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Review

Angiogenic factors as potential drug target: Efficacy and limitations of anti-angiogenic therapy

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ABSTRACT

Formation of new blood vessels (angiogenesis) has been demonstrated to be a basic prerequisite for sustainable growth and proliferation of tumor. Several growth factors, cytokines, small peptides and enzymes support tumor growth either independently or in synergy. Decoding the crucial mechanisms of angiogenesis in physiological and pathological state has remained a subject of intense interest during the past three decades. Currently, the most widely preferred approach for arresting tumor angiogenesis is the blockade of vascular endothelial growth factor (VEGF) pathway; however, the clinical usage of this modality is still limited by several factors such as adverse effects, toxicity, acquired drug resistance, and non-availability of valid biomarkers. Nevertheless, angiogenesis, being a normal physiological process imposes limitations in maneuvering it as therapeutic target for tumor angiogenesis. The present review offers an updated relevant literature describing the role of well-characterized angiogenic factors, such as VEGF, basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF), placenta growth factor (PLGF), hepatocyte growth factor/scatter factor (HGF/SF) and angiopoetins (ANGs) in regulating tumor angiogenesis. We have also attempted to discuss tumor angiogenesis with a perspective of 'an attractive target with emerging challenges', along with the limitations and present status of anti-angiogenic therapy in the current state-of-the-art.

Contents

Abbreviations: VEGF, vascular endothelial growth factor; CRC, colorectal cancer; VEGFR, VEGF receptors; PLGF, placental growth factor; HGF, hepatocyte growth factor; Il, Interleukin; Del-1, developmentally-regulated endothelial cell locus 1 protein; FGF, fibroblast growth factors; CXCL1/Groα, growth-regulated alpha protein; CXCL6/GCP2, granulocyte chemotactic protein 2; bFGF, basic fibroblast growth factor; PDGF, platelet derived growth factor; HGF/SF, hepatocyte growth factor/scatter factor; ANG, angiopoetin; VPF, vascular permeability factor; kDa, kilo Dalton; Flt, Fms-like tyrosine kinase; Flk, fetal liver kinase; KDR, kinase insert domain receptor; HIF-1α, hypoxia inducible factors; NRP, neuropilin; SAF-1, serum amyloid A activating factor 1; HPSGs, heparan sulfate proteoglycans; FGFR, fibroblast growth factor receptors; PDGF-B, platelet-derived growth factor-Beta; miR, microRNA; FP1039, Five Prime Therapeutics; EC, endothelial cell; MMP, matrix metalloproteases; ET-1, endothelin-1; TGF, transforming growth factor; TNF, tumor necrosis factor; PO_2, partial pressure of oxygen; SMCs, smooth muscle cells; HUVEC, human umbilical vein endothelial cell; MAPK, Mitogen-activated protein kinase; PI3K, Phosphoinositide 3-kinase; PKC-zeta, Protein kinase C zeta; Sp1, specificity protein 1; U1snRNA, U1 small nuclear RNA; Tie-2, tunica intima endothelial kinase 2; GBM, glioblastoma multiforme; Erk, extracellular signal-regulated kinase; TKIs, tyrosine kinase inhibitors; mTOR, mammalian target of rapamycin; EGFR, epidermal growth factor receptor; Dll4, delta-like ligand 4; ECP, endothelial cell progenitor; G-CSF, granulocyte colony-stimulating factor; SDF, stromal derived factor; CECs, circulating endothelial cells; VCAMs, vascular cell adhesion proteins; NPDD, nanoparticle mediated drug delivery; hCG, human chorionic gonadotropin; ESDN, endothelial and smooth muscle cell-derived neuropilin-like protein.

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1. Introduction

Since the publication of Judah Folkman's hypothesis that tumor growth is angiogenesis-dependent and a solid tumor must obtain an independent blood supply for its sustainable growth [106], the literature on angiogenesis research is accumulating in logarithmic fashion. Angiogenesis is a physiological process of development of new blood vascular network required for normal body functioning; however, clinically and pathologically it has been recognized as a basic prerequisite for progression, proliferation and metastatic spread of solid tumors. At the site of angiogenesis, new capillaries sprout from pre-existing vessels and there occurs remolding transition from avascular to vascular phases via neovascularization. Cascade of events activated by several pro-angiogenic factors happens during the process of tumor angiogenesis involving mainly dissolution of vascular basal membrane, increased vascular permeability and degradation of extracellular matrix resulting in endothelial cell migration, invasion, proliferation and tube formation [246]. Physiological angiogenesis is a complex process that is tightly controlled & regulated by numerous pro-angiogenic peptides as well as by an array of inhibitory factors; however, in pathological angiogenesis, there occurs an imbalance between pro- and anti-angiogenic factors [49]. Tumors can exist in dormant state for months or years without neovascularization by balancing pro- and anti-angiogenic factors. However, during tumor growth there is a change in angiogenic switch more in favor of pro-angiogenic phenotype. Subsets of the tumor with a pro-angiogenic phenotype secrete their own angiogenic factors and also retrieve angiogenic substances from the surrounding extracellular matrix, and induce host cells (monocytes/macrophages) to synthesize angiogenic molecules. Thus there occurs a shift in the microenvironment of the tumor in favor of the pro-angiogenic stimuli, either by down-regulation of endogenous angiogenic inhibitors or through up-regulation of pro-angiogenic cytokines. As a result of this shift, an angiogenic switch is activated causing a continuous neovessel formation emanating from the normally quiescent vasculature, which sustains tumor growth [6,129,130].

A plethora of research findings have accumulated in the literature, especially the pioneer angiogenesis research by Folkman [105–108], Senger et al. [257], and Ferrara [97,99,103,270] have unraveled the fundamental and baseline secrets of angiogenic switch and played a leading role in establishing angiogenesis as a therapeutic target in the mainstream of anticancer research. This fundamental research was successfully transformed into therapeutic modality by Dr. Ferrara and his team at Genentech Ltd. (San Francisco, USA) which led to the development of Bevacizumab (Avastin), the first (VEGF) targeted anti-angiogenesis cancer therapy, approved by the FDA in 2004. In the current clinical practices, Avastin has been prescribed as a treatment of first-line therapy for colorectal cancer (CRC), neoadjuvant chemotherapy for breast cancer, metastatic breast cancer, non-small-cell lung cancer, metastatic renal cell carcinoma, and as second-line therapy in CRC and glioblastoma multiforme [23,85,100]. Thus, development of a humanized anti-VEGF antibody for the treatment of cancer targeting angiogenesis stands out as landmark achievements in anti-cancer research.

Advances in the molecular biology, clinical biochemistry and pathophysiology of tumor growth led to a concrete understanding about the up- and down-regulation of angiogenic switch. Nevertheless, different strategies have been designed to stimulate or arrest the growth of new blood vessels and also identified potential ways to interfere with the process of tumor growth. The concept of treating solid tumors by targeting tumor angiogenesis is not new; rather it is more discussed in recent years owing to its significance as targeted anticancer therapy extending the life span of cancer patients. A plethora of literature has accumulated in recent years describing t\he significance of targeting tumor angiogensis for the design and development of novel antitumor agents that arrest tumor growth [47,49,114,115,161,194,218]. A review providing a comprehensive information on functional and structural peculiarities of the various angiogenic peptides, especially emphasizing more on structural opportunities available for manipulating functions of major angiogenic peptides has been recently published [113].

2. How many angiogenic factors support tumor growth?

A series of pro-angiogenic peptides especially the cytokines belonging to the vascular endothelial growth factor (VEGF) family such as VEGF A, B, C, D and VEGF receptors (VEGFR1, & 2), placental growth factor (PLGF), hepatocyte growth factor (HGF), axon guidance factors (semaphorin-4D, slit-2), interleukins (ILs-1, 6, 8 and stromal cell-derived factor 1), pro-angiogenic chemokines such as developmentally-regulated endothelial cell locus 1 protein (Del-1), β-estradiol, ephrins, fibroblast growth factors (FGF 1 & 2), follistatin, chemokines like Growth-regulated alpha protein (CXCL1/Groα), Granulocyte chemotactic protein 2 (CXCL6/GCP2) and angiopoietins have been reviewed in relation to their functional attributes with tumor angiogenesis [96,118,188,212,245]. Fig. 1 summarizes the role of various angiogenic factors discussed in this study.

Effective novel targeted therapies with improved therapeutic index are warranted and angiogenesis is being considered as an attractive target. Designing strategies for targeting the pro-angiogenic peptides for the treatment of angiogenesis linked human ailments remains an exciting research area for further investigation. Extensive research on angiogenesis in recent years has discovered a series of new pro-angiogenic factors having direct or indirect influence in tumor angiogenesis. An updated list of more than 40 endogenous molecules that directly or indirectly influence angiogenesis, along with few others, being assessed and suspected for their angio-regulatory activities are summarized in Table 1.

With the advancement of technology and thereby more clear understanding about the pathophysiology of tumor development and the signaling pro-angiogenic factors, significant efforts have been made in converting these factors as therapeutic targets for designing novel antiangiogenic drugs [47,94,148,218]. An updated literature describing the role of best-characterized angiogenic factors such as VEGF, bFGF, PDGF, PLGF, HGF/SF and ANGs in regulating tumor angiogenesis is described below with special reference to the currently available drugs designed against these pro-angiogenic factors.

