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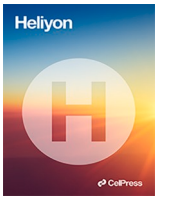

Review article

Research progress on the structure, function, and use of angiogenin in malignant tumours

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ABSTRACT

Angiogenin (ANG) is a specialised secreted ribonuclease, also known as RNase5, that is widely expressed in vertebrates. ANG dysregulation is closely associated with the development of breast, nasopharyngeal, and lung cancers. In recent years, studies have found that ANG not only induces neovascularisation by activating endothelial cells, but also plays a regulatory role in the plasticity of cancer cells. Cellular plasticity plays pivotal roles in cancer initiation, progression, migration, therapeutic resistance, and relapse. Therefore, it is a promising biomarker for cancer diagnosis, prognostic evaluation, and therapy. This review summarises the current knowledge regarding the roles and clinical applications of ANG in cancer development and progression.

1. Introduction

Cancer is a leading cause of death worldwide. The rise in cancer incidence and mortality has made it a serious public health problem [1,2]. Owing to the lack of early and effective diagnostic markers and detection methods, many patients have advanced disease at the time of diagnosis and the 5-year survival rate remains low [3]. Cancer is a complex disease involving alterations in genetic and epigenetic profiles, tumour cell proliferation, and angiogenesis [4,5], the formation of new blood vessels required for tumour growth. The development of solid tumours requires a continuous supply of oxygen, nutrients, and growth factors that are dependent on neovascularisation, which is mediated by the angiogenic factors secreted by cancer cells. In the absence of a blood supply, the growth of the primary tumour and metastatic spread is greatly inhibited [6]. Indeed, without neovascularisation, solid tumour growth cannot exceed 2–3 mm [7]. Similarly, bone marrow microvessel density (MVD) is markedly increased in patients with haematologic cancers, indicating that leukaemia also requires angiogenesis [8]. Neovessels grow rapidly in tumour tissue and provide the basis for distant metastasis.

In 1985, Vallee and coworkers isolated a small protein, named “angiogenin” (ANG), from the conditioned medium of human adenocarcinoma cells and found that it promoted neovascularisation [9]. ANG, also known as RNase5, is the fifth member of the vertebrate-specific secretory ribonuclease A superfamily [10] This protein is a multifunctional proangiogenic enzyme that is secreted upon cleavage of its signal peptide [11–13]. ANG induces neovascularisation and promotes tumour cell functions, including cell survival, proliferation, growth, and migration [13]. Recent studies indicate that ANG dysregulation plays a key role in the development and progression of breast, nasopharyngeal, and lung cancers, suggesting that it has the potential for use as a biomarker in cancer

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diagnosis, prognosis, and therapy [12,14]. These studies have offered novel perspectives on cancer diagnosis and treatment. Many research studies have focused on the role of ANG in cancer [13,14]. The current review focuses on the role and clinical application of ANG in cancer initiation and progression.

2. Molecular structure of ANG

ANG is a single-chain ribonuclease belonging to the RNase A superfamily with a molecular weight of 14.4 kDa [15]. It comprises 123 amino acids [16], of which 33 % share sequence identity and 65 % homology with bovine pancreatic RNase A, including the same general catalytic residues [17,18]. The ANG structure is characterised by two β-sheets arranged to form a β Motif (9) [19,20].

The protein has three domains that are distinct functional sites for biological activity [19,20]: (a) a cellular receptor binding motif consisting of amino acid residues in the loop Lys60, Asn68, and Asn109 segments that allows binding to motor neurons and endothelial cells [19], (b) a nuclear localization sequence (NLS) composed of residues Ile29–Leu35, which aid ANG nuclear translocation [15,19], and (c) a catalytic site located between the two arms of the V-shaped motif and consisting of residues His13, Lys40, and His114 to form the catalytic centre (P1) where phosphodiester bond cleavage occurs [17]. ANG also has a pyrimidine base binding centre (B1) and a purine base binding centre (B2). However, compared to the structure of RNase A, Gln-117 of ANG forms two hydrogen bonds, resulting in occlusion of the B1 centre. Ile1-19 and Phe120 form intramolecular hydrophobic bonds that help hold Gln-117 in its blocking position. Blocking the B1 centre partly explains why ANG reduces the ribonucleolytic activity. ANG also lacks a fourth disulfide bond, which results in a loop region (from Lys-60 to Lys-68) that interacts with a not-yet-identified cell surface receptor [15]. These structures explain the unique ribonucleolytic activity and diverse biological functions of this protein [15,20]. The structure of ANG is shown in Fig. 1.

3. Biological functions of ANG in tumourigenesis and tumour progression

ANG affects almost all steps of tumourigenesis, including cell proliferation, migration, invasion, and angiogenesis [12–14]. ANG can also regulate the sensitivity of tumour cells to chemotherapy and radiotherapy [19,21].

3.1. ANG promotes neoangiogenesis in tumour tissue

ANG binds to vascular endothelial cell-associated receptors to promote tumour angiogenesis, and the specific binding of ANG to the receptor tyrosine kinase (RTK)-type receptor Tie-2 on the surface of endothelial cells results in the phosphorylation and dissociation of perivascular Sertoli cells and dissolution of the subendothelial basement membrane. This promotes vascular structural migration channel formation and the activation and migration of vascular endothelial cells, endothelial cell proliferation, vascular remodelling, and the formation of neovascular sprouts, which in turn increase blood perfusion flow [10]. ANG induces angiogenesis in breast cancer tissue by activating protein kinase B/Akt by binding to its receptor (four-and-a-half LIM-only protein 3, FHL3) on endothelial cells, or entering cells via endocytosis and undergoing nuclear translocation. Nuclear translocation of ANG is important for angiogenesis initiated by other angiogenic factors (e.g. vascular endothelial growth factor (VEGF)). Indeed, if ANG is blocked, these factors can lose their angiogenic function [7]. Using a miRNA microarray in vascular endothelial cells, 26 miRNAs that responded to ANG stimulation were identified and their target genes were predicted and found to promote tumour angiogenesis [22]. ANG promotes tumour angiogenesis as shown in Fig. 2.

