung metastases of melanoma and colon cancer in murine models [45].

Gal-3 is a putative therapeutic target for anti-cancer therapies; thus, many molecules were synthesized to bind to gal-3 and inhibit its pleiotropic actions. Because of the fact that galectins have a high affinity for carbohydrates [8], inhibitors, based on carbohydrate scaffolds, such as galactose, lactose, or talose [46], and gal-3-binding neo-glycoproteins [47] were designed. Polysaccharides such as modified citrus pectin (MCP) [48], corn pectic polysaccharide (COPP) [49], arabinogalactan HH1-1 derived from safflower [50] and RN1, purified from the flower of Panax [51], generate high affinity to gal-3 and demonstrate promising results as anti-cancer agents. In a study by Nangia-Makker *et al.* [52], MCP inhibited capillary tube formation *in vitro* and tumour growth, angiogenesis, and spontaneous metastasis *in vivo* in mice. MCP activity was also evaluated in patients with various solid tumours, showing a positive impact on some of them [53]. COPP in the study conducted by Jayaram *et al.* [49] decreased the level of VEGF, matrix metallopeptidase 2 (MMP-2), and matrix metallopeptidase 9 (MMP-9) in the tumour tissue and inhibited metastasis *in vivo*. HH1-1 presented anti-cancer activity in PDA *in vitro* and *in vivo*, as it binds to gal-3, impairs the interaction between gal-3 and epidermal growth factor receptor (EGFR), and inhibits the galectin-3/EGFR/AKT/FOXO3 signalling pathway [50]. RN-1 activity, similarly to HH1-1, was also evaluated in PDA, showing inhibition of tumour cells growth both *in vitro* and *in vivo,* affecting multiple gal-3-associated signalling pathways [51]. Heparin derivates also pose as promising gal-3 binding agents – chemically modified heparin molecule does not show anticoagulant activity, but it destabilizes the structure of galectin-3 and, as a result, stops tumour progression *in vitro* and reduces metastasis in a murine model [45, 54]. Another molecule, galectin-3C, a truncated, dominant-negative form of galectin-3, is a competitive inhibitor of endogenous gal-3, which was shown to decrease endothelial cells tubule formation *in vitro* [55], and to be a putative treatment option for multiple myeloma and ovarian cancer [56, 57]. Finally, bergenin, a substance isolated from plants used in South Asian traditional medicine, was computationally proven to have an affinity for gal-3, and it could potentially be used to develop new anti-cancer therapies in the future [58].

Galectin-8 (gal-8), as a result of alternative splicing, occurs in 7 isoforms [59] and is expressed in several human carcinomas, including ovarian [60], prostate [61], and breast cancer [62]. It was found to induce angiogenesis, at least partially, via cross-linking of activated leukocyte cell adhesion molecule (ALCAM, CD166) [57, 59, 63]. The serum level of gal-8 is higher in patients with colorectal and breast cancer, especially with metastatic disease, when compared to healthy individuals [59]. In contrast to gal-1, galectin-8 expression was not reported to be up-regulated in tumour EC in response to anti-VEGF therapy [59]. Circulating gal-8 was reported to be responsible for increased secretion of other pro-angiogenic factors such as granulocyte colony-stimulating factor (G-CSF), interleukin 6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) [64]. Moreover, gal-8 has recently been proven to induce epithelial-mesenchymal transition by activating the FAK/EGFR/proteasome pathway in Madin-Darby canine kidney cells [65]. Gal-8 can also increase endothelial hyperpermeability through the destabilization of adherens junctions via S-nitrosylation mediated by nitric oxide synthase (eNOS), which was confirmed both *in vitro* and *in vivo* [66].

Galectin-9 up-regulation, and therefore increased expression, was described in kidney, lung, and liver tumour vessels [16]. Gal-9 may be expressed by EC in 5 different splice variants [16]. The effects of gal-9 actions depend on the different variables including splice variant, concentration, environment, and cellular context [67]. The best described, dominant form is galectin-9Δ5, and it can either promote or suppress angiogenesis, depending on the circumstances [67, 68]. In the study conducted by Aanhane *et al.* [69], all gal-9 isoforms inhibited angiogenesis *in vivo* in contrast to the previously described galectins. However, Enninga *et al.* [70] showed that gal-9 binds to CD206 on M2 macrophages, and they suggested that this interaction may increase the secretion of pro-angiogenic factors and chemokines from myeloid cells. This divergent information underlines the necessity of further investigation to assess the effect of galectin-9 on both angiogenesis and carcinogenesis.

