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REVIEW

Role of the Nervous System in Tumor Angiogenesis

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Abstract

The development of cancer involves an intricate process, wherein many identified and unidentified factors play a role. Tumor angiogenesis, growth of new blood vessels, is one of the major prerequisites for tumor growth as tumor cells rely on adequate oxygen and nutrient supply as well as the removal of waste products. Growth factors including VEGF orchestrate the development of angiogenesis. In addition, nervous system via the release of neurotransmitters contributes to tumor angiogenesis. The nervous system governs functional activities of many organs, and, as tumors are not independent organs within an organism, this system is integrally involved in tumor growth and progression via regulating tumor angiogenesis. Various neurotransmitters have been reported to play an important role in tumor angiogenesis.

Keywords Nervous system · Neurotransmitters · Neuropeptides · Neuro-cancer interaction · Angiogenesis · Cancer

Introduction

New growth in the vascular network (angiogenesis) is a normal physiological phenomenon that tumors utilize to aid in their growth, proliferation and metastatic spread. Angiogenesis involves migration and division of endothelial cells, generation of new basement membrane, arrangement into tubular structures and coverage by pericytes. Angiogenesis is regulated by a plethora of pro- and anti-angiogenic molecules such as, interleukin (IL)-8, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-α, TGF-β, angiogenin, platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) [1, 2]. The level of angiogenic factors in tissues reflects the aggressiveness of tumor cells which play a significant role in prognostic outcomes [3, 4]. In cancer, the balance between pro- and anti-angiogenic factors is lost, resulting in uncontrolled angiogenesis with irregular blood vessels lacking a clear hierarchal arrangement [1, 5]. As a consequence, anti-angiogenic therapies (in particular anti-VEGF) have been approved for cancer treatment [4, 6–8]. The interaction between VEGF with its receptor, VEGFR2, is responsible for the majority of the angiogenic stimulatory signals in vivo, however, their therapeutic value for long-term patient survival is relatively modest [3].

In addition to these factors, the impact of the tumor microenvironment in tumor angiogenesis has attracted much interest in recent years as another regulator of angiogenesis [9–12]. Furthermore, the role of the nervous system has also surfaced as one of the major contributors to cancer progression through the regulation of tumor angiogenesis via release of neurotransmitters. The nervous system governs functional activities of many organs, and, as tumors are not independent organs within an organism, this system is integrally involved in tumor growth and progression [13, 14]. Here we present an overview of the nervous system role in tumor angiogenesis.

Neurotransmitters Influencing Tumor Angiogenesis

Neurotransmitters are group of neurological chemical messengers synthesized by neurons and secreted at nerve terminals where they transmit signals to target cells through binding to their receptors. Studies have demonstrated that various cancers express receptors for different neurotransmitters which have been identified to play essential role in the control of tumor angiogenesis (Table 1, Fig. 1).

Vasso Apostolopoulos and Kulmira Nurgali contributed equally to this work.

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Table 1 Neurotransmitters influencing tumor angiogenesis