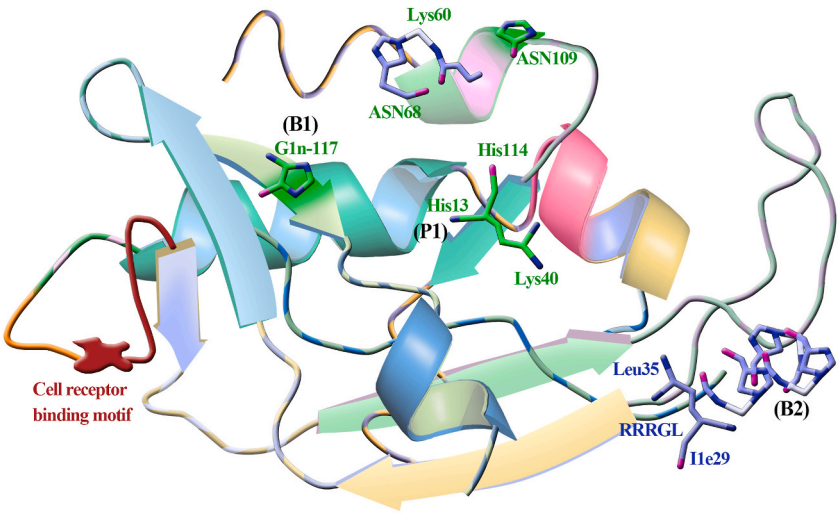

Fig. 1. The structure of ANG.

3.2. ANG regulates malignant cell proliferation, invasion, migration, and epithelial-mesenchymal transition (EMT)

ANG is expressed at high levels in many cancerous tissues, including tumours of the liver, breast, ovaries, prostate, and colon [12,14]. Tumour cells secrete ANG in response to stress, such as hypoxia, and can continuously translocate into the nucleus of tumour cells to promote cell proliferation [17]. ANG is phosphorylated by protein kinase C (PKC) and cyclin-dependent kinases (CDK) in cancer cells, and phosphorylated ANG evades the cytosolic ribonuclease inhibitors (RI) and translocates into the nucleus. Once ANG migrates to the nucleolus, the site of ribosome biogenesis, and enters the nucleus, it accumulates in the nucleolus. ANG cleaves promoter-associated RNA, stimulates ribosomal DNA (rDNA), and contributes to the uncontrolled proliferation of cancer cells [17].

In the tumour microenvironment, extracellular ANG binds to actin on the surface of endothelial cells and induces cytoskeletal changes that inhibit G-actin polymerisation. The interaction between ANG and cell surface actin may also lead to the activation of protease cascades, including the plasminogen activator, plasmin serine protease system, and matrix metalloproteinase system, ultimately leading to the degradation of the basement membrane and extracellular matrix and facilitating tumour cell invasion and migration across vascular endothelial cells [15]. In hepatocellular carcinoma (HCC) nest cells, ANG induces integrin α5/integrinβ1 phosphorylation of focal adhesion kinase (FAK), a tyrosine-protein kinase closely related to cell migration. The activation of FAK can further activate the signalling protein phospholipase C, which induces changes in the cytoskeletal structure and enhances HCC cell migration [14]. ANG expression is increased in HCC cell lines and its downregulation has been shown to inhibit HCC cell proliferation, migration, and EMT. Direct regulation of HMGA2 by ANG was verified using a luciferase activity reporter and Western blot assays. Furthermore, HMGA2 overexpression reversed the inhibitory effects of ANG downregulation on HCC cell behaviour. These findings suggest that ANG promotes EMT in HCC by targeting HMGA2, thus promoting tumour invasion [23].

The EMT is a process in which epithelial cells lose their apical-basal polarity, change their phenotype to a mesenchymal state, and exhibit reduced cell-cell adhesion leading to enhanced cell-extracellular matrix adhesion, while acquiring invasive and mesenchymal-like properties. In squamous cell lung cancer tissues, high ANG expression was positively correlated with the expression of mesenchymal markers and negatively correlated with epithelial markers. Vimentin and TGF-β1 play an important role in EMT and are key regulators of mesenchymal cell migration. Overexpression of ANG results in the upregulation of vimentin, TGF-β1, and N-cadherin and the downregulation of E-cadherin and β-catenin, indicating that ANG contributes to lung cancer invasion and metastasis by inducing EMT [24].

ANG can also promote tumour cell proliferation, invasion, migration, and EMT by cleaving mature tRNAs to generate tiRNAs, which regulate cell proliferation and apoptosis, gene expression and post-transcriptional modification, kinase activity, and translation [25,26]. In a study of colorectal cancer (CRC), 5′-tirRNA-Val, generated by ANG cleavage, was elevated in CRC tissues and serum. ANG levels and CRC invasion and metastasis were positively correlated, helping to establish a regulatory cell migration and invasion regulatory axis of ANG/tiRNAs in CRC cells [27]. A description of how ANG regulates malignant cell proliferation, invasion, migration, and EMT is shown in Fig. 3.