Pentraxin-3

Pentraxin-3 (PTX3/TSG14) is a member of the family of pentraxins, which is divided into short and long pentraxins [71]. The short pentraxin subfamily includes proteins such as C-reactive protein (CRP) and serum amyloid P component (SAP), well known for their important role in innate immunity [71]. PTX3, which belongs to the long pentraxin subfamily, is produced by innate immunity cells in response to inflammatory signals and acts as a multifunctional soluble pattern recognition receptor [72]. Its essential role in immunity, pathogen recognition, complement activation, and inflammation is well established [73, 74], but recent studies have revealed that it may also play an important inhibitory role in angiogenesis [75].

PTX3 binds with high affinity to FGF-2, one of the most important angiogenic factors [76], sequestering it and preventing it from activating its receptors on endothelial cells [77]. This interaction results in the inhibition of FGF2-dependent proliferation of endothelial cells *in vitro* and *in vivo* [76]. PTX3 activity was assessed in prostate cancer, highly dependent on FGF2 stimulation, revealing PTX3 anti-angiogenic and anti-neoplastic activity *in vitro* and *in vivo* [78]. Moreover, PTX3 expression was proven to be present in cells in healthy prostate but completely absent in high-grade prostate cancer, suggesting that the loss of its function may play an important role in tumour progression [78]. PTX-3 was found to inhibit the growth of fibrosarcoma *in vitro* and *in vivo,* by decreasing cell proliferation and tumour vascularization [79]. Its overexpression causes significant changes in the tumour microenvironment, reducing inflammatory infiltrate and vascular density in a murine model of fibrosarcoma [80]. In 2015, Ronca *et al.* found that overexpression of PTX3 inhibits angiogenesis, metastasis, and tumour growth in a transgenic

mouse model, and identified NSC12 – a small PTX3 derivative that acts as an FGF2 trap, that performs similar activity [81]. NSC12 was proven to be a promising therapeutic molecule because it inhibited cell proliferation and reduced fibroblast growth factor receptor 1 (FGFR1) and fibroblast growth factor receptor 3 (FGFR3) activation in fibrosarcoma models *in vitro* and *in vivo* [79]. It also impaired tumour growth and vascularization in a murine model of prostate cancer [82] and tumour growth of murine and human lung cancer cells *in vitro* and *in vivo* [83]. FGF trapping by PTX3 and NSC12 was also evaluated as a therapeutic strategy in murine melanoma model and human uveal melanoma cell lines, revealing inhibition of proliferation, survival, and migration of melanoma cells [84]. PTX3 may also bind to fibroblast growth factor-8b (FGF8b) and inhibit the activation of its receptor. Consequently, PTX3 inhibits the FGF8b-induced neovascularization and growth of hormonal tumours [85].

Even though most studies suggest an anti-angiogenic role of PTX3 in cancer, in 2016, Hida *et al.* [86] found that PTX3 is overexpressed in mouse and human tumour endothelial cells (TECs) in comparison to normal endothelial cells. Moreover, in the same study, knockdown of PTX3 inhibited TECs proliferation. PTX3 was also proven to have some pro-tumour effects in multiple tumours [75]. PTX3 promotes tumour cell migration in the pancreatic carcinoma cell lines, and its elevated level correlates with advanced clinical stage and poor prognosis in pancreatic carcinoma [87]. In cervical cancer, high expression of PTX3 is positively correlated with higher tumour grade and cell proliferation, invasion, and migration in human cervical HeLa cells [88]. Moreover, PTX3 knockdown inhibited tumour growth *in vitro* and tumourigenesis and metastasis *in vivo* [88]. PTX3 is expressed by tumour cells in glioma, and its level corresponds with the high-grade and severity of the tumour [89, 90]. Elevated levels of PTX3 were found in the serum of patients with prostate cancer [91] and lung carcinoma [92] and in tumour tissue of human soft tissue liposarcoma [93]. EGF-induced PTX3 promotes metastasis in HNSCC by regulating the expression of fibronectin, E-cadherin, and MMP-9 [94]. In gastric cancer [95] and breast cancer [96] PTX3 contributes to osteolysis and bone metastasis. That is why it remains unclear whether PTX3 plays a negative or positive role in the development of the tumour. These findings suggest that its action might depend on the tumour type and microenvironment [75].