Neurotransmitters	Receptor	Type of cancer	Model	Mechanism/pathway	Ref.
NE	β2-AR	Breast cancer	MCF-7, MDA-453, and MDA-231 cell lines, subcutaneous injection of 4 T1 cells in BALB/c mice	β2-AR expression is elevated in MDA-453, decreased in MCF-7 and intermediate in MDA-231 cells. Administration of β-AR agonist, isoproterenol upregulates Jagged 1 expression and enhances tumor microvessel density via NE-induced β2-AR/PKA/mTOR pathway in vivo.	[15]
		Colorectal cancer	HT-29 and CT26 cells in vitro and subcutaneous injection of HT-29 cells in nude miceand CT26 cells in BALB/c mice	Activation of β2-AR by NE enhances expression of VEGF, IL-8 and IL-6 in vitro and in vivo → stimulation of tumor angiogenesis via β-AR -cAMP-PKA signaling pathway.	[16]
		Melanoma	B16-F1 cells in vitro and subcutaneous injection in the flanks of C57BL/6 mice		[17]
		Lung adenocarcinoma	A549 cells in vitro		
DA	DR1 & DR2	Ovarian cancer	SKOV3p 1, HeyA8 cells in vitro and intraperitoneal injection of these cells in a chronic stress C57BL/6 mouse model	Activation of DR2 mediates inhibitory effect of DA on tumor angiogenesis cAMP-PKA signaling pathway.	[18, 19]
		Gastric cancer	Human gastric cancer tissues, subcutaneous injection of Hs746T cells in nude mice, MNNG-induced gastric cancer in rats	DA suppresses gastric cancer growth by inhibition of VEGF-stimulated angiogenesis. In both human gastric cancer and MNNG-induced animal model DA is depleted. Suppression of VEGFR-2 phosphorylation in endothelial cell → inhibition of angiogenesis.	[20]
		Lung cancer	Orthotopic injection of LLC1 cells in C57BL/6 mice and A549 cells in SCID mice	Administration of DR2 agonists inhibits in vivo lung tumor progression via suppressing angiogenesis and reducing myeloid-derived suppressor cells infiltration.	[21]
GABA	GABA	Cholangiocarcinoma	H-69, Mz-ChA-1, HuH28, and TFK-1 cells, subcutaneous injection of Mz-ChA-1 cells in BALB/c mice	$GABA_A$, $GABA_B$, and $GABA_C$ receptors were expressed by cells in vitro which inhibit cell growth and proliferation via IP3 /cAMP, PKA phosphorylation, and ERK1/2 dephosphorylation. GABA ↓ tumor size and VEGF-A/C expression in vivo.	[22]
	$GABA_A$	Ovarian cancer	OVCAR-3 cells in vitro	↑ Level of GABARBP inhibited VEGF expression and ↓ HIF-1α protein via PI3K-mTOR-4E-BP1 signaling pathway in vitro.	[23]
5-HT	5-HT receptor	Colon cancer	Subcutaneous injection of MC-38 cells in *Tph1*$^{-/-}$ mice	5-HT regulates angiogenesis by reducing MMP12 expression in TAMs, thus affecting the production of circulating angiostatin.	[24]
Glu	mGluR1 on endothelial cells	Breast cancer	4 T1 cells injected into the mammary fat pads of BALB/c mice	↓mGluR1 expression results in ↓ angiogenesis in vivo.	[25]
	GRM1	Melanoma	UACC903-G2, UACC903-G4, C8161-G21, C81–61-G6, and C81–61-G7 cells, subcutaneous injection of these cells into each flank of nude mice	In vitro ↑ expression of GRM1 → ↑ expression of IL-8 and VEGF via the AKT-mTOR-HIF1 signaling pathway activation. In vivo ↑ expression of GRM1 → larger melanoma tumors.	[26]
ACh	α7-nAChRs	Lung cancer	Human NSCLC A549 and H157 cell lines	Nicotine increases HIF-1 & VEGF expression. Nicotine mediates tumor angiogenesis through PI3K/Akt and ERK1/2 signalling pathway.	[27]
		Colon cancer	Subcutaneous injection of HT-29 cells in BALB/c mice	Administration of nicotine ↑ VEGF expression → ↑ microvessel densities and angiogenesis via stimulation of β2-AR.	[28]
	mAChR	Breast cancer			[29]

Table 1 (continued)

Neurotransmitters	Receptor	Type of cancer	Model	Mechanism/pathway	Ref.
			Intradermal injection of MCF-7 and MCF-10A cells in nude mice, intradermal injection of LMM3 cells in BALB/c mice	mAChR activation promotes VEGF-A production and neovascularisation in breast cancer models.	
		Mammary adenocarcinoma	Subcutaneous injection of LMM3 cells in BALB/c mice	↑ Expression of VEGF by activation of M1 and M2 mAChRs via arginine metabolic pathway.	[30]
NPY	Y5R	Breast cancer	4 T1 cell line	Activation of NPY ↑ the expression and secretion of VEGF → angiogenesis.	[31, 32]
	Y2R	Melanoma	Subcutaneous injection of B16F10 cells into C57BL/6 mice	Blockade of the Y2R inhibited tumor growth by ↓ tumor angiogenesis.	[33]
		Neuroblastomas	Human tissue	Y2R expression is observed in both tumor and endothelial cells.	[34]
NO		Breast cancer	MDAMB-231cell and human invasive breast cancer tissues	NO induces the expression of VEGF-C in both breast cancer cell line and human tissues.	[35]
		Ovarian cancer	Cystic fluid samples and human tissues	The expression of iNOS correlates with the degree of tumor differentiation; level of intracystic NO metabolite correlates with tumor stage.	[36]
		Gastric cancer	Human tissues (all stages)	NOS III protein is ↑ in both primary gastric tumors and lymph node metastases.	[37]