2.1. VEGF cytokine family

The pioneer work on vascular permeability factor (VPF) by [257], and the sequencing of VEGF by Ferrara and Henzel [99], revealed the identical nature of both factors that brought together important functions of this single molecule in angiogenesis. VEGF is perhaps the most extensively studied angiogenic cytokine and successfully targeted for developing therapeutic modality for the prevention of angiogenesis in

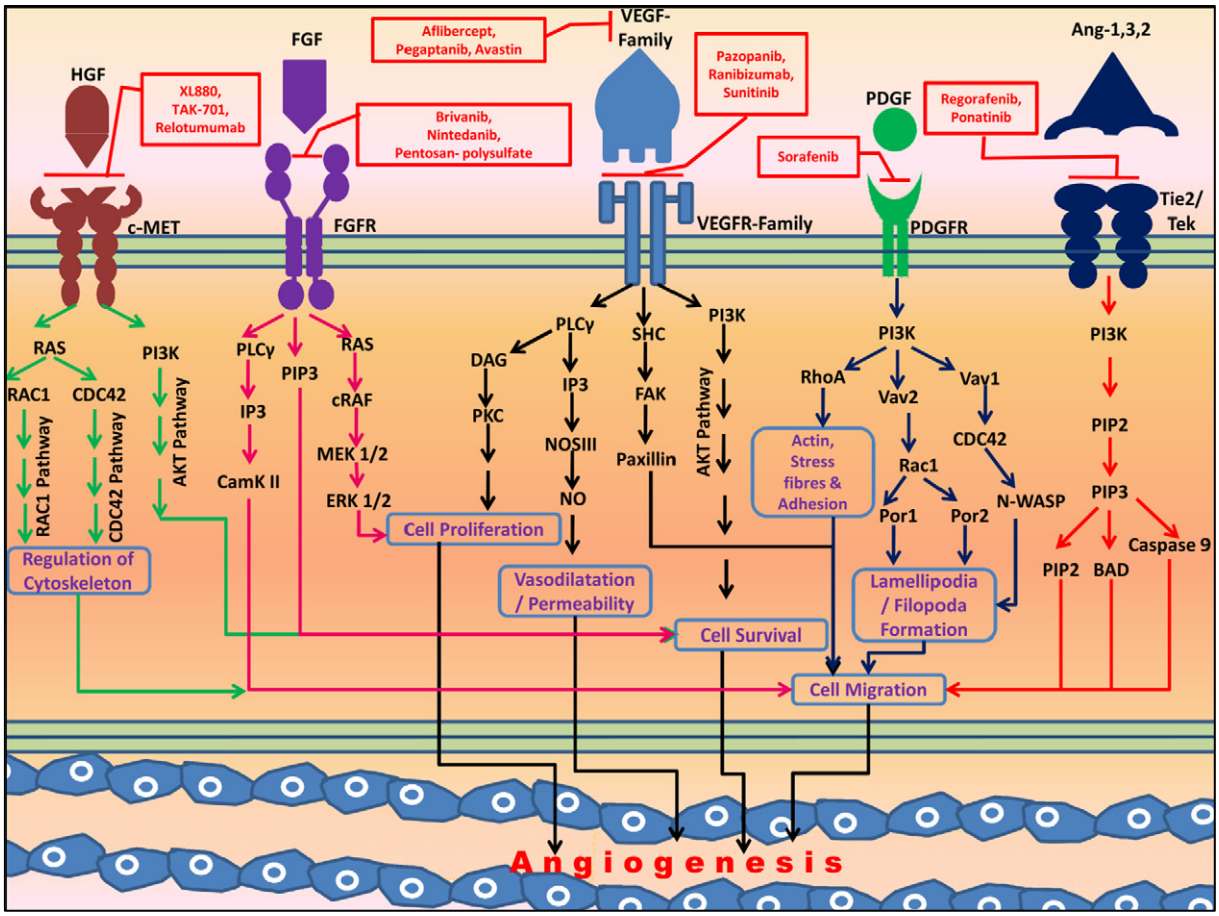

Fig. 1. Summary of role and mode of action of HGF, FGF, VEGF, PDGF and ANG in physiological processes leading to angiogenesis. Major therapeutic agents designed against these pro-angiogenic factors are shown in boxes (red color).

different types of cancers. VEGF has been figured out as a key player in recruiting physiological and pathological angiogenesis. The binding of VEGF to VEGFR-2, triggers a series of proangiogenic reactions resulting in proliferation and migration of endothelial cells and it is also implicated in leakiness of neovessels [24,102,117,127,164,215].

The VEGF family consists of seven different homologous factors, namely VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor (PLGF). VEGF-A is a hypoxia-inducible 45-kDa homodimeric glycoprotein and it is one of the most extensively studied members of VEGF family. The five different isoforms of VEGF such as, $VEGF_{123}$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{189}$ and $VEGF_{206}$ are produced by alternative splicing mechanism. A variety of tumor cell lines were found to express VEGF-A, while its receptors such as VEGFR-1 and VEGFR-2 were observed to be expressed in endothelial cells [98,127]. VEGF-C and VEGF-D play an important role in lymphangiogenesis and have a binding affinity for VEGFR-3 (also called Fms-like tyrosine kinase 4 or flt-4) [70]. VEGF-C is reported to regulate the differential expression of VEGF-A in ocular and cancer cells by promoting angiogenesis via RhoA mediated pathway [175]. $VEGF\text{-}A_{164}$ and VEGF-B have increased binding affinity for VEGFR-1 (Flt-1) and VEGFR-2 (Fetal liver kinase (Flk) or Kinase insert domain receptor (KDR). Although $VEGF\text{-}A_{164}$ can bind both VEGFR-1 and VEGFR-2, most of the investigation suggests that binding of $VEGF\text{-}A_{164}$ to VEGFR-2 is responsible for the majority of the angiogenic stimulatory signal observed in vivo. The recent report describes that the VEGFR-1 mediated signaling promotes mobilization of macrophage lineage cells from the bone marrow and stimulates solid tumor growth [209]. However, VEGFR-1 may, in fact, be a decoy receptor with limited signaling capacity. It is described that $VEGF\text{-}A_{164}$ induces angiogenesis by perturbing the cathepsin–cysteine protease inhibitor balance in venules, causing basement membrane degradation and mother vessel formation [56].

Various factors are known to regulate the expression of VEGF; one of the important factors is the availability of oxygen [270,76]. This unique requirement of hypoxic condition for up-regulated expression makes this molecule an important stimulator of aberrant angiogenesis in a wide array of major human ailments including arthritis [224], cardiovascular disease [285], diabetic complications like cataract [277], retinopathy [18,49,287], psoriasis [66], and cancer [164,288].

Hypoxia is the key factor in regulating VEGF expression through the hypoxia inducible factor (HIF-1α) transcription factor [32]. The levels of HIF-1α in turn are regulated by prolyl-hydroxilases, whose activity is directly regulated by the availability of oxygen. The central regions of solid tumors become hypoxic when tumors expand, thus promoting VEGF production and consequently induction of tumor angiogenesis [89,156]. In ocular model angiogenesis studies related to expression of VEGF, it was reported that the αB-crystallin plays a critical role in the regulation of the angiogenic response. It is reported that the upstream HIF-1α signals remain unaffected and VEGF-A transcription ensues, there is a significant inhibition of local VEGF-A protein expression owing to the loss of phosphorylated serine59 αB-crystallin chaperone function in the endoplasmic reticulum. The major physiological effect of locally deficient VEGF-A expression is the formation of defective neovasculature with increased frequency of endothelial apoptosis. The study highlights an important role of αB-crystallin as a chaperone for VEGF-A in angiogenesis [158].

Neuropilins (NRP1 and NRP2) are co-receptors for VEGF implicated in angiogenesis and tumor progression. VEGF binds to the NRP1 and NRP2 B domains. It was shown that mutagenesis of the soluble NRP2

Table 1
An updated list of pro-angiogenic factors having direct or indirect positive influence on process of angiogenesis.