RLIP76

The ral-interacting protein of 76 kDa (RLIP76), known also as Ral-binding protein 1 (RalBP1), occurs in different compartments of the cell, including the cell membrane, intracellular fluid, and the nucleus [97, 98]. The primary structure of RLIP76 might be divided into four main regions: the N-terminal region, the Rho-Gap region, the Ral binding region, and the C-terminal region [97]. Originally, RLIP76 was identified as a Ral GTPase effector protein, which links Ral to the Rho pathways [99]. Expression of RLIP76 was reported in a variety of human tissues, e.g. liver, heart, lung, kidney, ovary, and muscles [97, 99]. RLIP76 is a stress-responsive multifunctional protein, involved in processes such as apoptosis, cell proliferation, differentiation, migration, and metabolite transport [97, 98, 100]. It consists of 2 ATP binding sites (in the N-terminal region and C-terminal regions) and is able to catalyse the transport and conjugation of glutathione and xenobiotics across the biological membranes, contributing to anti-apoptosis and multidrug resistance mechanisms in cancer cells [97–99]. RLIP76 overexpression was observed in numerous malignancies such as non-small cell lung carcinoma, colon carcinoma, prostate cancer, melanomas, gliomas, meningiomas, breast cancer, and pancreatic cancer [97–99, 101–103].

RLIP76 is an essential mediator of angiogenesis and tumour growth associated with another basic angiogenesis mediator – VEGF. In the study by Wang *et al.* RLIP76 suppression in an unexplored mechanism decreased the VEGF secretion and VEGF-induced tube formation *in vitro* [100]. The angiogenic roles of RLIP76 are presumed to involve a combination of effects on VEGF expression through HIF-1 activation, and on VEGF secretion, possibly through regulation of phosphoinositide 3-kinase (PI3K) [99]. In neoplastic cells, VEGF transcription is induced by HIF-1 [104]. RLIP76 stimulates PI3 kinase – the element of the PI3K/Akt/mTOR signalling pathway that promotes the activation of HIF-1. In the nucleus, HIF-1 binds its cofactor and then the whole complex stimulates the expression of target genes, including *VEGF* [97, 99].

Moreover, RLIP76 was found to regulate the angiogenic response of epithelial cells. Studies implemented on RLIP76 knock-out mice, based on a 3D reconstruction of tumour vasculature, determined that in RLIP76-knockout mice the central tumour vessels and their branches were shorter and narrower compared to wild type mice [98]. In the implanted tumours in RLIP76-knockout mice, angiogenesis was inhibited. The potential mechanism was associated with the role of RLIP76 in efficient migration, proliferation, and cord formation of endothelial cells. Defects in endothelial cell function, due to the absence of RLIP76, lead to ineffective angiogenesis [98, 99].

Cell migration and spreading are necessary during angiogenesis. RLIP76 participates in these processes by regulating the Ras-related C3 botulinum toxin substrate 1 (Rac1) and ADP ribosylation factor 6 (Arf6) signalling pathways. On the molecular level, after pro-angiogenic stimulation, RLIP76 binds R-Ras in a GTP-dependent manner. This leads to the formation of R-Ras-dependent trisphosphate (PIP3), which contributes to the recruitment of a guanine nucleotide exchange factor for Arf6 (ARNO). The interaction between RLIP76 and ARNO enhances the activation of Arf6. Consequently, the activated Arf6 GTPase leads to the promotion of Rac1 GTPase activation. Given all the connections, RLIP76 plays a crucial role as a link in a small GTPase downstream effect in Rac1 and Arf6 pathway, being essential for tumour angiogenesis [98, 105, 106].

RLIP76 overexpression was indicated in samples derived from patients suffering from breast cancer and was positively correlated with the malignant status of these patients and associated with poor prognosis. Therefore,

some studies indicate that RLIP76 overexpression should be considered as a biomarker of poor prognosis in breast cancer [107]. The newest studies concerning breast cancer indicate a promising role of 2'-hydroxyflavanone (2HF), associated with RLIP76, in oncological therapies. Flavonoids are compounds ubiquitously present in many foods and beverages of plant origin. 2HF is a novel natural small phytochemical with no declared toxicity towards normal tissues [102, 108]. Administration of 2HF was shown to inhibit the development of triple-negative breast tumours in the mice xenograft model, which was correlated, among other effects, with RLIP76 suppression [102]. In the study by Singhal *et al*., it was confirmed that 2HF may suppress breast cancer by targeting RLIP76 both *in vivo* and *in vitro*. Because 2HF decreases RLIP76 and VEGF expression and regulates critical proliferative and differentiation proteins, 2HF may be proposed as an improvement of breast cancer treatment schemes [109, 110].