α7nAChR, α7 nicotinic acetylcholine receptor; ACh, acetylcholine; β2-AR, β_2-adrenergic receptor; cAMP, cyclic adenosine monophosphate; AKT, serine/threonine kinase or protein kinase B; DA, dopamine; DR1 & DR2, dopamine receptor 1 & 2; $ERK_{1/2}$, extracellular signal-regulated kinase; GABA, gamma-aminobutyric acid; GABARBP, $GABA_A$ receptor-binding protein; $GABA_{A,B\&C}$, gamma-aminobutyric acid receptor $_{A,B\&C}$; Glu, glutamate; GRM1, glutamate receptor metabotropic 1; HIF-1α, hypoxia inducible factor-1alpha; 5-HT, 5-hydroxytryptamine (serotonin); iNOS, inducible nitric oxide synthase; IL-6, interleukin 6; IL-8, interleukin 8; mGluR1, metabotropic glutamate receptor 1; mAChRs, muscarinic acetylcholine receptors; M1 & M2, muscarinic 1 & 2 receptors; MMP12, matrix metallopeptidase 12; MNNG, N-methyl N′-nitro-N-nitrosoguanidine; mTOR, mammalian/mechanistic target of rapamycin; NE, norepinephrine; NO, nitric oxide; NOS, nitric oxide synthase; NPY, neuropeptide Y; NSCLC, non-small cell lung carcinoma; PI3K, phosphoinositide 3-kinase; 4E–BP1, phosphorylated 4E binding protein 1; PKA, protein kinase A; TAMs, tumor-infiltrating macrophages; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; Y2R & Y5R, neuropeptide Y receptor 2 & 5