Angiogenin	Matrix metalloproteases (MMP 2 & 9)
Angiopoietin-1	MicroRNAs (miR-10b and miR-196b)
AC133	Neuregulin
Adrenomedullin	Neuropilin-1 & 2
Adiponectin	Neuropeptide-Y
Angiotensin II	NOS (Nitric oxide synthase)
Aldose reductase	Norepinephrine & epinephrine
β-estradiol	Oestrogens
Cathepsin B and D	Osteogenic protein-1
Chemokines CXCL1-3 & CXCL5-8	Phosphatase and tensin homolog (PTEN)
COX-2	Phospholipase A2
Del-1 & 4	Placental growth factor (PlGF)
Dynamin 2	Platelet-derived endothelial-cell growth factor (PD-ECGF)
Elastase	Platelet-derived growth factor-BB (PDGF-BB)
Endothelial p70 S6 Kinase 1	Pleiotrophin (PTN)
Endothelin (ET-1)	Proadrenomedullin N-terminal 20 peptide
Epidermal growth factor (EGF)	Progranulin
Ephrins	Proliferin
Erythropoietin	Resistin
Fibroblast growth factor-1 (acidic FGF, FGF1)	Semaphorin-4D (Sema4D)
Fibroblast growth factor-2 (basic FGF, FGF2)	Slit-2
Follistatin	Soluble heat shock protein beta-1 (HSPβ1)
FoxC2	Stromal cell-derived factor-1 (SFD-1)
Galectin-3	Transforming growth factor-α (TGF-α)
Granulocyte-colony-stimulating factor (G-CSF)	Transforming growth factor-β (TGF-β)
Hepatocyte growth factor/scatter factor (HGF/SF)	Tumor necrosis factor-α (TNF-α)
Hepatoma-derived growth factor (HDGF)	Urokinase plasminogen activator (uPA)
Human chorionic gonadotropin (hCG)	Urotensin-II
Hypoxia inducible factor-1α (HIF-1α)	Vascular endothelial growth factor/vascular permeability factor (VEGF/VPF)
Id1/Id3 (helix–loop–helix proteins)	VE cadherin
Insulin like growth factor (IGF)	Vasoactive intestinal peptide and pituitary adenylate
Integrins, α Vβ3, αVβ5, α5β1	Cyclase-activating polypeptide
Intermedin	
Keratinocyte growth factor (FGF-7)	
Leptin	
MCP-1	
Midkine	
Matriptase	

B domain (MutB-NRP2) increased affinity to VEGF by 8-fold [119,168,203]. However, MutB-NRP2 inhibited ^{125}I-VEGF binding to NRP1, NRP2, and VEGFR-2. It prohibited VEGF induced complex formation of VEGFR-2/NRP2 and arrested VEGF-induced activation of Akt, which is a mediator of cell survival [120]. The function of NRPs in tumor cells is still not fully understood. Expression of VEGFR-2 by tumor cells is rare therefore; NRPs very often represent the only VEGF receptors on tumor cells, as a result of this it is believed that NRPs might be transducing a signal independent of VEGFR-2 in tumor cells. The previous findings have attributed the expression of NRPs with tumor cell survival; which is observed in the survival of NRP1-mediated breast carcinoma cells [15]. Recently, over-expression of thromboxane synthase (an enzyme converting prostaglandin H2 into thromboxanes and biologically active on cancer cells) is linked with higher levels of VEGF, microvessel density, reduced apoptosis in xenograft tumors and increased tumor growth in-vivo, in non-small cell lung cancer [52]. In other recent studies, a transmembrane protein called ESDN (endothelial and smooth muscle cell-derived neuropilin-like protein), expressed in ECs, was reported to regulate VEGF responses in ECs, through a mechanism distinct from neuropilins [213].

While describing the functions of VEGF that are independent of its pro-angiogenic activity, Cao et al. [43] have reported that VEGF produced by tumor cells acts in an autocrine manner to promote cell growth, through interaction with the VEGF receptor NRP-1. It was observed that the down-regulation of VEGF expression by tumor cells induced a differentiated phenotype in vitro and the tumor forming capacity was inhibited in vivo, independent of effects on angiogenesis. More recently, a transcription factor serum amyloid A activating factor 1 (SAF-1) is reported to regulate the VEGF expression in triple-negative breast cancer cells. Inhibition of SAF-1 by antisense short hairpin RNA profoundly reduced VEGF expression along with a reduction in endothelial cell proliferation and migration. By both in vitro and in vivo molecular studies, it was convinced that the effect of SAF-1 was mediated through its direct interaction with the VEGF promoter [241]. Recent studies on VEGF family genes in relation to cancer susceptibility and survival that have described the genetic variation in VEGFA and Flt-1 (VEGFR1) may contribute to cancer susceptibility. These findings although carried out in breast cancer, provide clues for future studies on VEGF family genes in relation to cancer susceptibility and survival [24].

In recent years VEGF has been decoded in the light of both positive and negative regulator of tumor growth. A vast body literature has accumulated supporting the positive role of VEGF in tumor angiogenesis. Contrary to the angiogenic role of VEGF, Stockmann et al. [271] observed that VEGF deficient myeloid cells accelerate tumorigenesis in a mouse model of breast and lung cancer, focusing the protective role of VEGF. This study highlights that VEGF, derived from innate immune cells, plays an intricate role in orchestrating angiogenesis and tumorigenesis. The research carried out by Greenberg et al. [124] showed that VEGF–VEGFR2 complex acts as a negative regulator of angiogenesis by affecting the function of angiogenic vascular smooth muscle cells and pericytes through induction of a receptor complex with the platelet-derived growth factor receptor, leading to the loss of vessel stabilization. Consistent with these works, the report of Cervi et al. [53] described the tumor inhibitory attributes of VEGF by showing that a 2-fold overexpression of systemic levels of VEGF in mice heterozygous for a VEGF "hypermorphic" allele decelerates tumorigenesis in a retroviral-induced, spontaneous murine leukemia model. The circumstantial studies have clearly provided evidence to support antiangiogenic mechanisms in which VEGF inhibits the growth and progression of various cancer types through recruitment of tumor inhibitory monocytic cells and the negative regulation of tumor angiogenesis [293]. The VEGF signaling pathway is also attributed with neuroprotective effects mediated by placental growth factor in an in vitro ischemic model [82].

Targeting VEGF for developing novel anti-angiogenic agents is consistent and has remained a major thrust area in the mainstream of anti-tumor research [202]. In the currently conducted clinical trials, Avastin is being tested either alone or in combination, against a variety of cancers such as gliomas, breast, ovarian and cervical [10,50,164,176]. Moreover, a series of new anti-VEGF antibodies have been developed, which are either clinically tested or are in various phases of clinical trials [85,164,202,226], and it is likely that Avastin™ will not remain the only anti-tumorigenic drug tailored for the inhibition of VEGF functions.

2.2. Basic fibroblast growth factor (bFGF)

FGFs are secreted glycoproteins that are generally readily sequestered to the extracellular matrix, as well as the cell surface, by heparan sulfate proteoglycans (HPSGs). During signal transduction, FGFs are released from the extracellular matrix by a set of enzymes such as heparinases, proteases or specific FGF binding proteins, and the released FGFs subsequently bind to cell surface HPSGs [221]. As of today there are 18 mammalian FGF ligands (out of which FGF11, FGF12, FGF13 and FGF14 do not function as ligands) and 4 fibroblast growth factor receptors 1–4 (FGFRs 1–4) identified [25,289]. FGF2, also known as basic fibroblast growth factor (bFGF) is the most extensively studied peptide as compared to other forms of FGFs. FGF2 mediates its activity by primarily binding with FGFR-1 and recruit vascular sprouting [25,159].

FGF2 is a known promoter of angiogenesis and lymphangiogenesis [238]. Further, FGF2 stimulates cell growth and migration, and also, in some cases, differentiation [238]. The coordinated activity of FGF2 and FGFR-1, in close association with platelet-derived growth factor-Beta (PDGF-B) and VEGFR-3, is described to be strongly attributed in angiogenesis [165]. FGF2 has been attributed as a key player in inducing different angiogenic and lymphangiogenic pathways [238]. Nissen et al. [214] described a reciprocal relationship between FGF2 and platelet-derived growth factor-B (PDGF-B) through their corresponding receptors. Kubo et al. [173] found FGF2 induced lymphangiogenesis to be blocked by vascular endothelial growth factor receptor-3 (VEGFR-3) inhibitors. There is little information available regarding the angiogenic concerns of the other FGF family members. However the other members of the FGF family such as FGF-3, FGF-4, FGF-5 and FGF-8b as well as additional FGF family members have also been characterized as inducers of endothelial cell proliferation and as inducers of angiogenesis [78,212,238]. Recently, FGF-9 was reported to induce microvessel formation, having enhanced capacity to receive flow and was more vasoreactive. Moreover, the vessels formed persisted beyond 1 year, and remodeled into multilayered arteries paired with peripheral nerves [112].

FGFs induce angiogenesis by promoting endothelial cell proliferation, extracellular matrix degradation, altering intercellular adhesion and communication by affecting cadherins, gap junctions and by modulating integrin expression [42,83,238]. Although most of these effects are transduced through mitogen-activated protein kinase activation, protein kinase C activation is also required for FGF induced endothelial cell proliferation and migration [289]. Recently it is reported that FGF-2 regulates cell proliferation, migration and angiogenesis through an NDY1/KDM2B-miR-101-EZH2 pathway, wherein the FGF-2 induced up-regulation of NDY1 (histone demethylase) triggers the recruitment of basally expressed EZH2 (histone methyltransferase), which binds and represses miR-101 (microRNA-101) in concert with NDY1. The inhibition of expression of miR-101 results in the up-regulation of its targets, including EZH2, which thereby stimulates cell proliferation, cell migration and angiogenesis [171,192]. A cooperative functional mechanism between bFGF and angiogenin has been studied for inducing angiogenesis. The study revealed that endogenous bFGF affected the expression of angiogenin in melanoma cells and directly stimulated A375 cell proliferation. It was also reported that bFGF underwent nuclear translocation and bFGF protein was co-localized with angiogenin in A375 cells [316]. Recently, the interplay of bFGF with human chorionic gonadotropin (hCG) and adipokines is reported to stimulate angiogenesis in HUVEC [236].