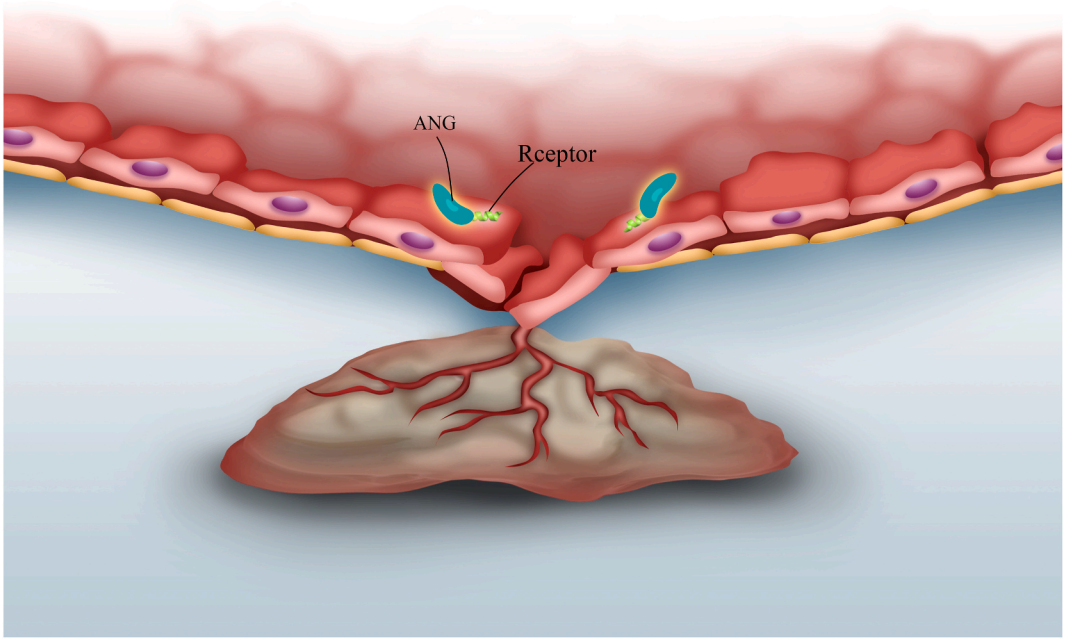

Fig. 2. ANG promotes tumour angiogenesis.

3.3. ANG regulates the sensitivity of malignant tumours to radiotherapy and chemotherapy

Radiation can destroy blood vessels that supply nutrients and oxygen to a tumour, playing a vital role in eliminating cancer [21]. Studies indicate that combining radiotherapy and anti-angiogenic drugs has a synergistic effect and ANG inhibitors together with radiotherapy show promise in reducing recurrence after tumour radiotherapy and increasing survival [28,29]. However, the specific molecular mechanisms of this effect require further elucidation. Studies have also shown that ANG has a radiotherapy (RT)resistance function. Using a RayBio human cytokine antibody array, 297 protein levels were examined simultaneously, and the conditioned media from HONE1 and HONE1-IR-resistant nasopharyngeal carcinoma cells were analysed. ANG expression was significantly higher in HONE1-IR cells treated with 4-Gy radiation, inducing nasopharyngeal cancer (NPC) cell resistance to radiation and reducing progression-free survival (PFS), overall survival (OS), and local relapse-free survival (LRFS) in NPC patients [30].

ANG is a ligand of the epidermal growth factor receptor (EGFR) and can act as a biomarker to predict responsiveness to the EGFR tyrosine kinase inhibitor erlotinib in patients with pancreatic cancer. In this context, ANG is associated with reduced sensitivity to erlotinib treatment both *in vitro* and *in vivo* [31]. In one patient cohort, high levels of plasma ANG in patients with pancreatic cancer were positively associated with erlotinib treatment responsiveness. The Q93 of ANG is required for efficient binding and activation of EGFR. Activation of the ANG-EGFR axis renders tumours more sensitive to erlotinib treatment, and ANG knockdown decreases sensitivity to erlotinib treatment and maintains colony formation, cell viability, and fluidity [31].

4. Role and mechanism of ANG in cancer

ANG, which regulates many cellular biological functions, is significantly upregulated in many cancers, and the occurrence and development of cancer are related to the upregulation of ANG [12,14]. In this section, we will introduce the corresponding roles and mechanisms of ANG in cancer, and the details are provided in Fig. 4.

4.1. Digestive tumours

A previous study on hepatitis B virus (HBV) infection-related HCC demonstrated that HBV mediates the expression of ANG by regulating the activity of IL-6, and ANG-induced activation of the NF-κB pathway inhibits apoptosis of hepatoma cells. The upregulation of ANG promotes the proliferation of tumour cells through positive feedback of the NF-κB/IL-6 pathway. In addition, ANG promotes an increase in 45S rRNA transcript levels in the nucleus, which may induce abnormal proliferation of tumour cells [15].

LV et al. demonstrated that the ANG mRNA and protein expression levels were significantly higher in HCC cell lines than in normal cell lines. ANG through targeting the expression of high mobility group AT-hook 2 (HMGA2), overexpression of HMGA2 increases the expression of N-cadherin and vimentin but decreases the expression of E-cadherin and β-catenin, thereby promoting proliferation, migration, and EMT of HCC cells [23].

ANG expression is upregulated in colorectal cancer (CRC) tumour tissues under hypoxic conditions. The hypoxia-inducible factor-1 subunit alpha (HIF1α)/ANG axis is activated to produce 5′-tiRNA-His-GTG, which targets large tumour suppressor kinase 2 (LATS2) and inhibits the hippo signalling pathway, ultimately promoting proliferation and apoptosis by activating yes associated protein (YAP) activity, thus promoting the occurrence and development of CRC [32].

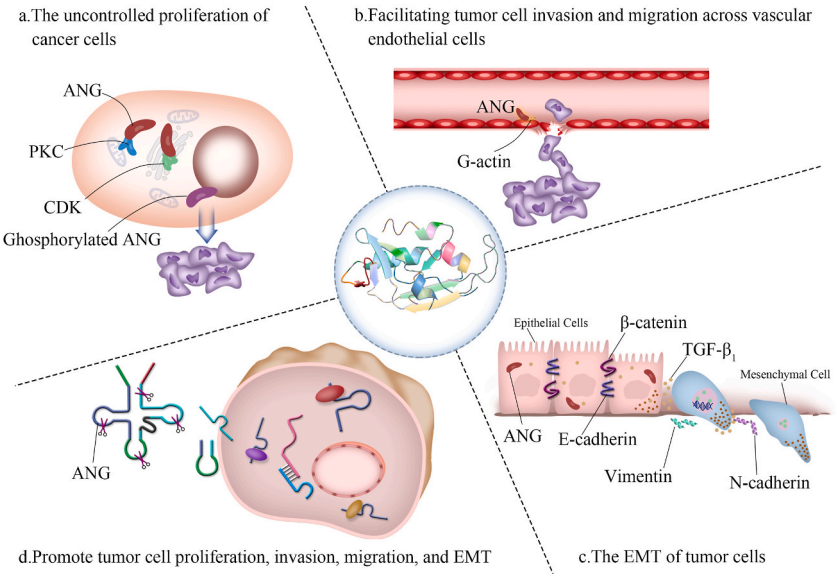

Fig. 3. ANG promotes malignant cell proliferation, invasion, migration, and EMT.