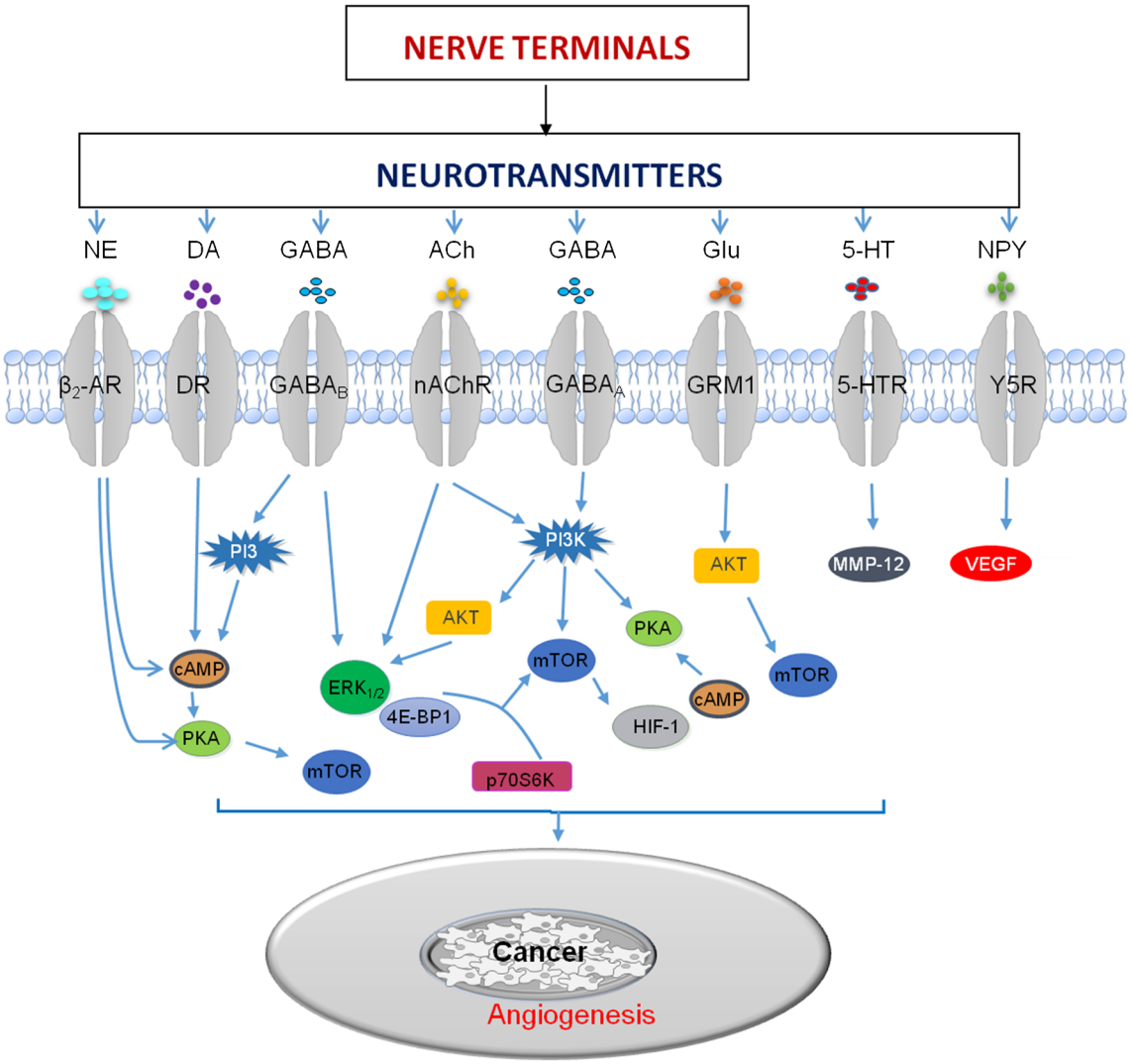

Fig. 1 Neurotransmitter signalling pathways in cancer angiogenesis. Neuro-cancer communication is through the release of neurotransmitters activating different signalling kinases which promote cancer progression via angiogenesis. ACh, acetylcholine; β2-AR, β_2-adrenergic receptor; cAMP, cyclic adenosine monophosphate; AKT, serine/threonine kinase or protein kinase B; DA, dopamine; DR, dopamine receptor; $ERK_{1/2}$, extracellular signal-regulated kinase; GABA, gamma-aminobutyric acid; $GABA_{A\&B}$, gamma-aminobutyric acid $receptor_{A\&B}$; Glu, glutamate; GRM1, glutamate receptor metabotropic 1; HIF-1, hypoxia inducible factor 1; 5-HT, 5-hydroxytryptamine (serotonin); 5-HTR, 5-hydroxytryptamine receptor (serotonin); MMP12, matrix metallopeptidase 12; mTOR, mammalian/mechanistic target of rapamycin; nAChR, nicotinic acetylcholine receptor; NE, norepinephrine; NPY, neuropeptide Y; PI3, phosphoinositide 3; PI3K, phosphoinositide 3-kinase; 4E–BP1, phosphorylated 4E binding protein 1; PKA, protein kinase A; p70S6K, serine/threonine kinase; VEGF, vascular endothelial growth factor; Y5R, neuropeptide receptor

Catecholamines are a group of neurotransmitters that are synthesized from amino acid tyrosine. These neurotransmitters are intricately involved in the normal physiological response of fight or flight response during stress [38, 39]. Epinephrine and norepinephrine released during chronic stress play an important role in tumorigenesis via regulation of angiogenesis through β-adrenergic signaling. The β-adrenergic signaling pathway is involved in regulation of cancer initiating factors such as apoptosis, DNA damage repair, inflammation, cellular immune response, angiogenesis and epithelial-mesenchymal transition. Numerous in vitro and animal studies have demonstrated that epinephrine and norepinephrine acting on their receptors expressed on tumor cells, stimulate angiogenesis via increased VEGF synthesis [16, 38–41] through the cAMP-PKA signaling pathway [40]. In fact, activation of the β-adrenergic signaling pathway in primary mammary tumors has been shown to elevate tumor-associated macrophages (TAMs) expressing *vegf* gene which enhances angiogenesis [42]. Moreover, in some breast cancer cell lines, direct activation of β-adrenergic signaling can amplify expression of VEGF and cytokines, IL-6, and IL-8 that stimulate tumor angiogenesis [43]. Jagged 1 is essential factor mediating Notch signaling which regulates tumor angiogenesis through β2-AR-PKA-mTOR pathway.

Upregulation of Jagged 1 in breast cancer patients correlates with poor prognosis [44, 45]. Knockdown of Jagged 1 by siRNA in MDA-231 breast cancer cells inhibits Notch signaling in endothelial cells and impairs tumor angiogenesis induced by norepinephrine [15].

In contrary, dopamine inhibits angiogenesis by down-regulation of VEGFR-2-mediated signaling pathway in both tumor endothelial and endothelial progenitor cells through D_2 dopamine receptors (DR2) [38, 39, 46, 47]. Furthermore, in mouse models of breast cancer induced by MCF-7 cell line and colon cancer induced by HT29 cell line, dopamine administration in combination with anti-cancer drugs (eg. doxorubicin and 5-fluorouracil) impairs tumor growth and improves survival outcome [48]. However, dopamine effect was found to have no direct impact on tumor growth and survival but by inhibiting tumor endothelial cell proliferation and migration via the suppression of VEGFR-2 and mitogen-activated protein kinase as demonstrated in vitro [48]. In tissues from gastric cancer patients and in rats with chemically-induced as well as mice with Hs746T cell-induced gastric cancer, administration of dopamine decelerates tumor growth by suppressing angiogenesis via inhibition of VEGFR-2 phosphorylation in endothelial cells [20]. This concurs with results obtained in ovarian cancer mouse models induced by systemic injection of SKOV3ip1 and HeyA8 cells in which exogenous administration of dopamine inhibits angiogenesis by a stimulation of DR2, however stimulation of DR1 stabilizes tumor blood vessels via cAMP-PKA signaling pathway [18].