Sufficient literature is available in relation to deregulated FGF signaling in tumor angiogenesis. The circumstantial clinical research indicates that FGF may also play an integral role in the resistance to anti-VEGF therapy. Therefore targeting both the VEGF and FGF pathways may be beneficial for improving the life quality of cancer patients [189]. Efforts to develop anti-FGF or FGFR agents are under progress. The FGF ligand traps, such as FP1039 (Five Prime Therapeutics), could potentially block the activity of multiple FGF ligands and receptors, and exert both antiangiogenic and antiproliferative effects. The FGF and FGFR targeting therapies belonging to small molecular tyrosine kinase inhibitors (targeting FGFR, PDGFR and VEGFR), FGFR antibodies and FGF ligand traps are either in clinical phase I or II trials (FGF and FGFR-targeting therapies). The emerging data on FGF signaling has sparked several pharmaceutical companies to develop drugs that target FGFRs. These are now entering the clinic, and many more are in preclinical development [289].

2.3. Platelet derived growth factor (PDGF)

PDGF is a 30 kDa dimer encoded by two genes (PDGF-A and PDGF-B), resulting in three dimeric isoforms of proteins: PDGF-AA, PDGF-BB, and PDGF-AB. The biological actions of these heparin-binding families of polypeptide growth factors are known to be mediated by three dimeric receptor structures (PDGFR-αα, PDGFR-ββ, and PDGFR-αβ). There are two additional forms of PDGF such as PDGF-C and PDGF-D [31,186]. The chains A–D are encoded by an individual genes located on chromosomes 7, 22, 4, and 11, respectively [110]. A highly conserved growth factor domain of nearly 100 amino acids, also found in the VEGF family is conserved in all PDGF chains. Total five dimeric compositions have been identified: PDGF-AA, −BB, −AB, −CC, and –DD [137]. The signaling action of PDGF–PDGFR is mediated by autophosphorylation of the receptors on tyrosine residues [196].

The PDGF family members are reported to play a key proangiogenic role in in vivo model studies; therefore the PDGF-B/PDGFRβ axis has attracted the researchers in deciphering its role in angiogenesis. PDGF-B from endothelial cells and its receptor (PDGFRβ) on pericytes play important roles in pericyte recruitment to blood vessels [12,33,86,249]. Pericytes are involved in a series of angiogenic functions such as blood vessel maturation, maintaining the normal endothelial cell (EC) function, vascular stability, and also contribute in the regulation of blood flow through vessels ([8]; [33,295]). The calcium-mediated generation of reactive oxygen species has been described as a key player in the differentiation of embryonic stem cells into endothelial cells by PDGF-B [178]. PDGF-B can directly induce ECs proliferation, migration and tube formation, whereas PDGF-A lacks such effects, PDGF-D regulates VEGF signaling in various cancer cell types. Li et al. [184] found that PDGF-D is a potent transforming growth factor for NIH/3T3 cells, and the transformed cells displayed increased proliferation rate, induced tumors in nude mice, and up-regulated VEGF. In gastric cancer, the decreased cell invasion and angiogenesis are attributed with matrix metalloproteases (like MMP-9 and MMP-2) mediated inhibition of PDGF-D [298,317]. Moreover, PDGF stimulates not only ECs proliferation, but also VEGF secretion [240]. Recently it has been justified that the co-expression of VEGF-A together with PDGF-B is necessary to induce the formation of invasive, solid skin squamous cell carcinomas with a stable, and functional tumor vasculature [179].

Targeting inhibition of PDGF–PDGFR signaling pathway has become an attractive pursuit in anticancer therapy [222]. Nevertheless, combined inhibition of PDGF and VEGF has emerged as a promising strategy for suppressing angiogenesis in tumor progression [30,87]. Different strategies have been employed to arrest the PDGF/PDGFR signaling pathway, which includes neutralizing antibodies for PDGF ligands and receptors, aptamers, N-terminal processing-deficient PDGFs, and soluble receptors excluding the kinase domain [11]. The inhibition of PDGF-B (strongly implicated in angiogenesis) has multiple effects on tumors, including loss of pericytes, regression of some vessels, normalization of other vessels, and reduction of interstitial pressure. PDGF-B inhibition is also reported to increase the efficacy of cancer therapeutics [93].

2.4. Placenta growth factor (PLGF)

PLGF is a multitasking cytokine of VEGF family, which has a 42% amino acid sequence identity with VEGF-A [195]. [319] first time reported the PLGF as pro-angiogenic factor [319]. Although PLGF is mainly expressed in placental tissues [79,244], various other cell types such as vascular cells, fibroblasts, leukocytes, hepatocytes, bone marrow derived cells, neurons, epithelial cells, and tumor cells express PLGF in pathological conditions [80]. Different isoforms (PLGF 1–4) generated due to alternative splicing are encoded by human *plgf* gene 9 [195,244]. Except PLGF-2, no other isoform has heparin binding affinity. PLGF-2 is also able to bind the two co-receptors, Neuropilin 1 and 2 (NRP1 and NRP2), discovered as co-receptors of class 3 semaphorins, via the recognition of their b1b2 domain [199]. The minimal receptor domain required for the binding of VEGF-A, VEGF-B and PLGF is the Ig-like domain two, as well as documented by co-crystal three-dimensional studies [59,149]. The proangiogenic functions such as the growth, migration and survival of endothelial cells are evidently attributed with PLGF [4,48,104]. It is implicated in the proliferations of fibroblasts, smooth-muscle cells, stimulates collateral vessel growth, and induces

vasodilatation [26,309]. It also promotes the recruitment and maturation of angiogenesis-competent myeloid progenitors to growing sprouts and collateral vessels [133,234,254]. Moreover, PLGF activates and attracts macrophages that release angiogenic and lymphangiogenic molecules [256]. PLGF signaling participates directly in the tumoral angiogenic switch by stimulating the proliferation of ECs, acting on mural cells (including pericytes), smooth muscle cells, and indirectly by up-regulating the expressions of VEGF-A, FGF2, PDGFB, MMPs, and other angiogenic factors [200,248]. PLGF is also dispensable for physiological angiogenesis induced in the heart and muscle by exercise [121]. Endothelin-1 (ET-1) a multifunctional cytokine derived from ECs is described as promoter of tumor angiogenesis [17]. It is reported that PLGF augments ET-1 and endothelin-B receptor expression via HIF-1α [227].

The binding of VEGF is considered to increase vascular permeability through VEGFR-2 [210]. However, the role of PLGF, which specifically binds VEGFR-1, has been more controversial with both pro- and anti-angiogenic effects [47,244]. It is reported that PLGF-2 deficiency protects mice against vascular permeability [193], while mice having up-regulation of PLGF-2 have increased VEGF-induced permeability [217]. The latter is perhaps counterintuitive, since VEGFR-1 is considered to be a potent negative regulator of VEGFR-2 activity [14,39,44]. Most of the studies carried out for addressing the role of PLGF in VEGF-induced permeability conclude their findings in supporting PLGF-2 as a key factor for enhancing VEGF-induced permeability [48,88,223,244,305]. It is reported that variations in outcomes of PLGF-2 blockade on tumor angiogenesis [19,292] and the arrest of VEGF induced angiogenesis by PLGF-1 in some models [34,267] outline the unclear role of PLGF in angiogenesis. It is also reported that a placental growth factor variant PLGF1-DE is unable to recognize VEGFR-1 and inhibits VEGF-dependent tumor angiogenesis via heterodimerization [278]. In any case, it is worth noting that a larger number of studies reports a pro-angiogenic effect for PLGF, when it is expressed endogenously by tumor or stroma cells, or when a PLGF transgene is modestly over-expressed by tumor cells [4,74,162,183,200,278].

Several stimuli up-regulate the expression of PLGF in disease conditions, ranging from hypoxia, growth factors such as VEGF, TGF, TNF, HIF-1α, interleukines-1β, hormones, and oncogenes to physical stimuli are reviewed by Dewerchin and Carmeliet [80]. Oxygen is described to be a key regulator for maintaining the balance between VEGF and PLGF functions [5,198,250]. PLGF expression is stimulated under elevated partial pressure of oxygen (PO_2) and down-regulated by a low PO_2 [5,163], whereas VEGF and its receptors are up-regulated under hypoxia [319]. Angiotensin II, a cytokine that regulates cell growth, inflammation and fibrosis, up-regulates the expression of PLGF in human vascular endothelial cells and smooth muscle cells (SMCs) [225]. Recently it is reported that endothelial cell-released H_2O_2 as well as exogenously added H_2O_2 acts as a positive regulator of PLGF gene and protein expression in vascular SMCs. The PLGF regulatory role of H_2O_2 in SMCs was confirmed by inducing physiological stimulus of shear stress which elevates survival of endothelial cells resulting in vascular tubulogenesis and branching morphogenesis [263].

The current literature clearly figures out PLGF as a possible therapeutic target for the management of angiogenesis linked pathological conditions such as rheumatoid arthritis [310], diabetic retinopathy [172], diabetic wound healing [62], atherosclerosis [139] various types of cancers and inflammatory disorders [167]. Moreover, there are several other diseases such as ischemic cardiovascular disease, limb ischemia, skin wound healing, bone fracture repair, colitis, sepsis, nervous system disorders, and preeclampsia, which are aggravated by PLGF deficiency and improved by PLGF therapy. Paradoxically, there are still other diseases such as liver cirrhosis, cutaneous delayed-type hypersensitivity, and pulmonary emphysema, which can be improved following PLGF blockade [80]. A series of gain and loss of function experiments in animal models have clearly indicated that PLGF promotes pathological angiogenesis at different levels [74,80]. The circumstantial literature accumulated in recent years strongly encouraged the search for novel inhibitors of PLGF for therapeutic use. A neutralizing anti-PLGF antibody was developed and is currently in phase two of clinical trials [200]. Contrary to the above results, PLGF neutralizing antibodies give limited anti-angiogenic effects in an in vitro organotypic angiogenesis model [35]. Considering the therapeutic potential, the scientific enquiry for physiological functions of endogenous PLGF still continues, because the decipheration of its physiological role became crucial to predict the possible adverse affects of PLGF inhibitors [74].