The expression of RLIP76 is positively correlated with the pathological stages of meningiomas – the highest level was observed in anaplastic meningiomas classified as grade III according to the WHO [103]. Moreover, some studies suggest that discussed overexpression might lead to a highly proliferating phenotype due to its significant correlation with the proliferation marker Ki-67. Given all the information, patients suffering from meningiomas with high expression of RLIP76 are in the group of shorter recurrence-free survival (RFS), which was confirmed in the study by Fan *et al.* [103]. Apart from the angiogenic role of RLIP76, the possible mechanism associating RLIP76 with poor prognosis relates to apoptosis inhibition through interactions with a spectrum of functionally distinct proteins, encompassing Caspase 3 and Bcl-2 [103, 111].

LncRNA

Long non-coding RNAs (LncRNAs) are a group of ribonucleic acids consisting of more than 200 base pairs, which might be transcribed by RNA polymerase II and then undergo co-transcriptional modifications (i.e. polyadenylation or pre-RNA splicing), but they mostly cannot be translated into proteins [112–114]. They might possess their promoters and be localized between protein-coding genes (intergenic) [112]. It has been discovered that lncRNAs are involved in various conditions, e.g. hypoxia and hyperglycaemia [112]. LncRNA presents 3 main mechanisms of action.

1. LncRNA may fold into a tertiary structure and supply a scaffold for the formation of a quaternary structure for proteins and regulatory RNA [112]. LncRNAs can serve as adaptors to bring 2 or more proteins into discrete complexes. The primary example of scaffolds is HOX transcript antisense intergenic RNA (HOTAIR) simultaneously binding both polycomb repressive complex 2 (PRC2) and a complex of lysine-specific demethylase 1 (LSD1) and corepressor protein – CoREST. Consequently, this combination ensures gene silencing through histone H3 lysine 27 (H3K27) methylation and histone H3 lysine 4 (H3K4) demethylation [115].

2. LncRNA regulates the gene expression at the post-transcriptional level [112]. LncRNAs control processes such as RNA maturation and transport or protein synthesis. They affect the stability of mRNAs and might compete for miRNA-mediated inhibitor or function as a miRNA precursor. These attributes of lncRNAs lead to increased mRNA expression [116].

3. LncRNA may directly bind DNA sequences and form RNA-DNA triplex complex [112]. Forming these complexes may represent a type of epigenetic regulation in which lncRNA serves as a molecular guide, described as "decoys" [115, 116].

Nevertheless, it must be underlined that there are probably many other mechanisms of lncRNA action to be discovered. In most tissues, the expression level of lncRNA is lower than that of mRNA [112], apart from the brain, in which the expression level of lncRNA is higher than that of mRNA [112]. LncRNAs may be located in the nucleus (lncRNA Heih, Hotair, 18 Malat1, 19 Evf-2,20 Lethe21, and Xist22), in the cytoplasm (lncRNA Ptenp1 Ror, HULC, linc-MD1, 1/2-sbs RNAs, and Gadd, LncRNA Tincr), or in both the nucleus and the cytoplasm [112, 114]. It is suspected that the specific function of lncRNAs is related to their subcellular localization [117].

LncRNA can promote and inhibit angiogenesis, drug resistance, and proliferation. Importantly, their role in drug resistance affects the main treatment strategies in oncology: chemotherapy, hormone therapy, targeted therapy, and immunotherapy [118]. Moreover, lncRNAs and miRNAs (e.g. miR-345-5p) participate in epithelial-mesenchymal transition (EMT), cell growth, and angiogenesis in multiple cancers: gastric, thyroid, breast, bladder, and non-small cell lung cancer [119]. LncRNAs also regulate synapse formation, reprogramming of human-induced pluripotent stem cells, nuclear organization, nuclear-cytoplasmic trafficking, and promote pluripotency and neuronal differentiation [112, 117]. LncRNAs such as HOTAIR, Tie-1AS, and lncRNA, associated with microvascular invasion in HCC (lncRNA MVIH), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), F630028O10Rik (F63), highly up-regulated in liver cancer (HULC), and maternally expressed gene 3 (MEG3), play an important role in angiogenesis [112, 117, 120, 121].