Acetylcholine and Nicotine Nicotinic acetylcholine receptors (nAChRs) can have either stimulatory or inhibitory effect on the production and release of angiogenic factors [49]. Indeed, the expression of VEGF, TGF-β, FGF and PDGF in endothelial cells is increased by nicotine [50–53]. Nicotine-mediated angiogenesis via activation of α7 and α9-nAChRs is cell-type specific, e.g. in lung cancer cells angiogenesis is promoted via activation of α7-nAChRs [53, 54], whereas in breast tumors overexpression of α9-nAChRs [55] stimulates release of pro-angiogenic factors [56]. In colon tumor tissues from HT-29 cell-bearing BALB/c mice, VEGF expression is elevated by nicotine which correlates with enhanced microvessel density [28]. The molecular pathways of nicotine-induced angiogenesis have been extensively reviewed [57]. The role of muscarinic acetylcholine receptors (mAChRs) in tumor angiogenesis is not well understood, however administration of autoantibodies against mAChRs in mouse models of breast cancer (Table 1) mediates tumor angiogenesis via activation of mAChRs through release of VEGF-A [29]. In addition, in BALB/c mice bearing LMM3 mammary adenocarcinoma cells, administration of muscarinic agonist, carbachol, in the presence or absence of various muscarinic antagonists shows an increase in VEGF expression [30, 58]. Furthermore, tumor macrophages stimulate angiogenesis via activation of M1 and M2 mAChRs which trigger arginine metabolic pathway [30].

Y-Aminobutyric Acid (GABA), Neuropeptide Y (NPY), Nitric Oxide (NO) and Serotonin have varying effects on angiogenesis and tumor progression. In a mouse model of cholangiocarcinoma, GABA inhibits VEGF-A/C, decreases cell proliferation and tumor mass [22]. NPY enhances the expression of VEGF and its secretion promoting angiogenesis and breast cancer progression [31]. The suggested mechanism by which NPY induces angiogenesis is by its influence on endothelial cells dependent on endothelial nitric oxide synthase (eNOS) activation and partly on VEGF signaling pathway The release of NO results in endothelial activation inducing tumor cells lysis [59], although NO can also promote tumor growth and metastasis by enhancing angiogenesis [36, 59–65]. For instance, NO increases VEGF-C and nitrite/nitrate production in MDA-MB-231 breast cancer cells and high levels of nitrotyrosine correlate with increased VEGF-C, lymph node metastasis, reduced disease-free and overall survival in invasive breast carcinoma [35]. The expression of iNOS and VEGF in colorectal cancer correlates with enhanced intratumor micro-vessel density suggesting that NO can promote tumor angiogenesis [60]. In gastric cancer, overexpression of NOS III via abnormal activation of sequence-specific DNA-binding protein (Sp1) correlates with enhanced micro-vessel density and poor survival [37]. Serotonin has also been implicated in tumor angiogenesis. In C57BL/6 mice bearing MC-38-induced tumors, serotonin regulates angiogenesis by plummeting matrix metalloproteinase 12 (MMP12) expression (eg. [66]) in macrophages infiltrating the tumor, as well as reducing angiostatin (an endogenous inhibitor of angiogenesis) levels [24].

Glutamate is an excitatory neurotransmitter that regulates synaptic and cellular activity via binding to its receptors including metabotropic glutamate receptors (mGluRs). The expression of mGluRs has been implicated in tumor angiogenesis as noted in mouse models of melanoma and breast cancer [25, 26, 67]. As such, decreased activity of mGluR1 inhibits angiogenesis in an orthotopic breast cancer (4 T1) model suggesting that mGluR1 acts is a pro-angiogenic and pro-tumorigenic factor [25]. Likewise, in an experimental non-small cell lung cancer in A549-bearing nude mice, inhibition of mGlu1 receptor with BAY36–7620 led to suppression of angiogenesis via inhibiting AKT/HIF-1α/VEGF signaling pathway [68]. Similarly, high expression of glutamate receptor GRM1 in several human melanoma cell lines (Table 1) leads to increased expression of IL-8 and VEGF via activation of the AKT/mTOR/HIF1 signaling pathway [26].