2.5. Hepatocyte growth factor/scatter factor (HGF/SF)

The name hepatocyte growth factor (HGF) was assigned to this factor as it was discovered independently as a mitogen for hepatocytes and it is also called as scatter factor (SF) owing to its induced scattering in polarized epithelial cells. The angiogenic attributes of HGF is manifested primarily by binding to its endothelial cell transmembrane receptor tyrosine kinase, encoded by the *MET* proto-oncogene (c-met) [81]. HGF and its receptor are often up-regulated in cancer cells.

The HGF/c-Met axis is described to play a significant role in different stages of development and also in tumorigenesis [311]. HGF is expressed and secreted by a wide variety of tumor cells and can activate endothelial c-Met receptors in a paracrine fashion. In addition, c-Met is broadly expressed in several other pro-angiogenic cell types including ECs, neural cells, hematopoietic cells and pericytes. Expression of c-Met and HGF has also been identified in the vast majority of solid tumors [233]. Additionally, systemic blood levels of HGF are frequently elevated in tumor-bearing patients, and these levels correlate with tumor microvessel densities [7,265]. In the process of neovascularization, c-Met activation, through paracrine HGF, regulates tumor angiogenesis mainly by induction of proliferation, migration and survival of ECs.

While describing the mechanism of promotion of angiogenesis by HGF, it is described that HGF enhances vascular matrix degradation, endothelial cell invasion, migration by enhancing MT1-matrix metalloproteases (MMP) synthesis, activation of MMP-2 in human dermal microvessel ECs and coronary arterial EC lines. It is reported that HGF/SF can induce angiogenesis independently of VEGF, possibly through the direct activation of the Akt and ERKs pathways [259]. HGF also promotes angiogenesis, through up-regulation of VEGF and also via down-regulating thrombospondin-1 (a potent angiogenic inhibitor) expression [315]. Induction of VEGF by HGF was shown to be mediated by Mitogen-activated protein kinase (MAPK), Phosphoinositide 3-kinase (PI3K), Protein kinase C-zeta (PKC-zeta) and phosphorylation of specificity protein 1 (Sp1), which is a transcription factor and an efficient regulator of the VEGF promoter [242,315]. It is not clear whether activation of the c-Met receptor promotes angiogenesis directly. It was demonstrated that the activation of c-Met leads to VEGF expression which then contributes to the induction of angiogenesis [252,315]. However, this cannot be the only mechanism by which HGF promotes angiogenesis, since VEGF and HGF synergize in vitro as well as in vivo [303,304].

Controversial research findings are reported in relation to the mechanism of HGF mediated pro-angiogenic activity. In one study, TGF-β has been attributed in promoting angiogenesis and tumor invasion by stimulating HGF expression [61,181]. Conversely, the other study describes the TGF-β as inhibitor of HGF transcription, possibly by binding to a TGF-β inhibitory element situated around 400 bp upstream of the HGF transcription initiation site [191,235]. The molecular mechanisms and microenvironments controlling the positive or negative effects of TGF-β signaling on HGF regulation are not fully understood [58,142]. Similar to VEGF, expression of both c-Met and HGF is induced by HIF-1α (hypoxia inducible factor), further providing a role for c-Met/HGF in adverse microenvironment conditions to assist angiogenesis, cell survival and invasion [231,296].

Successful attempts of arresting the HGF and thereby angiogenesis have been described in the literature. A chimeric U1 small nuclear

RNA, i.e. U1snRNA/ribozyme transgenes designed for this purpose significantly inhibited the HGF and c-Met expression in human glioma cells; also histologic analysis of tumors treated with U1snRNA/ribozymes showed a significant decrease in blood vessel density [1–3]. Cao et al. [41] developed and tested antibodies against HGF. Their results showed that no single monoclonal antibody was capable of neutralizing the in vitro activity of HGF. The authors concluded that HGF possesses a minimum of three epitopes, that must be blocked to prevent Met tyrosine kinase activation [41]. Michieli et al. developed a soluble c-Met receptor consisting of a recombinant protein corresponding to the entire extracellular domain of c-Met, truncated before the transmembrane domain. This decoy c-Met, inhibited c-Met activation by HGF as well as ligand-independent mechanisms in various in vitro and in vivo cancer models. The authors showed that decoy c-Met impairs HGF-induced EC migration and vessel branching [205].

2.6. Angiopoietins

The Angiopoietins (ANGs), is a family of growth factors belonging to secreted glycoproteins with a dimeric molecular weight of approximately 75 kDa and described to be essential for blood vessel formation [13,280]. There are four types of ANG ligands such as ANG-1 ANG-2, ANG-3 and ANG-4. ANG-1 and ANG-2 are the best characterized angiopoietins, while ANG-3 and ANG-4 are orthologs found in mouse and human, respectively. As compared to other members of ANG family, controversial investigations have been made in relation to the role of ANG-3 and ANG-4 in angiogenesis [268]. Valenzuela et al. reported the antagonistic role of ANG-3, which interferes with ANG-1 activation of tunica intima endothelial kinase 2 receptor (Tie-2 receptor) [291] and also the function of Akt in tumor growth [306]. However, in another investigation, ANG-3 was strongly attributed with activation of mouse Tie-2 receptor, but the same was not found to occur in human counterpart, whereas ANG-4 did not demonstrate any such species selectivity with Tie-2 activation [180]. ANG-3 is reported to inhibit pulmonary metastasis by inhibiting tumor angiogenesis [306], while ANG-4 promotes in vivo growth of human glioblastoma multiforme (GBM) cells by promoting tumor angiogenesis, and directly activating extracellular signal-regulated kinase 1/2 (Erk1/2) in GBM cells [37].

The ligand ANGs signals their activity by binding with tunica intima endothelial kinase 2 receptor Tie-2 receptor [72,166,197,291]. It is interesting to note that ANG-1 and ANG-2 have different effects on neovascularization and development; however, they bind to Tie-2 receptor with distinct kinetics of release following binding, thus indicating that activation of Tie-2 receptor is regulated independently by these two molecules. In fact, ANG-2 is a natural antagonist of ANG-1 which binds to Tie-2 receptor without its activation, while ANG-1 acts as an agonist of the Tie-2 receptor [320,197]. Although ANG-1 and -2 exert antagonistic functions in tumor angiogenesis, yet both were observed to induce lymphangiogenesis [91]. There are several angiopoietin-like molecules that share the same structure and have sequence similarity to the angiopoietins but do not bind Tie receptors [282].

In the process of angiogenesis, ANGs are actually involved in the regulation of maturation and neovascular remodeling [95]. Among the regulators of vessel maturation, ANG-2 plays a key role. ANG-2 and VEGF act in synergy to induce angiogenesis and for the expression of MMPs that degrade the basement membrane [90]. ANG-2 binds the endothelial-specific receptor tyrosine kinase 2 and acts as a negative regulator of ANG-1/Tie2 signaling during angiogenesis, thereby controlling the responsiveness of endothelial cells to exogenous cytokines [13]. Under physiological conditions Ang-2 is only weakly expressed in endothelial cells (ECs). However, ANG-2 expression is dramatically increased during vascular remodeling, e.g., during tumor growth [321]. It acts in autocrine manner, endothelial cell-derived antagonistic ligand of the vessel maturation and remodeling–controlling ANG-1/Tie2 signaling pathway. The role of ANG-2 in Tie-2 receptor activation is similarly controversial. Embryonic ANG-2 overexpression results in a major disruption of the developing vascular system, suggesting an antagonistic role in angiogenesis [197]. Furthermore, it counteracts the angiogenic activity of VEGF and antagonizes the synergistic effect of VEGF with basic fibroblast growth factor in angiogenesis [65,182]. ANG-2 expression is increased in activated and hypoxic vascular endothelial cells in tumors, where it acts as an ANG-1 antagonist and promotes tumor angiogenesis and growth [92,94,141]. Elevated circulating ANG-2 was observed in patients with pancreatic ductal adenocarcinoma, and hence was associated with the extent of lymphatic metastasis [255].

Besides the destabilizing functions of ANG-2 towards resting ECs [253,281], ANG-2 has been reported to play an anti-apoptotic protective role for ECs under stress [69], which themselves are known for producing ANG-2 [77,273]. The vast body of literature published during a decade clearly suggests the possible binding of ANG-2 with integrins and activating them in non-ECs like myocytes, fibroblasts, glioma and breast cancer cells [45]. Nevertheless, recently ANG-2 has been shown to co-immunoprecipitate with $\alpha5\beta1$ integrin in ECs stimulated by TNF-α [171]. A hypothesis that ANG-2 may differentially signal via its cognate receptor Tie-2 and through integrins has been stated, owing to the differential expression pattern displayed by Tie-2 and angiogenic integrins in ECs [96]. It is reported that in genetically ablated ANG-2 mice, there occurs initial transient inhibition of tumor growth and angiogenesis [211]. Moreover, the blockade of ANG-2 with antibodies and peptide-Fc fusion proteins results in suppression of primary tumor growth and angiogenesis [36,94,220].