In the studies conducted both *in vivo* and *in vitro* on nasopharyngeal carcinoma cells, the HOTAIR directly activates the transcription of VEGF-A and indirectly through immunoglobulin protein (BiP) mediates up-regulation of VEGF-A and angiopoietin-2 (Ang2) expression, which leads to the promotion of angiogenesis [121]. Furthermore, HOTAIR can promote cancer progression through negative regulation of chromosomal transcription or recombination of the chromatin [117]. Significant overexpression of HOTAIR in HCC tissues is correlated with the poor prognosis of the patients, and it predicts tumour recurrence. In HCC cell lines, HOTAIR can downregulate RNA binding motif protein-38 and promote cell invasion and migration. Moreover, it is suggested that HOTAIR ucRNA takes part in an intercellular signalling mediator of growth because its presence was observed in extracellular vesicles released from HCC cells [113].

In endothelial cells, hyperglycaemia and hypoxia increase the level of MALAT1. It was reported that the genetic deletion of the MALAT1 gene leads to reduced retinal

vascular growth and endothelial growth in experiments *in vivo* [122, 123]. Moreover, during pharmacological inhibition of MALAT1, blood-flow recovery and capillary density after hind-limb ischaemia are reduced due to impaired expression of cell cycle regulators [124]. MALAT1, through interacting with miR20416, modulates proliferation, migration, and invasion of cholangiocarcinoma cells [119].

The tie-1AS causes specific defects in endothelial cell contact junctions and tube formations through selective binding to tie-1 mRNA and regulation of its transcription [125]. MVIH inhibits the secretion of phosphoglycerate kinase 1 (PKG1). It is correlated with reduced serum PKG1 levels and leads to increased microvessel density in HCC patients and promotes angiogenesis [126]. HULC knockdown suppresses angiogenesis via the PI3K/Akt/mTOR/ESM-1 signaling pathway [127].

Differentiation Antagonizing Non-Protein Coding RNA (DANCR) participates in cell progression in various cancers, and thus DANCR is predicted as an emerging therapeutic target in human malignancies [119, 128, 129]. In the study by Zhu *et al.* [119], it was proven that inhibition of the mentioned lncRNA could inhibit cholangiocarcinoma cell proliferation, migration, and invasion and induce apoptosis. Angiogenesis was inhibited after the silencing of DANCR in the studied samples. The possible mechanism of this phenomenon was related to the association between DANCR and the expression of VEGF-A. The crucial role of VEGF-A during DANCR inhibition of the tumour angiogenesis was also proven in studies conducted on ovarian cancer cells [130].

Plasmacytoma variant translocation 1 (PVT1), a lncRNA encoded by the human *PVT1* gene, is in the well-known cancer-connected region. The role of PVT1 as a cancer biomarker is gradually becoming established [131]. The upregulation of PVT1 has been confirmed in studies conducted on tissues derived from patients suffering from gastric cancer [132]. In the study by Zhao *et al.* [120] it was proven that PVT1 can promote angiogenesis in gastric cancer, for the first time. The results of the mentioned research indicated that PVT1 activates the STAT3 signalling pathway, and consequently elevates the expression of VEGF-A. The mechanism of action of PVT1 is quite complex. PVT1 can directly bind activated p-STAT3 protein and enhance its stability by disrupting its poly-ubiquitination and sequential proteasomal proteolysis. Nuclear p-STAT binds with the *VEGF-A* promoter and leads to the expression of VEGF-A protein, inducing angiogenesis [120].

The existence of lncRNA inhibiting angiogenesis was proved in the latest studies. Qin *et al.* [117] discovered a new lncRNA called F630028O10Rik (abbreviated as F63), which inhibits VEGF-A secretion, endothelial cell clone formation, migration, invasion, and tube formation.

LncRNAs take part not only in cancer angiogenesis but also in the other aspects of vascularization, encompassing heart development, which was shown in various studies [133–135].