Table 2 Other factors influencing tumor angiogenesis

Factors	Type of cancer	Model	Mechanism/pathway	Ref.
ANG	Breast cancer	Human tissues	The level of ANG correlates with clinical progression. ANG derived from tumors activates angiogenesis via suppression of miR-543-2p.	[69]
	Bladder cancer	Human tissues, T24, UROtsa and HeLa cells subcutaneously injected in athymic BALB/c (nu/nu) mice	↑ ANG expression correlates with high grade, and muscle-invasive tumors via ERK 1/2 and MMP2. Downregulation of ANG inhibits tumor angiogenesis via AKT/GSK3β/ mTOR pathways.	[70, 71]
TNF-α	Lung cancer	LLC1 cells subcutaneously injected in wild type, p75 knockout (KO) and double p55KO/p75KO mouse xenograft models	Tumor growth ↓ in both LLC and B16 p75KO mice. Decreased tumor growth correlates with ↓ VEGF expression and capillary density via TNFR2/p75.	[72]
	Melanoma	B16 cell subcutaneously injected in C57BL/6 mice. Wild type, p75 knockout (KO) and double p55KO/p75KO mouse tumor xenograft models		
TGF-β	Colon cancer	Human tissues, FETα/DNRII cell	TGF-β signaling is inversely correlates with the expression of VEGF-A in tissues. TGF-β ↓ VEGF-A expression via ubiquitination and deterioration in a PKA- and Smad3-dependent and Smad2-independent pathways in vitro.	[73]
BDNF	Chondrosarcoma	JJ012 cell line, JJ012 cells subcutaneously injected in CB17-SCID mice	The expression of BDNF and VEGF correlates with tumor grade. BDNF knockdown ↓ angiogenesis and tumor growth in mouse model. BDNF ↑ expression of VEGF and stimulates angiogenesis via the TrkB receptor, PKCα, PLCγ and HIF-1α signaling pathways.	[74]
FGF	Mammary cancer	Mouse 66c14 mammary carcinoma and inguinal mammary fat pad injection in BALB/c mice	In tumor cells suppression of FGFR signaling inhibits expression of VEGF-C and induces VEGFR-3, netrin-1, prox1 and integrin α9 expression.	[75]
	Glioma	Rat C6 glioma cancer cells injected subcutaneously into rats		
EGFR	HNSCC	Human tissues, CAL27 cells subcutaneously injected in nude mice	In human tissues, ↑ EGFR correlates with ↑ HIF-1α and microvessel density. EGFR inhibitors ↓ the regulation of HIF-1α & Notch1 → ↓ angiogenesis and tumor size.	[76]
NGF	Breast cancer	MDA-MB-231 cells subcutaneously injected into SCID mice	NGF ↑ the release of VEGF in breast cancer cells and mediates angiogenic effect via the activation of PI3K-Akt, ERK, MMP2 and NO synthase pathways.	[77]
HGF	ESCC	Serum samples, human tissues, HKESC-1, HKESC-2 and SLMT cells	In tissues, ↑ level of HGF correlates with tumor metastasis and poorer survival. In serum samples, ↑ HGF level correlated with expression of VEGF and IL-8. HGF stimulates cells to express VEGF and IL-8 in vitro via extracellular signal-regulated kinase signaling pathways.	[78]
	Prostate cancer	Castration-resistant prostate cancer blood samples and PC3 cell line	HGF levels ↑ in both blood samples and cell line.	[79]

AKT, serine/threonine kinase or protein kinase B; ANG, angiogenin; BDNF, brain-derived neurotrophic factor; EGFR, epidermal growth factor receptor; ESCC, esophageal squamous cell carcinoma; $ERK_{1/2}$, extracellular signal-regulated kinase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GSK3β, glycogen synthase kinase 3β; HNSCC, head and neck squamous cell carcinoma; HGF, hepatocyte growth factor; HIF-1α, hypoxia inducible factor 1α; IL-8, interleukin-8; MMP2, matrix metalloprotease 2; mTOR, mammalian/mechanistic target of rapamycin; NGF, nerve growth factor; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKCα, protein kinase C alpha; PLCγ, phospholipase Cγ; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; TNFR2/p75, tumor necrosis factor receptor 2/neurotrophin receptor; TrkB, tropomyosin related kinase B; VEGF, vascular endothelial growth factor

Hence, these studies clearly demonstrate involvement of neurotransmitters in tumor angiogenesis; however, most of the studies have been performed mainly in animal models and cell lines. Understanding their relevance to human pathology may aid in the development of better anti-angiogenic therapies.

Other Factors Influencing Tumor Angiogenesis

Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), angiogenin (ANG), FGF, TNF-α, TGF-β, hepatocyte growth factor (HGF) and epidermal growth factor receptor (EGF) are important signaling molecules promoting angiogenesis (Table 2, Fig. 2). NGF is a neurotrophic factor that is upregulated in tumor microenvironment of various cancers including breast cancer [77]. NGF, secreted by MDA-MB-231 breast cancer cells, stimulates angiogenesis in vivo after injection of these cells subcutaneously to immunodeficient mice and enhances endothelial cell proliferation, invasion, migration and tubule formation in vitro [77]. Furthermore, NGF enhances secretion of VEGF by breast cancer cells; in vivo administration of anti-VEGF antibody inhibits its angiogenic capacity [77]. In human glioma microvascular endothelial cells, NGF mediates tumor angiogenesis by interaction with α9β1 integrin [80–83]. Another neurotrophic factor, BDNF has been shown to play a role in tumor angiogenesis. For instance, in chondrosarcoma patients, BDNF and VEGF protein expression is significantly higher which is correlated with