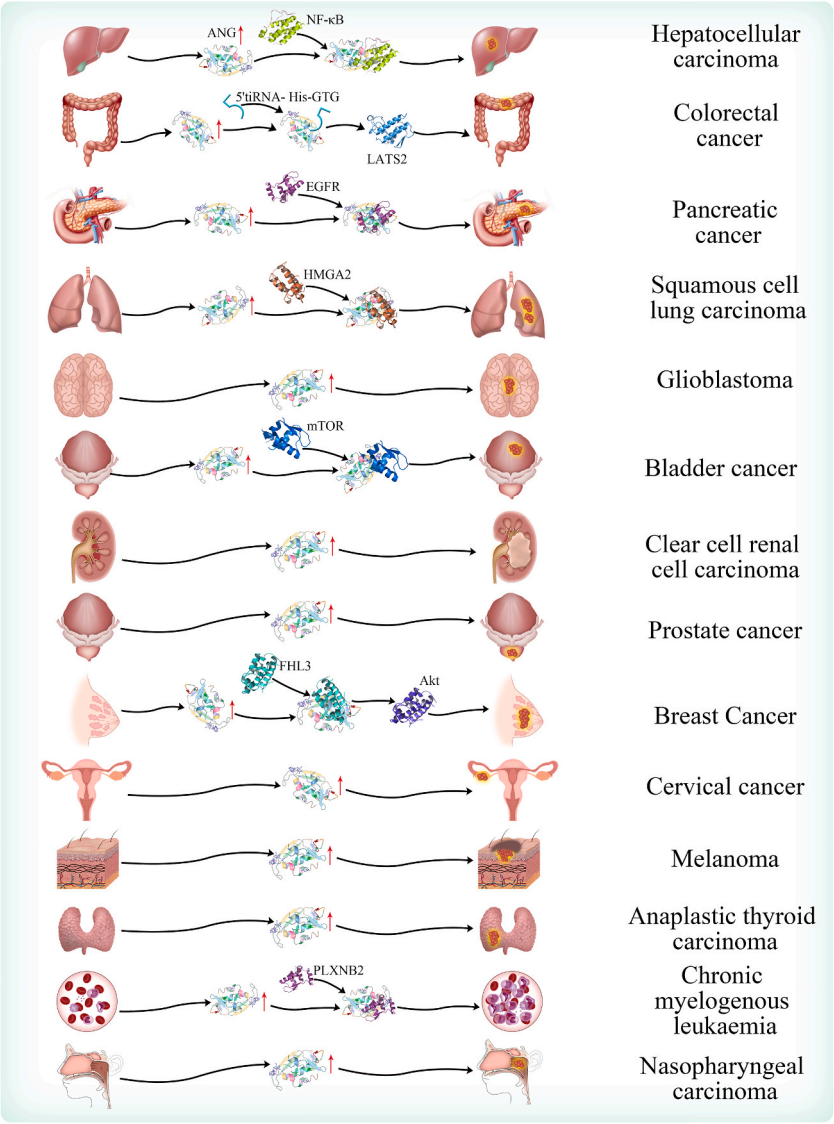

Fig. 4. Possible mechanism of action of ANG in malignant tumours.

Li et al. reported that ANG expression is upregulated in CRC tissues and correlates with metastasis in patients, and they identified a cluster of stress-induced small RNAs (tiRNAs) produced by ANG cleavage. The tiRNA (5′-tiRNA-Val) from mature tRNA-Val is significantly elevated in CRC patients with metastasis, and it may promote CRC metastasis by regulating protein translation or combining with cytochrome *c* to prevent apoptosis and other mechanisms. These findings suggested that ANG promotes CRC metastasis via the ANG/tiRNA regulatory axis [33].

Wang et al. established a model of ANG, which acts as an EGFR ligand in pancreatic cancer, and reported that ANG is sensitive to erlotinib treatment. The knockdown of ANG gene expression by small hairpin RNA (shRNA) in CFPAC-1 cells resulted in decreased EGFR phosphorylation levels without affecting the total expression of EGFR. These findings suggest that ANG binds to EGFR and activates EGFR signalling, ultimately promoting tumourigenesis in patients with pancreatic cancer. Moreover, erlotinib effectively inhibited ANG-induced activation of EGFR, indicating that ANG suppressed the effectiveness of erlotinib treatment in pancreatic cancer [31].

4.2. Respiratory system tumours

A previous study on the mechanism of ANG in the development of squamous cell lung carcinoma (SQCLC) demonstrated that the levels of ANG and HMGA2 mRNA in SQCLC tissues were higher than those in benign tissues and that the expression of ANG mRNA was linearly correlated with HMGA2 expression. Research has confirmed that ANG directly binds to the HMGA2 promoter and enhances its

activity of the HMGA2 promoter, promoting the expression of the oncogenic gene, HMGA2. These studies suggested that ANG promotes the proliferation, migration, and invasion of SQCLC cells by targeting HMGA2 expression [18].

Xu et al. demonstrated that ANG is overexpressed in SQCLC and is closely related to cell line differentiation. Overexpression of ANG induces abnormal expression of vimentin, E-cadherin, N-cadherin, β-catenin, and TGF-β1, which significantly enhances the migration and invasion of tumour cells. Therefore, ANG plays an important role in the EMT of SQCLC [34].