LncRNA might also interact with microRNA (miRNA). It was established that lncRNA may serve as an endogenous sponge to regulate the function and expression of miRNA. On the other hand, miRNA binds to lncRNA, regulating their stability. LncRNA might also compete with other RNA transcripts for the same miRNA and, as a result, perform the function of a competing endogenous RNA (ceRNA), which leads to interactions and subsequent regulation. Furthermore, the existence of many lncRNA/miRNA pathways, playing an important role in angiogenesis (e.g. SNHG1/miR-199a, SNHG12/miR-199a), has been discovered recently

Table 1. Functions of lncRNAs

LncRNA	Function
HOTAIR	Binds simultaneously with PRC2, LSD1, and CoREST and ensures gene silencing through H3K27 methylation and H3K4 demethylation [115] Promotes angiogenesis via direct and indirect up-regulation of VEGF-A expression and indirect up-regulation of Ang2 expression [121] Promotes cancer progression through negative regulation of chromosomal transcription or recombination of the chromatin [117] Significant overexpression of HOTAIR in HCC tissues correlates with poor prognosis and predicts tumour recurrence [113]
Tie-1AS	Plays an important role in angiogenesis via causing a specific defect in endothelial cell contact junctions and tube formations through selective binding to the tie-1 mRNA and regulation of its translation [125]
MVIH	Increases microvessel density in HCC patients and promotes angiogenesis via inhibition of the secretion of PKG1 [126]
MALAT1	Plays an important role in angiogenesis [112] Through interaction with miR20416 modulates proliferation, migration, and invasion of cholangiocarcinoma cells [119]
F63	Inhibits angiogenesis via supressing VEGF-A secretion and endothelial cells clone formation, migration, invasion, and tube formation [117]
MEG3	Plays an important role in angiogenesis [112]
HULC	Its knockdown suppresses angiogenesis via the PI3K/Akt/mTOR/ESM-1 signalling pathway [127]
DANCR	Its inhibition supresses proliferation, migration, and invasion of cholangiocarcinoma cell and induces apoptosis [119] Its silencing inhibits angiogenesis (an important role may be played here by the association between DANCR and expression of VEGF-A) [119, 130]
PVT1	Promotes angiogenesis in gastric cancer via activation of the STAT3 signalling pathway and consequently elevates the VEGF-A expression [120]

[136]. The aforementioned functions of lncRNAs are summarized in Table 1.

B7-H3

B7-H3, also known as CD276, belongs to the B7-CD28 immune checkpoint family, well-known examples of which include programmed death-ligand 1, CD80, and CD86 [137]. It was first described in 2001 by Chapoval *et al*. [138]. This transmembrane glycoprotein is mainly expressed by lymphocytes and activated dendritic cells; however, its role in modulating immune response remains unclear because different studies have shown both its inhibitory and co-stimulatory effects on lymphocytes [138]. B7-H3 in humans has 2 isoforms: 2IgB7-H3 and 4IgB7-H3, which is preferentially expressed on immunocytes [139]. It consists of an exon duplication of the extracellular IgV-IgC domain, a transmembrane domain, and a short cytoplasmic carboxyl tail without a distinctive signalling motif [140]. High levels of B7-H3 mRNA were found in a wide range of human tissues, while B7-H3 protein is expressed at low levels. It suggests tight post-transcriptional regulation [141], including methylation of *B7-H3* promoter and interference with the miRNA-29 family [142]. Expression of B7-H3 was also reported in neoplasms such as lung, prostate, breast, or colorectal cancer [137].