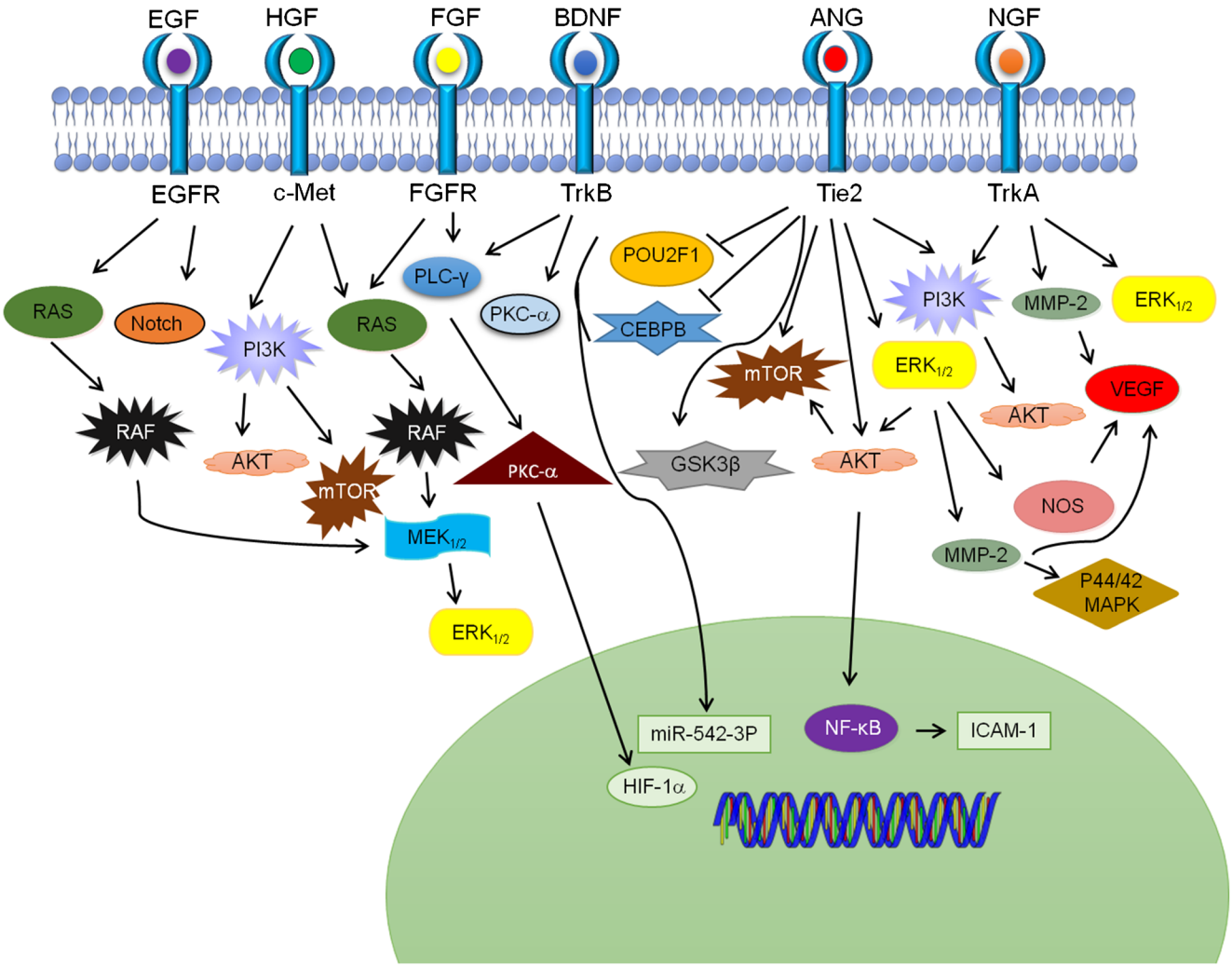

Fig. 2 Growth factors intracellular signalling pathways in cancer angiogenesis. The binding of growth factors to their respective receptors (eg, EGF to EGFR) activates multiple kinase pathways which are involved in cancer angiogenesis. AKT, serine/threonine kinase or protein kinase B; ANG, angiogenin; BDNF, brain-derived neurotrophic factor; CEBPB, CCAAT/enhancer-binding protein beta; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; $ERK_{1/2}$, extracellular signal-regulated kinase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GSK3β, glycogen synthase kinase 3 beta; HGF, hepatocyte growth factor; c-Met, hepatocyte growth factor receptor; HIF-1α, hypoxia inducible factor 1 alpha; ICAM-1, intercellular adhesion molecule-1; MAPK, mitogen activated protein kinase; $MEK_{1/2}$, MAPK/ERK kinase; MMP2, matrix metallopeptidase 2; mTOR, mammalian/mechanistic target of rapamycin; NGF, nerve growth factor; NF-kB, nuclear factor-kappa B; NOS, nitric oxide synthase; PI3K, phosphoinositide 3-kinase; PKC-α, protein kinase C alpha; PLC-γ, phospholipase C-gamma; POU2F1, POU domain class 2 transcription factor 1; RAF, mitogen activated protein kinase; RAS, mitogen activated protein kinase; Tie2, angiopoietin receptor 2; TrkA, tropomyosin related kinase A; TrkB, tropomyosin related kinase B; VEGF, vascular endothelial growth factor

tumor stage [74]. Furthermore, BDNF knockdown decreases the expression of VEGF and abolishes angiogenesis in in vitro studies and animal models of chondrosarcoma [74].

In addition to neurotrophic factors, angiogenic factor ANG is upregulated in number of cancers [84–86] and is associated with worse clinical prognosis in urothelial carcinoma patients [87]. ANG regulates tumor angiogenesis via activation of endothelial and smooth muscle cells triggering various molecular pathways involved in the initiation of angiogenesis (Fig. 2) [69–71, 88]. Elevated expression of ANG associates with high grade and muscle-invasive human bladder tumors involving increase p-ERK1/2 and MMP2 expression [70]. Similarly, downregulation of ANG inhibits tumor angiogenesis via AKT/GSK3β/ mTOR pathways [71]. FGF is involved in angiogenesis by suppressing VEGF-C expression and stimulating expression of pro-lymphangiogenic factors including integrin α9, VEGFR-3, prox1 and netrin-1 [75]. In fact, blocking of FGF2 with anti-FGF2 monoclonal antibody results in impaired angiogenesis of B16-F10 cell induced melanoma in mice [89]. In addition, TNF-α binding to TNFR1/p55 and TNFR2/p57 receptors has been implicated in the secretion of cytokines and pro-angiogenic factors [72]. For example, blocking p75 by short-hairpin RNA in cultured Lewis lung carcinoma cells results in decreased TNF-mediated expression of VEGF, placental