4.3. Nervous system neoplasms

Studies have found that the occurrence and development of glioblastoma (GBM) are highly correlated with ANG. Hypoxia stimulates the transcription of ribosomal RNA (rRNA) in endothelial cells, leading to the upregulation of ANG, allowing it to enter glioma cells and induce proliferation. In glioma cells, the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signalling pathway phosphorylates ANG, which prevents its binding to RI. Consequently, free ANG affects the nucleus, promoting DNA transcription and cell proliferation [20]. In addition, PLXNB2 was recently found to be a functional receptor for the secretory ANG protein [8,35,36], and PLXNB2 may promote ANG nuclear translocation, increase rRNA transcription in the nucleus, and mediate GBM cell proliferation, angiogenesis, and invasion [36,37].

4.4. Genitourinary tumours

A previous study on clear cell renal cell carcinoma (CCRCC) demonstrated that the expression level of phospholipase D2 (PLD2) was higher in primary tumour sites than in normal renal tissues. Moreover, phosphatidic acid (PA) produced by PLD2 promotes the proliferation and invasion of renal cancer cells by upregulating ANG expression in CCRCC cells [38]. However, the regulation and potential roles of ANG in CCRCC remain unclear.

Shu et al. demonstrated ANG overexpression in bladder cancer (BC) cells under oxidative stress conditions. ANG promotes the migration, proliferation, and differentiation of tumour vascular endothelial cells by activating the serine-threonine kinase (Akt)/mammalian target of the rapamycin (mTOR) signalling pathway, thus promoting tumour growth [39]. The concentration differences of ANG and anti-inflammatory interleukin 13 (IL13) in patients with BC compared to healthy controls have been detected and analysed. ANG may have a dual mechanism of action in cancer progression, including stimulation of new blood vessel formation and induction of rRNA transcription, leading to cancer cell proliferation. A previous study verified the relationship between IL13 and ANG, suggesting that IL13 may indirectly participate in angiogenesis and BC tumourigenicity [40]. At present, the specific mechanism requires further study.

Research on BC has shown that ANG expression results in the hypomethylation of the MMP2 gene, leading to increased gene expression of MMP2. Global DNA methylation microarray analysis has shown that manipulation of ANG affects a variety of pathways, such as cell migration and angiogenesis, as well as tumour suppressor genes. Mechanistically, ANG negatively regulates the enzymatic activity of DNA methyltransferase 3b (DNMT3b) by downregulating its expression and inhibiting its recruitment to the MMP2 promoter. Consistently, ANG-MMP2 overexpression and DNMT3b knockdown correlated with a reduction in disease-free survival in patients with BC. Together, these results establish ANG as an oncoprotein and further reveal that ANG contributes to oncogenesis by activating MMP2 through the modulation of DNMT3b function [41].

Prostate cancer research has demonstrated that the anticancer drug oxaliplatin effectively binds to and reduces the activity of ANG and inhibits nucleic acid metabolism, leading to a decrease in the number of actively transcribed ribosomal DNA (rDNA), thereby weakening the transcription and processing of rRNA and ultimately inhibiting tumour cell proliferation and tumour angiogenesis. These results indicate that ANG may be a target of oxaliplatin, suggesting that the antitumour activity of platinum drugs has a potentially new mechanism [19].

4.5. Female reproductive system cancers

The transformation of breast cancer from benign to malignant is accompanied by ANG overexpression and secretion. ANG binds to its receptor, FHL3 on endothelial cells, induces angiogenesis by activating protein kinase B/Akt, or enters the cells for nuclear translocation through endocytosis. Nuclear translocation of ANG leads to massive production of other angiogenic factors, such as VEGF, and promotes tumour angiogenesis. Therefore, the targeted reduction of ANG expression significantly inhibits breast tumour angiogenesis and leads to tumour suppression [7].

ANG expression is increased in cervical cancer cells As cervical cancer progresses from stage I to stage II, the expression level of ANG significantly increases. After radiotherapy and chemotherapy, however, both ANG expression and tumour MVD significantly decrease [40]. In the absence of VEGF, research has shown that ANG promotes damaged tumour blood vessels, induces loosened vasculature, eliminates the restriction of angiogenesis by the vascular basement membrane and surrounding cells, and activates endothelial cells. Under hypoxic conditions, peripheral residual tumour cells produce an abundance of VEGF, and activated endothelial cells become sensitive to the effects of VEGF, leading to rapid proliferation, invasion, and migration. Simultaneously, VEGF upregulates ANG in tumours adjacent to the vascular endothelial tissue through the VEGFR2/KER pathway, ultimately promoting tumour progression [42].

4.6. Blood tumours

Leukaemia research has demonstrated that stromal and vascular endothelial cells in the bone marrow secrete ANG, which activates endocrine signalling in leukaemia cells, resulting in ANG secretion from leukaemia cells. Increased ANG secretion enhances the proliferation and lifespan of leukaemic and endothelial cells, contributing to disease development. Additionally, some studies have indicated that the ANG-TIE system is a potential target for the treatment of leukaemia. The ANG-TIE system has several functions in angiogenesis as well as in the proliferation and maturation of bone marrow vascular endothelial cells, making it an effective therapeutic target for haematological malignancies [43]. However, the specific mechanism requires further study.

4.7. Other tumours

A recent study found that ANG expression in recurrent NPC tissues is significantly increased after radiotherapy, which induces radioresistance in NPC cells and is significantly associated with shorter PFS, OS, and LRFS in patients with NPC. ANG may act as a stress-inducible factor that protects adjacent and distant cells from the harmful effects of environmental stress. Studies have shown that ANG induces cell survival, proliferation, migration, angiogenesis, and expression of tumour suppressor genes. Therefore, ANG may protect NPC cells from radiation-induced hypoxia and environmental stress and may induce cell survival, proliferation, and radioresistance [30]. However, the precise mechanism requires further study.

Using an anaplastic thyroid cancer (ATC) cell line *in vitro*, researchers have reported that ANG may be a downstream target of the Akt/glycogen synthase kinase 3β (GSK3β) signalling pathway. Apatinib is a novel tyrosine kinase inhibitor (TKI) that inhibits various tumour-related kinases. Studies have found that apatinib exerts its antitumour angiogenesis effect by inhibiting the Akt/GSK3β/ANG signalling pathway, thereby inducing apoptosis, and blocking the cell cycle [44].