As compared to ANG-2, ANG-1 has been studied less. ANG-1 activates Tie-2 and triggers remodeling and stabilization of the newly formed vasculature which leads to its maturation [144,276]. ANG-1 is primarily expressed by mesenchymal cells and acts in a paracrine manner on the endothelium. It is also expressed by tumor cells [318], neuronal cells of the brain [274], also detected in CD68, CD163-positive macrophage, CD3-positive T lymphocytes, and CD22-positive B cells [111]. ANG-1 is secreted by peri-endothelial support cells [275], the recruitment of which is an important stage in the formation of new blood vessels. It has been reported that administration of ANG-1 independently of support cells, restores normal vascular remodeling, suggesting that ANG-1 acts directly on endothelial cells, reducing vessel permeability and promoting vascular integrity [290]. It is described that overexpression of ANG-1 modulates vascular endothelium to facilitate tumor cell dissemination and metastasis establishment [140]. In the newly sprouting vessels, ANG-1 shows diffused localization behind the leading edge of the new vessels [276]. In adenovirus-mediated gene transfer studies in a rat model, it was observed that ANG-1 induces broader, longer neovessels, with no increase in branching or sprouting. The study also revealed that ANG-1 and VEGF use different physiological mechanisms to enhance neovascularization of relatively avascular tissue. Administration of both growth factors combines these physiological mechanisms to give greater enhancement of neovascularization than either growth factor alone, suggesting the collaborative role during angiogenesis [27].

Although administration of exogenous ANG-1 protein induces vascular enlargement along with increased number of endothelial cells [16,284], the role of ANG-1 in tumor-associated angiogenesis remains controversial [268,280]. Surprisingly, ANG-1 has been implicated in the inhibition of pathologic vascular expansion via its effect on vessel maturation. Studies conducted in several tumor models have concluded that ANG-1 overexpression is associated with reduced tumor growth [134,135,272]. The down-regulation of ANG-1 in HeLa cells by antisense RNA was observed to have reduced tumor growth and angiogenesis. The observations described here indicates that ANG-1 promoting or inhibiting functions are dependent on the tumor cell type, the dosage and possibly on the amount of ANG-2 in the tumors.

As a part of designing novel anti-angiogenic agents, ANG-2 is one of the most intensely explored target molecules for the design and development of second-generation anti-angiogenic drugs arresting tumor growth and proliferation [144,169,201]. Nevertheless, a series of agents designed for targeting the ANG/Tie-signaling pathway, either alone or in

combination with VEGF inhibitors, are currently in phase I and phase II clinical trials (www.clinicaltrials.gov). Consistent with an anti-angiogenic mechanism of action, ANG-2 blockers decrease tumor vascularity [36,93,132,94], apparently via inhibition of vessel sprouting and/or reduction of vessel size [132]. Antibodies developed against ANG-2 not only inhibited ANG-2 but also VEGF-induced endothelial cell migration and proliferation during angiogenesis [40], which demonstrated enhancing functions of ANG-2 during VEGF induced angiogenesis. The results are also important in designing novel therapeutic approach in the case of VEGF resistant cancers. There is also evidence that targeting the ANG-2/Tie-2 signaling pathway may inhibit the functions of Tie-2-expressing macrophages, a subset of tumor-associated macrophages endowed with pro-angiogenic activity in mouse tumor models [75].

3. Targeting tumor angiogenesis: an attractive target with emerging challenges

From pathophysiological point of view, it is clinically substantiated that in the absence of neovascularization, tumors neither grow beyond a size of 2 mm, nor does it undergo metastasis. On the other hand, from a pharmacological point of view, it is practically not possible to make an access of anti-cancer drugs to the whole tumor body without an appropriate blood supply. This may be a paradoxical limiting factor for the efficacy of anti-angiogenic agents as well as for other anticancer drugs.

Consistent with the above situation, RK Jain in 2001, put forward a counterintuitive hypothesis of 'normalization of tumor vasculature' for improved efficacy of combination therapy with anti-angiogenic drugs [150]. After observing several clinical evidences in mice and even in humans, it was stated that the blood vessels of tumor are more complex, dilated, tortuous, hyperpermeable and not organized, so as to make the access of drug molecules with every cell of tumor body. Therefore, the complex orchestration of tumor vessels was the limiting factor for improving the efficacy of combination therapy [73]. Hence, it was argued that instead of killing the entire tumor vessels, let us normalize (organized vessel complex) it initially, so that the therapeutic efficacy of the combination therapy with anti-antiangiogenic therapy will improve. Preliminary preclinical studies in mice have demonstrated that anti-VEGF agents can successfully transform the complex nature of tumor vessels into a more mature and organized or normal phenotype of vasculature. The process of 'vessel normalization' was accompanied with formation of vessels having full basement membrane, increased vascular pericyte coverage, and reduction in hyperpermeability. It was also observed that, as a result of vessel normalization there was reduced hypoxia, interstitial fluid pressure and overall improvement in metabolic activity of tumor microenvironment. These changes in vessels are more conducive for improving the delivery and efficacy of exogenously administered anti-tumor agents. Similar a kind of clinical observations was made in patients taking anti-VEGF therapy for various kinds of solid tumors [123]. Therefore 'tumor vessel normalization' hypothesis and perhaps reality to a certain extent, advocates killing of blood vessels as a costly affair from therapeutic point of view.

'Targeting tumor angiogenesis' as therapeutic strategy has been described by many authors with different perspectives, such as angiogenesis: a curse or cure? [128], tumor angiogenesis: cause or consequence of cancer? [264], and tumor angiogenesis as a target for dietary cancer prevention [185]. We endeavor to describe tumor angiogenesis as an "attractive target with emerging challenges", owing to the current clinical status of anti-angiogenic therapy, experiencing limitations and challenges. Although tumor angiogenesis is an appropriate target and the benefits of anti-angiogenic therapy are well established for several tumor types however, an inbuilt threat of targeting tumor angiogenesis cannot be ignored, if the anti-angiogenic agents indiscriminately react equally with both physiological and pathological angiogenesis. Moreover, lack of efficacy of anti-angiogenic agents due to prevalence of compensatory angiogenesis pathways, and off-target toxicities unrelated to blockade of physiological angiogenesis, are few more alarming factors, limiting the clinical usage of this therapeutic approach [63,67,170].

With the advancement of technology and thereby more clear understanding of pathophysiology of tumor growth, a series of molecular targets have been described in the present 'target rich-lead poor' scenario of anticancer research. Folkman should be credited for describing the process of tumor angiogenesis as an attractive therapeutic target, besides the observations that tumors harbor heavy angiogenesis around themselves, was described nearly 100 years ago [46]. The discovery that tumors secrete diffusible angiogenic substance made in 1968 [125], followed by Folkman's proposal in 1971 attributing the tumor growth and metastasis as angiogenesis-dependent processes, tailored the idea of 'blocking angiogenesis' for therapeutic purpose [106].

The clinical and experimental data accumulated in the recent past has clearly figured out the requirement of up-regulated angiogenesis as a basic prerequisite for growth, proliferation and metastasis of tumor. Physiological angiogenesis process required for natural growth and development of animals is tightly regulated by maintaining a tight balance between endogenous pro-angiogenic and anti-angiogenic factors, what is termed as 'angiogenic switch' [188,212]. In general physiological notion, it is generally accepted that, the angiogenic switch is 'off' when there exist a balance between pro-angiogenic and anti-angiogenic factors. Conversely, it is made 'on', when the overall balance is in favor of pro-angiogenic factors [46,216]. It is described that this switch is specifically made 'on' during tumor growth and progression; however, this situation argues a question, as what is the status of angiogenic switch in tissues/organs other than tumor microenvironment? The clinical and epidemiological investigations cited in the recent past clearly warrant the decoding of detailed molecular mechanisms of regulation of angiogenic switch in physiological and pathological conditions. Such findings of integrated understanding might be helpful in tailoring novel and safe anti-angiogenic agents with improved therapeutic index.

4. Decoding the 'angiogenic switch': a key issue in developing tumor specific anti-angiogenic agents

Unraveling the molecular mechanisms of regulation of angiogenic switch both in physiological and pathological condition in general and the chaotic orchestration of neovascularization in tumor in specific, may rationalize the design and development of novel anti-angiogenic agents targeting tumor angiogenesis and perhaps escaping or making less impact on physiological angiogenesis. A series of scientific reviews have been cited in the recent past describing the role of pro-angiogenic and anti-angiogenic factors involved in the regulation of angiogenesis [28,47,54,128,161,188,216,243]. Concise and detailed information regarding the process of angiogenesis in physiological and pathological state with special reference to cancer and other diseases has been reviewed by [46]. The authors have attempted to focus on the integrated understandings of molecular events in physiological and pathological angiogenesis. A very informative review on genetic loss-of-function experiments in relation to different pro-angiogenic factors in developmental and tumor angiogenesis has been described with more focus on unstable and remodeling nature of vascular bed in tumors [152]. The role of endogenous inhibitors in regulating the angiogenic switch 'on–off' at the interface of pathological and physiological angiogenesis is not completely decoded [28,243]. Besides the significant efforts made towards understanding the regulation of angiogenesis process, the underlying mechanisms of regulation of angiogenic switch at the interface of pathological and physiological state are poorly understood (Fig. 2).