As well as its immunomodulating effects, B7-H3 was recently found to play an important role in angiogenesis, with many potential mechanisms for its involvement described [143, 144]. High levels of B7-H3 mRNA were observed in late epithelial progenitor cells (LEPCs), a subpopulation of circulating endothelial progenitor cells involved in new vessel formation [143], Son *et al*. found that B7-H3 facilitates LEPC proliferation and migration *in vitro*, however, is associated with a decreased rate of angiogenesis and endothelial cell differentiation [143]. Wang *et al*. showed a correlation of B7-H3 expression and angiogenesis based on analyses of the Chinese Glioma Genome Atlas and the Cancer Genome Atlas datasets [142]. This correlation was further confirmed by *in vitro* research. In the colorectal cancer model, Wang *et al*. showed that B7-H3-associated angiogenesis is promoted through NF-kB pathway activation, causing induction of VEGF-A expression [144]. In the cancer angiogenesis context, the NF-kB pathway is known for its role in inflammatory regulation by activation of lymphocytes and macrophages, cell proliferation, and differentiation. A wide range of factors play important roles in signal transduction, especially cytokines – TNFα, IL-1, IL-2 [145]. In light of those, the role of NF-kB in cancer development is very complex [146]. Han *et al*. found that higher expression of B7-H3 was correlated with an increase of transforming growth factor β (TGF-β) and interleukin 10 (IL-10) levels in the studied group of mice injected with cervical cancer cells [147]. This may lead to activation of the JAK-STAT pathway and induce the expression of VEGF and promote angiogenesis [148]. Moreover, B7-H3 was shown to directly activate the JAK2/STAT3 pathway, followed by activation of MMP-9 and Slug transcription factor [149, 150]. Furthermore, other metastasis-promoting agents such as tissue inhibitors of metalloproteinases 1 and 2 (TIMP1 and TIMP2) and MMP-2 were found to be connected to B7-H3 expression [151]. Lim *et al*. [152] showed that B7-H3 can inhibit the transcription factor nuclear factor erythroid 2-like 2 (NRF2) [145]. NRF2 is a transcriptional master regulator element that recognizes cellular oxidative stress. Down-regulation of this factor leads to increased reactive oxygen species generation, HIF1-α activation, and VEGF up-regulation [152, 153].

B7-H3 expression in tumour tissue was described in different neoplasms, i.e. renal [154], bladder [155], pancreatic [156], cervical [147], and breast cancers [157], sarcomas [158], and gliomas [142]. Higher expression of B7-H3 relates to larger tumour size, infiltrative growth pattern, and poor differentiation of neoplastic cells. In pancreatic cancer, Inamura *et al*. showed that B7-H3 positive patients had significantly shorter 2- and 5-year-survival: 57% and 23% for B7-H3(-) patients vs. 34% and 12% for B7-H3(+) cases, respectively [156]. In invasive bladder cancer, the presence of B7-H3 expression was associated with even more striking differences in long-term survival – the 5-year-survival rate was 58.1% for B7-H3-negative patients, while in the B7-H3-positive group it was only 4.5% [155]. Inamura *et al*. found that worse prognosis of renal cell carcinoma patients relates to both B7-H3 level and FOXP3+ regulatory T cell density [154].

A novel therapeutic approach using anti-B7-H3 agents was proposed by Bao *et al*., who showed that combined treatment of murine breast cancer models with anti-PD-1/PD-L1 agent and photodynamic therapy targeting B7-H3 resulted in suppression of tumour growth, and prevented lung metastasis and recruitment of CD8(+) T cells in tumour mass in comparison with single anti-PD-1/PD-L1 treatment [159]. Based on the results of pre-clinical studies, several phase I clinical trials involving anti-B7-H3

Table 2. The most recent clinical trials involving anti-B7-H3 agents (data from ClinicalTrials.gov)

Identifier	Agent/Drug	Description	Status
NCT02982941	Enoblituzumab	Children with B7-H3-expressing solid tumours	Completed
NCT04185038	B7-H3-Specific chimeric antigen receptor T Cell (CAR-T)	Phase 1 study of B7-H3-specific CAR T cell locoregional immunotherapy for diffuse intrinsic pontine glioma/diffuse midline glioma and recurrent or refractory paediatric central nervous system tumours	Recruiting
NCT04432649	CAR-T Cell with 4th generation B7-H3-specific chimeric antigen receptor (4SCAR-276)	T cells genetically modified with a 4th-generation lentiviral chimeric antigen receptor (4SCAR fused with an inducible apoptotic caspase 9 domain) targeting CD276 (B7-H3). This study will evaluate the side effects and effective doses of 4SCAR-276 in treating refractory and/or recurrent tumours	Recruiting