5. Application value of ANG in cancer

Despite technological progress, the diagnosis and treatment of cancer are still challenging, requiring in-depth research to discover new tumour biomarkers [45,46]. Increasing evidence shows that ANG is closely related to the progression of cancer and may be a promising biomarker for cancer diagnosis, prognosis, and treatment [7,19,40,42]. In this section, we further discuss the potential application value of ANG in cancer.

5.1. Diagnosis

Early screening and diagnosis of tumours are conducive to the survival of cancer patients. The identification of suitable biomarkers has been a focus of cancer research [47–50]. ANG is abnormally expressed in tumours of various systems such as the digestive, respiratory, nervous, genitourinary, haematological, and endocrine systems. Several studies have demonstrated that ANG can be used as a diagnostic marker for various cancers.

ANG is overexpressed in SQCLC and is closely associated with cell line differentiation Overexpression of ANG results in abnormal expression of vimentin, E-cadherin, N-cadherin, β-catenin, and TGF-β1, which significantly enhances the migration and invasion of tumour cells. Therefore, ANG could be used as a diagnostic marker for SQCLC [34].

Detection of serum ANG levels in patients with CRC and healthy controls using ELISA indicated that serum ANG levels in patients are significantly higher than those in healthy controls ($p < 0.01$). Receiver operating characteristic (ROC) analysis has been used to calculate the diagnostic accuracy of serum ANG levels in patients with CRC, resulting in an area under the ROC curve (AUC) of 0.740 [95 % confidence interval (CI): 0.705–0.744], thereby suggesting that ANG may be a potential diagnostic biomarker for CRC [51]. ANG is upregulated in CRC tissues, and a previous study has identified a novel NG-tiRNA cell migration and invasion regulation axis that promotes CRC metastasis, suggesting that ANG may be used as a diagnostic marker for CRC [33].

Shu et al. confirmed the overexpression of ANG in BC cells under oxidative stress and reported that ANG promotes the migration, proliferation, and differentiation of tumour vascular endothelial cells by activating the Akt/mTOR signalling pathway, thus promoting tumour growth. Thus, ANG may be a good diagnostic marker for monitoring the progression of BC [39]. A previous study on the diagnostic role of urinary ANG in patients with bladder tumours has reported a sensitivity of 0.71 (95 % CI: 0.66–0.75), specificity of 0.78 (95 % CI: 0.73–0.81), LR+ of 3.34 (95 % CI: 2.02–5.53), LR-of 0.37 (95 % CI: 0.32–0.44), DOR of 9.99 (95 % CI: 4.69–21.28), and AUC of 0.789 and Q* index of 0.726, indicating the diagnostic value of urinary ANG in identifying BC [52].

A previous study on CCRCC demonstrated that PA produced by PLD2 promotes the proliferation and invasion of renal cancer cells by upregulating ANG expression in CCRCC cells, suggesting that ANG can be used as a diagnostic marker for CCRCC [38].

ANG expression is increased in cervical cancer cells With the progression of cervical cancer from stage I to stage II, the expression level of ANG significantly increases, and significantly decreases after radiotherapy and chemotherapy. Moreover, tumour MVD decreased after radiotherapy and chemotherapy. These findings suggest that ANG can be used as a diagnostic marker for cervical cancer [42].

Studies have found that the transformation of breast cancer from benign to malignant is accompanied by ANG overexpression and secretion. ANG binds to its receptor, FHL3, on endothelial cells and induces angiogenesis by activating protein kinase B/Akt. Additionally, reducing ANG expression through targeted knockdown can lead to tumour suppression. These findings suggest that ANG could be used as a diagnostic marker for breast cancer [7].

ANG expression is significantly increased in recurrent NPC after radiotherapy, which induces radioresistance in NPC cells and is

significantly associated with shorter PFS, OS, and LRFS in patients with NPC. Thus, ANG has a potential diagnostic value and may be used as a biomarker of NPC [30].

Leukaemia research has indicated that stromal cells, vascular endothelial cells, and leukaemia cells in the bone marrow secrete a large amount of ANG, which enhances the proliferation and lifespan of leukaemia and endothelial cells. These results indicate that ANG has a potential diagnostic value for leukaemia [43].

In summary, ANG is highly expressed in tumour tissues and the serum of patients with tumours. ANG regulates tumour cell proliferation and vascular growth by directly or indirectly targeting oncogenic proteins and binding to vascular endothelial-related receptors and is closely related to tumour growth, invasion, and metastasis. Therefore, ANG can be used as a diagnostic biomarker for certain cancers.

5.2. Prognosis prediction

Early acquisition of tumour prognostic information is important in cancer treatment decisions [53–57], and some evidence shows that ANG is valuable in predicting tumour prognosis [30,34,42,52].

ANG is an independent prognostic factor of clinical outcomes in patients with NPC. After regular follow-up, the researchers reported that the 5-year LRFS rate was significantly better in the low-ANG expression group than in the high-ANG expression group (95.1 vs. 85.4 %, $p = 0.026$). Similarly, the 5-year PFS rate was significantly higher in the low-ANG expression group than in the high-ANG expression group (83.6 vs. 68.5 %, $p = 0.049$). Moreover, the 5-year OS was also significantly better in the low-ANG expression group than in the high-ANG expression group (90.0 vs. 81.1 %, $p = 0.034$) [30]. Upregulation of ANG independently predicts worse survival of GBM patients, particularly in patients with the pro-neural subtype [58]. These studies indicate that ANG is of great significance in the evaluation of cancer prognosis. Further studies on the relationship between ANG and cancer prognosis are needed in the future.