An updated list of endogenous inhibitors of angiogenesis is summarized in Table 2. Apart from the many small peptides and other factors, some new group of molecules like catecholamines have been implicated in the inhibition of tumor angiogenesis [54,55,251,279]. *Per say*, very limited research has been carried out in this area. From regulation

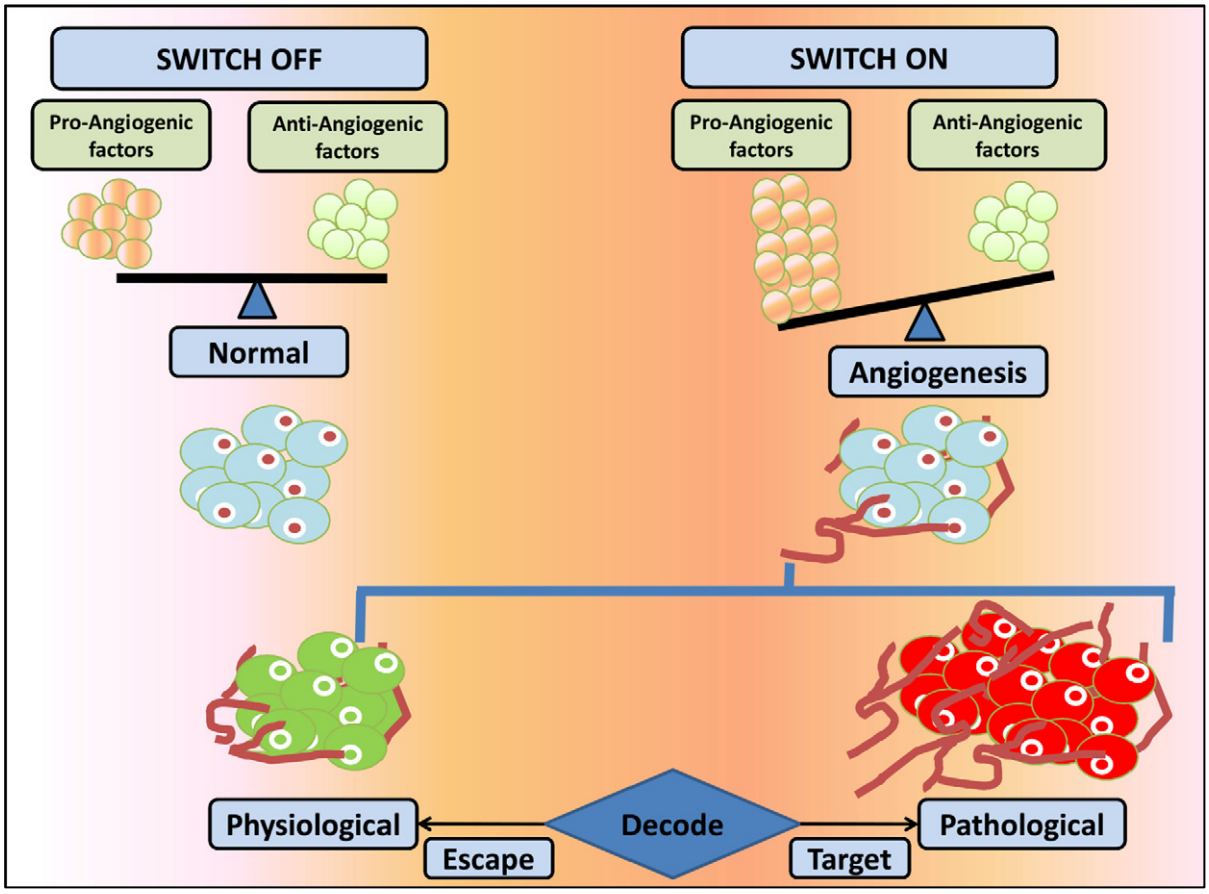

Fig. 2. Diagramatic illustrations of regulation of angiogenic switch with respect to balance between pro-angiogenic and anti-angiogenic factors (the upper portion). The lower portion describes two types of angiogenesis i.e. physiological (cells in green color) and pathological (cells in red color) and a hypothetical model proposed for targeting tumor angiogenesis and escaping physiological angiogenesis through decoding the angiogenic switch.

point of view, this pathway may be instrumental, in case the neurotransmitters happen to be an integral part of angiogenic switch and involved in regulating tumor angiogenesis. It is a well-known fact that there occurs a change in the expression of receptors of neurotransmitter in the pathological angiogenesis, thereby may be leading to change in the balance between stimulatory and inhibitory attributes of these molecules on neovascularization, resulting in rapid proliferation and metastasis of tumor [54]. Considering the pivotal role played by the catecholamines in regulation of angiogenesis, further research addressing the more specific implications of these neurotransmitters in angiogenic switch is needed, so as to develop it as a therapeutic target.

In a recent study, α-MSH (α-melanocyte stimulating hormone) has been described to inhibit angiogenesis through attenuation of VEGF/VEGFR2/Akt signaling in ECs. The results of the study revealed that administration of α-MSH significantly suppressed the microvessels sprouting in organotypic aortic rings, perturbed the vessel development in zebrafish and chicken embryos. α-MSH treatment also resulted in inhibition of MMP-2 secretion, migration and tube formation of HUVECs. Moreoevr, α-MSH decreased the VEGF expression and release in HUVECs [297]. Such type of studies opens new avenues for manipulating the angiogenic pathways.

Even more interesting and exciting investigations have been described in recent years, linking the role of microRNAs (miRs) in the negative regulation of angiogenesis [229]. These small miRs (non-coding), abundantly present in the eukaryotic genome are described to regulate gene expression at posttranscriptional level [21]. The function of miRNAs is mostly linked with the regulation of physiological processes such as cell differentiation, proliferation, and apoptosis [9,21]. Nevertheless, these molecules are also reported to drive the process of oncogenesis [68]. The miRs, especially the miR-200 family have been investigated for inhibition of angiogenesis. The results of the recent investigation clearly demonstrated that the miR-200 inhibit angiogenesis in ovarian, lung, renal and breast cancers by direct/indirect interactions with interleukin-8 and CXCL1 molecules, which are secreted by the tumor endothelial and cancer cells [229].

In another recent investigation, miR-542-3p was reported to inhibit angiogenesis and tumor progression by impairing the ANG-2's pro-angiogenic activity. It was observed that in cultured ECs, miR-542-3p inhibited translation of ANG-2 mRNA by binding to its 3′ UTR, and addition of miR-542-3p to cultured ECs inhibited angiogenesis [136]. In an interesting investigation involving gain- and loss-of-function studies, miR-26a has reported to inhibit VEGF-A expression in human hepatocellular carcinoma (HCC) cells. Through a series of experiments, it was verified that miR-26a suppresses tumor angiogenesis of HCC, through HGF-cMet signaling pathway [308]. The miR-101 was reported to inhibit cholangiocarcinoma angiogenesis through targeting VEGF [312].

Moreover, the angiogenesis research in the last three decades resulted in describing the additional complementary angiogenic pathways cantered around HIF, PDGF, FGF, ANG, Notch pathway and many other inflammatory messengers of angiogenesis [237,301]. These pathways might help in deciphering the molecular aspects of angiogenic switch. More kinds of such fine molecular investigations may raise a significant hope of maneuvering miRs as well as other players as novel tools for manipulating the angiogenic switch [22,229]. Perhaps these tools may possibly allow manual regulation of angiogenic switch preferentially respecting the physiological angiogenesis and discriminating the tumor angiogenesis.

Table 2
An updated list of endogenous angiogenesis inhibitors having direct or indirect negative impact on process of angiogenesis.

Angioarrestin	Natriuretic peptides
Angiopoietin-2	Osteopontin fragment
Angiostatin (Plasminogen fragment)	PEX
Antiangiogenic antithrombin fragment III	PEDF (Pigment epithelium-derived factor)
Arresten	PAI (Plasminogen activator inhibitor)
Canstatin	Placental ribonuclease inhibitor
Chondromodulin I	PF-4 (Platelet factor-4)
CD59 complement fragment	Prolactin 16-kDa fragment
CTGF (Connective tissue growth factor)	Proliferin-related protein
Decorin	Prothrombin kringle 2
Dopamine	Restin
Endorepellin	Retinoids
Endostatin (collagen XIII fragment)	Soluble fms-like tyrosine kinase-1 (S-Flt-1)
Fibronectin 20-kDa fragment	Somatostatin
Fragment of SPARC	Targeting fibronectin-binding integrins
Ghrelin	Tetrahydrocortisol-S
Gro-beta	TIMPs (Tissue inhibitors of matrix metalloproteinases)
HCG	Thrombospondin-1 and -2
Heparinases	Transforming growth factor-β (TGF-β)
Heparin hexasaccharide fragment	Troponin-1
Interferons-$\alpha\beta\gamma$	TSP-1
IL-4 (Interleukin-4)	Tumstatin
IL-10 (Interleukin-10)	Vasculostatin
IL-12 (Interleukin-12)	Vasostatin (calreticulin fragment)
IL-18 (Interleukin-18)	
IP-10 (Interferon-inducible protein-10)	Vascular endothelial growth factor inhibitor (VEGFI)
Kallistatin	
Kringle 5 (Plasminogen fragment)	
Maspin	
α-MSH (α-melanocyte stimulating hormone)	
Metastatin	
METH-1	
METH-2	
miR 200 family	
2-Methoxyestradiol	