Table 3. Recent anti-DLL-4 agents

Author	Year	Agent	Study type	Effectiveness
Zhou *et al.* [179]	2019	HB-32 bispecific antibody against VEGF and Dll-4	Preclinical study, xenograft breast cancer model	Inhibits HUVEC migration and proliferation. More effective on cancer cells than monospecific tested antibodies
Xu *et al.* [180]	2016	MMGZ01 anti-Dll-4 antibody murine	Preclinical study, xenograft breast cancer model	Inhibits HUVEC migration and proliferation. Inhibits angiogenesis and promotes tumour cell death
Jia *et al.* [181]	2016	MMGZ01 anti-Dll-4 antibody humanized	Preclinical study, xenograft breast cancer model	Inhibits HUVEC migration and proliferation. Inhibits angiogenesis and promotes tumour cell death
NCT03292783	2017	NOV1501(ABL001) VEGF/DLL4 targeting bispecific antibody	Phase I clinical trial; patients with advanced solid tumours after failure of standard of care	Status: ongoing, unknown
Chiorean *et al.* [182]	2015	Enoticumab (REGN421) fully human Dll-4 antibody	Phase I clinical trial; patients with ovarian, colon, breast, and thyroid cancer and sarcomas	36% of patients had stable disease as best response

agents were carried out or are currently recruiting, as summarized in Table 2.

DLL4-NOTCH

The Notch family is a group of transmembrane receptors with 4 different members: Notch 1 to 4, and 5 complementary ligands known in mammals – 3 delta-like ligands (DLL 1, 3, 4) and 2 Jagged [160]. Their interactions take part in highly conservative signalling pathways responsible for a wide range of growth and differentiation processes, including angiogenesis [161, 162]. In this paragraph, we focus on the role of DLL4, because of its recently described potential in cancer therapy.

DLL4 is an endothelial-specific Notch ligand with expression restricted to small arteries and capillaries [162–164]. DLL4 is mainly expressed in arterial endothelial cells, where it is involved in growth, sprouting, and artery specification [165–167]. Muller *et al*. showed that the presence of DLL4 in tumour tissues has a positive correlation with microvessel density [168]. Interestingly, in a different study, inhibition of the DLL4 pathway was shown to cause an increase of tumour vascular density, but at the same time, newly formed vessels were generally poorly perfused, leading to hypoxia in tumour tissue [169–171].

Complex system of connections between DLL4 and signalling pathways related to angiogenesis include the following: VEGF-A/VEGFR2 [165], Angiopoietin-1 [172], hypoxia-inducible factor 2α (HIF-2α) [173], Wnt/β-catenin [174], and DLL4 itself [165]. Expression of DLL-4 can mediate the up-regulation of VEGFR1 and down-regulation of VEGFR-2, which causes the 'stalk' phenotype of endothelial cells [175]. Moreover, in a study conducted by Mendoça *et al.*, impairment of DLL4 signalling inhibited EMT by the decrease in Snail, Twist, and TGF-β expression [176]. DLL4 may be a potential factor linking hypoxia with EMT, because DLL4 loss-of-function tumour cells did not undergo EMT in a hypoxemic environment [176]. In line with the aforementioned studies, Wang *et al.* showed that the non-small cell lung cancer patients with expression of DLL4 had impaired OS when compared to DLL4-negative patients: 29.4±16.4 months and 55.4±16.1, respectively [177].

In the last few years, several agents against DLL4 were designed. The short characteristic of preclinical and clinical research assessing their utility is presented in Table 3. Surprisingly, Iwamoto *et al.* showed that the effectiveness of agents impairing the Notch/Dll4 pathway is dependent on placental growth factor (PlGF) [178].

Conclusions

The angiogenic factors described in this review have a broad influence on angiogenesis and overall tumour progression. The increased expression of galectins has been reported in several malignancies, and their interaction with VEGFR plays a key role in the formation of new vessels. Recognition of FGF-2 by pentraxin-3 inhibits angiogenesis, but the role of this molecule remains unclear, as some studies suggest its tumour-promoting effects. RLIP76 regulates VEGF expression and secretion in tumour cells through HIF-1 activation. The existence of many lncRNAs playing an important role in angiogenesis (HOTAIR, Tie-1AS, MALAT1, DANCR, PVT1) has been discovered recently. LncRNA both promotes and inhibits angiogenesis, drug resistance, and proliferation. B7-H3 promotes angiogenesis by activating the NF-kB pathway to induce VEGFA expression. DLL4 interacts with important pro-angiogenic molecules such as VEGF-A/VEGFR2, angiopoietin-1, HIF-2α, and Wnt/β-catenin. High cancer mortality is driving scientists to seek new treatments, and molecules related to angiogenesis have become promising material for the development of new – and improvement of existing – anti-angiogenic therapies. They are not only promising targets for therapeutic agents but can also potentially serve as prognostic markers in many malignancies.

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