5.3. Cancer treatment

Despite rapid developments in treatment methods, cancer remains a challenging problem worldwide. In the current era of personalised tumour therapy, the use of targeted therapy to combat cancer is an increasingly common choice [59,60], and tumour targeted therapy has a significant therapeutic effect in a variety of cancers [61,62]. Many studies have confirmed that ANG plays a regulatory role in the occurrence and development of malignant tumours [63–65]. Theoretically, therapeutics can be designed to alter the expression of ANG, suggesting that a targeted therapy strategy based on ANG is a novel approach for cancer treatment [66–68]. The therapeutic effects of ANG in various malignancies are summarised below.

ANG expression is upregulated in CRC tissues and is significantly correlated with CRC metastasis. Studies have shown that ANG promotes the proliferation and migration of tumour cells *in vitro* and *in vivo*. Researchers have discovered that a specific metastasis-related tiRNA, namely, 5′-tiRNA-Val, is upregulated in tissues and sera of patients with CRC. This tiRNA positively correlated with the ANG level, and is associated with CRC progression and metastasis. These findings uncovered a new function of ANG in CRC metastasis and elucidated a novel ANG-tiRNA cell migration-metastasis regulatory axis, suggesting that ANG may be a therapeutic target for metastatic CRC [33]. In addition, the expression of ANG and miR-141 is negatively correlated in CRC tissues, and ANG promotes tumour vascular growth by downregulating an angiogenesis-inhibitory miRNA (miR-141) *in vitro* and *in vivo*. These results suggest that ANG may serve as a promising therapeutic target for patients with CRC [69].

ANG expression is significantly increased in HCC cell lines. Research has shown that ANG regulates the proliferation, migration, and EMT of HCC cells by targeting HMGA2, suggesting that ANG may be a therapeutic target for HCC [23].

In SQCLC, ANG overexpression promotes the proliferation and invasion of tumour cells. HMGA2 is a target gene associated with ANG that promotes cell proliferation, migration, and invasion. Downregulation of HMGA2 significantly alleviated the inhibitory effects of ANG on cancer cell proliferation, migration, and invasion. Therefore, ANG is a potential molecular target for SQCLC treatment SQCLC [18].

ANG expression is increased in cervical cancer and increases with cervical cancer progression. In the absence of VEGF, ANG damages tumour blood vessels, induces loosened vasculature, eliminates the restriction of angiogenesis by the vascular basement membrane and surrounding cells, and activates endothelial cells. Under hypoxic conditions, peripheral residual tumour cells produce abundant VEGF. Simultaneously, VEGF upregulates ANG in tumours adjacent to the vascular endothelial tissue through the VEGFR2/KER pathway, ultimately promoting tumour progression. Therefore, targeting ANG may be a new method for the treatment of cervical cancer [42]. Breast cancer research has found that overexpressed ANG binds to vascular endothelial cell-related receptors, which induces tumour angiogenesis, and ANG promotes tumour growth by activating protein kinase B/Akt. Therefore, the targeted reduction of ANG expression may be a new method for breast cancer treatment [7].

ANG expression is significantly increased in melanoma tissue [70]. Studies have shown that under normoxic and hypoxic conditions, Ginkgo biloba golden leaf extract (GGLE) significantly inhibits the ANG activity of melanoma cells in a dose-dependent manner, and the concentration of ANG is significantly reduced in the conditioned medium of melanoma cells treated with GGLE. GGLE inhibited the migration and invasion of melanoma cells by reducing ANG activity and concentration in a dose-dependent manner. Therefore, GGLE may be an effective cancer treatment for inhibiting melanoma cell invasion and tumour angiogenesis by targeting ANG activity [70].

Prostate cancer research has demonstrated that oxaliplatin, an anticancer drug, effectively binds to ANG and inhibits its effects on cell proliferation and migration. These findings suggest that ANG may be a target of oxaliplatin, providing a new molecular pathway and drug target for the antitumour activity of this platinum drug [19].

Studies have reported that ANG protects NPC cells from radiation-induced hypoxic environmental stress and induces tumour cell survival, proliferation, and radioresistance. Elevated ANG expression was significantly associated with shorter PFS, OS, and LRFS in patients with NPC. Therefore, targeted inhibition of ANG expression may enhance the effectiveness of radiotherapy for NPC [30].

Table 1
The roles and possible mechanisms of ANG in malignant tumours.