growth factor and HGF, suggesting that p75 is essential factor for tumor angiogenesis [72]. Similarly, blocking TNF-α inhibits angiogenesis in metastatic oral squamous cell carcinoma cells (sh-IFIT2 meta cell) in NOD/SCID mice [90]. TGF-β negatively regulates VEGF-A expression via a PKA- and Smad2-independent and Smad3-dependent pathways as demonstrated in FETα/DNRII colon cancer cell lines [73]. HGF is an angiogenic factor secreted predominantly by fibroblasts; it stimulates invasiveness of cancer cells via c-Met receptor tyrosine kinase activation [79, 91, 92]. In fact, high HGF serum levels is correlated with VEGF and IL-8 expression, advanced tumor stage and poor survival of esophageal squamous cell carcinoma (ESCC) patients [78]. High expression of another pro-angiogenic factor, EGFR correlates with increased microvessel density resulting in enhanced tumor angiogenesis via the HIF-1α and Notch1 pathways in tissues from head and neck squamous cell carcinoma patients [76]. Neuropilin is a transmembrane glycoprotein which serves as a receptors or co-receptor for multiple ligands including VEGF, HGF, EGF and FGF which are involved in tumor angiogenesis [93, 94]. In gastric cancer, high expression of neuropilin correlates with advanced clinical stages (III and IV) [95]. Depletion of neuropilin-1 inhibits the activation of EGF/EGFR, VEGF/VEGFR2 and HGF/c-Met angiogenic pathways activated by recombinant human VEGF-165, HGF and EGF proteins [91, 95]. Thus, the role of neurotrophic factors such as NGF, BDNF and their molecular pathways should be considered in the development of anti-angiogenic therapies.

Concluding Remarks

Despite the increasing interest to the role of the nervous system in cancer development and progression, the knowledge in this area is scarce. Most neurotransmitters released by nerve fibers promote tumor angiogenesis, however, some neurotransmitters induce anti-cancer effects. Whether these effects are cancer type or receptor dependent need further elucidation.

To date, most studies investigating the role of the nervous system in modulation of tumor angiogenesis have been performed in cell lines and animal models. Limited studies are available from cancer patients and at different stages of disease. Understanding molecular mechanisms by which nervous system modulates tumor angiogenesis may open new avenues for understanding mechanisms of tumor angiogenesis, identification of new biomarkers for cancer diagnosis and prognosis, and, defining novel targets for therapeutic interventions.

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Compliance with Ethical Standards

Conflict of Interest The authors confirm that this article content has not conflict of interest.

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