Cancer types	ANG status	Biological function	Upstream regulators	Downstream regulators	Target molecules	Predictive use	References
Hepatocellular carcinoma (HCC)	The serum ANG increased	Regulation of tumour cell proliferation	IL-6	NF-κB/IL-6	_	Biomarkers for diagnosis and targeted therapy	15
Hepatocellular carcinoma (HCC)	The tissue ANG increased	Regulation of tumour cell proliferation, migration, and EMT	_	HMGA2/E-cadherin and β-catenin	_	Biomarkers for diagnosis and targeted therapy	23
Colorectal cancer (CRC)	The tissue ANG increased	Regulation of tumour cell proliferation	HIF1α	5′tiRNA- His-GTG	LATS2	Biomarkers for diagnosis and targeted therapy	32
Colorectal cancer (CRC)	The tissue ANG increased	Regulation of tumour cell migration	_	5′-tiRNA-Val	_	Biomarkers for diagnosis and targeted therapy	33
Pancreatic Cancer	The plasma ANG increased	Regulation of tumour cell proliferation and migration	_	EGFR	_	Biomarkers for diagnosis and targeted therapy	31
Squamous cell lung carcinoma (SQCLC)	The tissue ANG increased	Regulation of tumour cell proliferation, migration, and invasion capacity	_	HMGA2	_	Biomarkers for diagnosis and targeted therapy	18
Squamous cell lung carcinoma (SQCLC)	The tissue ANG increased	Regulation of tumour cell epithelial-mesenchymal transition (EMT)	_	vimentin, E-cadherin, N-cadherin, β-catenin and TGF-β1	_	Biomarkers for diagnosis and targeted therapy	34
Glioblastoma	The serum ANG increased	Regulation of tumour cell proliferation	(MAPK)/(ERK)	_	_	Biomarkers for diagnosis	20
Clear cell renal cell carcinoma (CCRCC)	The tissue ANG increased	Regulation of tumour cell invasion	PLD2/PA	_	_	Biomarkers for diagnosis and targeted therapy	38
Bladder cancer (BC)	The cell ANG increased	Regulation of tumour cell proliferation and invasion and metastasis	_	AKT/mTOR	_	Biomarkers for diagnosis, prognosis prediction and targeted therapy	39
Bladder cancer (BC)	The tissue ANG increased	Regulation of tumour cell proliferation and invasion and metastasis	_	DNMT3b	MMP2	Biomarkers for diagnosis and targeted therapy	41
Prostate cancer	The cell ANG increased	Regulation of tumour cell proliferation and migration	_	_	_	Biomarkers for diagnosis and targeted therapy	19
Breast Cancer	The serum ANG increased	Regulation of tumour growth	_	FHL3	Protein kinase B/Akt	Biomarkers for diagnosis and targeted therapy	7
Cervical cancer	The tissue ANG increased	Regulation of tumour cell proliferation and invasion and metastasis	VEGF	_	_	Biomarkers for diagnosis and targeted therapy	42
Chronic myelogenous leukaemia (CML)	The blood plasma/serum ANG increased	Regulation of chemoresistance in tumour cells	_	PLXNB2	_	Biomarkers for diagnosis and targeted therapy	8
Melanoma	The tissue ANG increased	Regulation of tumour cell proliferation, migration, and invasion	GGLE	_	_	Targeted therapy	70
Anaplastic thyroid cancer (ATC)	The cell ANG increased	Regulation of endothelial cell activities including migration, proliferation, and tube formation	Akt/GSK3β	_	_	Biomarkers for diagnosis	44
Nasopharyngeal carcinoma (NPC)	The tissue ANG increased	Protect tumour cell from the radiation induced hypoxia-modulated environmental stress and induce cell survival, proliferation, and radioresistance	_	_	_	Biomarkers for diagnosis, prognosis prediction and targeted therapy	30

Increasing numbers of studies have demonstrated that ANG is overexpressed in various types of cancer tissues and serum [19,23,61,62]. It has been established that ANG regulates tumour cell proliferation and angiogenesis by either directly or indirectly targeting oncogenic genes and binding vascular endothelial receptors, and ANG is closely related to tumour growth, invasion, and metastasis. Hence, the targeted inhibition of ANG has emerged as a potential novel therapeutic approach for cancer treatment [7,18,33,42,59,60,70]. Furthermore, recent studies have shown that suppressing ANG expression can augment the effectiveness of chemotherapy and radiotherapy for certain cancers [19,30].

6. Conclusions and future perspectives

Although ANG was first identified in 1985, its exact function in cancer remains a subject of intensive research. ANG is highly involved in the initiation and progression of cancer, promoting tumour neovascularisation; and regulating cancer cell proliferation, invasion, migration, and sensitivity to radiochemotherapy in several cancer cell types. Table 1 outlines the role and possible mechanisms of ANG in malignant tumours.

ANG is aberrantly expressed in digestive, respiratory, nervous, genitourinary, musculoskeletal, endocrine, and other cancers, suggesting its potential as a diagnostic marker. However, most relevant experiments are based on tissue and cell studies. Ideal and efficient molecular markers should be stably expressed in plasma, serum, and other body fluids, as such molecules have greater potential for clinical applications. ANG expression can also be targeted to monitor and control cancer progression and is a promising biomarker for cancer therapy. Further research is needed to identify agents that can stably control ANG expression for use as new antitumour drugs and clinical tumour interventions. Additional studies are required to further understand the structure and function of ANG, and the mechanisms by which this protein regulates malignant tumour processes. This will provide a deeper understanding of the role of ANG in tumour initiation and progression, and inform the development of new diagnostic markers for adjuvant tumours and immunotherapy.

Consent for publication

All authors have agreed on the contents of the manuscript.

Data availability statement

The authors declare that no data associated with our study has been deposited into a publicly available repository since no data was used for the research described in the article.

Ethics declarations

Review and/or approval by an ethics committee was not required for this study because our article is a narrative review and therefore does not require ethical approval.

Informed consent was not required for this study because it was a narrative review.

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CRediT authorship contribution statement

Mingwen Mao: Writing – review & editing, Writing – original draft. **Weina Chen:** Writing – review & editing, Project administration. **Dong Ye:** Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Foundation (grant no. 2023J213), and the 2022 postgraduate course construction project of Medical School of Ningbo University, and Key Project of Huili Foundation(grant no. 2022ZD003).

List of abbreviations

ANG	angiogenin
MVD	microvessel density
NLS	nuclear localization sequence
RTK	receptor tyrosine kinase
PKC	protein kinase C
CDK	cyclin-dependent kinases
HCC	hepatocellular carcinoma
FAK	focal adhesion kinase
EMT	epithelial-mesenchymal transition
CRC	colorectal cancer
RT	radiotherapy
NPC	nasopharyngeal carcinoma
EGFR	epidermal growth factor receptor
PDAC	pancreatic ductal adenocarcinoma
HBV	Hepatitis B virus
PCR	polymerase chain reaction
tiRNAs	tRNA-derived stress inducible small RNAs
shRNA	small hairpin RNA
SqCLC	squamous cell lung carcinoma
MAPK	mitogen-activated protein kinase
ERK	extracellular signal-regulated kinase
RI	ribonuclease inhibitors
PLD2	phospholipase D2
CCRCC	clear cell renal cell carcinoma
PA	phosphatidic acid
BC	bladder cancer
mTOR	mammalian target of rapamycin
AKT	serine/threonine kinase
IL13	interleukin 13
DNMT3b	DNA methyltransferase 3B
FHL3	four and a half Lim only protein 3
PLXNB2	Plexin B2
mAb17	monoclonal antibody
ATC	Anaplastic Thyroid Cancer
ELISA	Enzyme-Linked Immunosorbent Assay
GGLE	Ginkgo biloba golden leaf extract

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