5. Current status of anti-angiogenic therapy

Undoubted, antiangiogenic therapy has significantly contributed in extending the survival of cancer patients across the world. However, limited efficacy, drug resistance, side effects, toxicity and other clinical problems have re-accredited this therapeutic approach as a paradigm of 'successful therapy with challenges'. Currently, there is information of twenty antiangiogenic drugs described at the website of drug bank (www.drugbank.ca). An information displayed at 'Angiogenesis Foundation' website (www.angio.org), stated that there are thirteen US-FDA approved anti-angiogenic drug categorized as a) monoclonal antibodies designed against the specific pro-angiogenic growth factors and/or their receptors; b) tyrosine kinase inhibitors (TKIs) of multiple pro-angiogenic growth factor receptors; and c) inhibitors of mTOR (mammalian target of rapamycin). Among the monoclonal antibodies bevacizumab is the most widely prescribed combination therapy for the treatment of a variety of cancers [47]. The other antibodies approved for limited cancer treatment includes cetuximab (binding Epidermal growth factor receptor (EGFR), trastuzumab (binding HER-2), and panitumumab (binding human EGFR). In August 2012, US-FDA has approved ziv-aflibercept (Zaltrap®): a recombinant fusion protein, for the treatment of patients with metastatic colorectal cancer in combination with other anticancer drugs (www.cancer.gov). Many other antibodies such as HuMV833 (binding VEGF121 and VEGF165 isoforms), IMC-18F1, IMC-1121B, ImClone (Binding VEGFR-1 or 2) are under testing at various stages of clinical trials [94]. Recently, a novel and economically affordable human anti-VEGF neutralizing antibody, MIL60, has been developed. MIL60 has almost the same affinity like Avastin, and demonstrated inhibition of VEGF-induced endothelial cell proliferation, migration and tube formation. Moreover, MIL60 also inhibited tumor growth and angiogenesis in in vivo xenograft models of human colon carcinoma and ovarian cancer [307]. A single chain antibody (scFv), has been successfully developed against Ang-2, and the scFv–Ang-2 complex showed remarkable in vitro and in vivo inhibitory effects on the angiogenesis and tumor growth of human hepatocellular carcinoma [313].

There are seven TKIs that are currently approved as anti-angiogenic agents, like axitinib (Inlyta), cabozantinib (Cometriq), pazopanib (Votrient), regorafenib (Stivarga), sorafenib (Nexavar), sunitinib (Sutent), and vandetanib (Caprelsa) to be prescribed as combination therapy for the treatment of different cancers (Angiogenesis Foundation; www.angio.org). Moreover, currently there are over 3954 clinical trial studies in angiogenesis that are displayed at the website of the U. S. National Institute of Health (www.clinicaltrial.gov). In the recent past, a series of reviews have described a variety of anti-angiogenic agents being tested at various levels of clinical trials [60,85,94,128,148,218]. At the end of 2011, around 21 anti-VEGF pathway agents have successfully completed phase III trials and unfortunately, 30 agents were terminated from phase III clinical trials [85]. In 2010, FDA withdrew its approval for Bevacizumab as a therapeutic drug for the treatment of metastatic breast cancer, (HER2-negative) on accounts of its toxicity and lack of survival benefits to patients and even Sunitinib has remained ineffective in treating this disease [299]. The data described above indicates the overall upsurge, excitement, sensitivity and challenges in designing novel agents of anti-angiogenic therapy.

6. Factors limiting the efficacy of anti-angiogenic therapy

6.1. Limited efficacy

Perhaps the most discouraging clinical evidence observed in recent years, limiting the efficacy of antiangiogenic therapy, is the aggressive recurrence of tumors after withdrawal of anti-angiogenic treatment [84]. A recent clinical observation in the case of renal cell carcinoma patients, also reported the accelerated proliferation of endothelial cells and thereby rapid angiogenesis after withdrawal of sunitinib anti-angiogenic drug [126]. Similar kind of observations were made by Pa'ez-Ribes et al. [239], wherein, it is reported that although the anti-VEGFR2 antibody DC101 arrest tumor growth, but at the same time it increases the rate of tumor invasion and metastasis. Various tumor-dependent molecular events such as increased expression of prometastatic proteins (c-Met, IL-6, IL-8, and urokinase-type plasminogen activator receptor), suppression of antimetastatic mediators (myoglobulin), altered adhesion (up-regulation or activation and secretion of exomal proteolytic enzymes, such as matrix metalloproteinases), acute hypoxic stress, instigation of tumor epithelial–mesenchymal transition, increased vascular co-optive behavior, activation of alternative angiogenic pathways (FGF and ephrin), induction of stromal autophagy, and resistance of cancer stem cells are described as possible molecular mechanisms for aggressive invasion and metastasis of tumor after withdrawal of anti-angiogenic drugs. Apart from this, there are several possible tumor-independent mechanisms described in this relation [85].

Owing to the genetic stability and quiescent nature of endothelial cells under normal physiological conditions, it was earlier believed that anti-angiogenic therapy may not be toxic as compared to other chemotherapeutic anticancer drugs, however, this turned out to be an illusion. There are several reports accumulated in the recent time, focusing on the adverse effects such as bleeding, thrombotic events, hypertension, proteinuria, leukopenia, lymphopenia, hyperthyroidism and many others [157,174,294]. Apart from these classical angiogenesis-related side effects, there are several symptomatically apparent toxicities associated with different classes of anti-angiogenic drugs (Supplementary Table 1).

6.2. Emergence of acquired drug resistance

Like toxicity, it was also initially thought that the anti-angiogenic drugs may bypass the barrier of drug resistance owing to the same rational described for toxicity. However, a plethora of clinical literature has cited, describing the cases of VEGF-pathway targeted drug resistance in a variety of cancer treatments [29,63,138]. Besides the initial encouraging effect of angiogenesis inhibitors in clinical practice, majority of the metastatic colorectal cancer (mCRC) patients showed very poor response to anti-angiogenic therapy in the subsequent treatment [138]. Therefore, the emergence of acquired resistance is an upcoming and perhaps the most important efficacy limiting factors of the anti-angiogenic therapies [160].

Various factors have been attributed in addressing the mechanisms of resistance to anti-angiogenic therapies. Broadly, three important possible mechanisms (Fig. 3), such as VEGF dependent, VEGF independent and mechanisms involving stromal cell interactions are described as the underlying causes of acquired drug resistance [63,138,160]. The extent of drug resistance mechanisms outlined above, cannot be equally applied to all cancers; however, they are highly variable with respect to type of cancer and depend on the type of anti-angiogenic drug used for blocking VEGF axis. While explaining the mechanism of VEGF-dependent drug resistance, it has been proposed that when VEGFA is targeted for arresting its activity by bevacizumab; the other pro-angiogenic peptides like VEGFB, VEGFC, VEGFD and PLGF may be involved in VEGFR signaling and thereby supporting tumor angiogenesis [63]. Evidence to this hypothesis was observed in patients, wherein it was observed that the plasma levels of PLGF, VEGFC and VEGFD were found to be elevated even when the treatment of anti-angiogenic drugs like FOLFIRI with bevacizumab was in progress [170]. In addition, VEGF-blocked induced prevalence of hypoxic environment has been implicated as one of the culprits for acquired drug resistance. It is described that the inhibition of VEGF causes hypoxia in tumor tissues. Under such circumstances, majority of the tumor cell proliferation ceases due to lack of sufficient oxygen, which ultimately may result in the death of major population of tumor cells. There is every possibility of survival of hypoxia tolerant clad of tumor cells, which can be called as cancer stem cells [208]; having a role in eliciting tumor angiogenesis. There are some reports which focus the role of such tumor cells, which are adapted to poorly oxygenated niches and increasing the tumor invasiveness and metastasis [84,239]. However, the clinical and preclinical data does not support the concept of VEGF-blocked induced tumor aggravation [206].

The VEGF-independent mechanism of drug resistance is centered on FGF, which plays a significant role in tumor angiogenesis. In many model studies, FGF2 or bFGF has demonstrated hyperactive pro-angiogenic activity, even better than VEGFA. Moreover, synergistic activity of FGF2 or bFGF with VEGFA is also responsible for recruiting angiogenesis via endothelial cell migration, proliferation and survival [232]. A similar kind of synergy is observed in inhibiting tumor angiogenesis when anti-VEGF and anti-FGF drugs are given in combinations [64]. It is believed that the up-regulation of proangiogenic factors NRP1 and HIF 1 might be a consequence of interplay between FGF and VEGF signaling through multiple mechanisms, resulting in increased VEGF signaling and thereby increased angiogenesis [190,266]. Clinical evidence to this paradigm was observed by Kopetz et al., wherein he observed the elevated levels plasma FGF and PDGF in mCRC patients receiving FOLFIRI with bevacizumab as combination therapy [170].

Two more signaling pathways i.e. delta-like ligand 4 (Dll4)-Notch and Ang-Tie axis are also described to be associated with VEGF-independent mechanisms of acquired drug resistance. Dll4 is mainly expressed on endothelial cells of arteries and up-regulated in malignant tumors. The

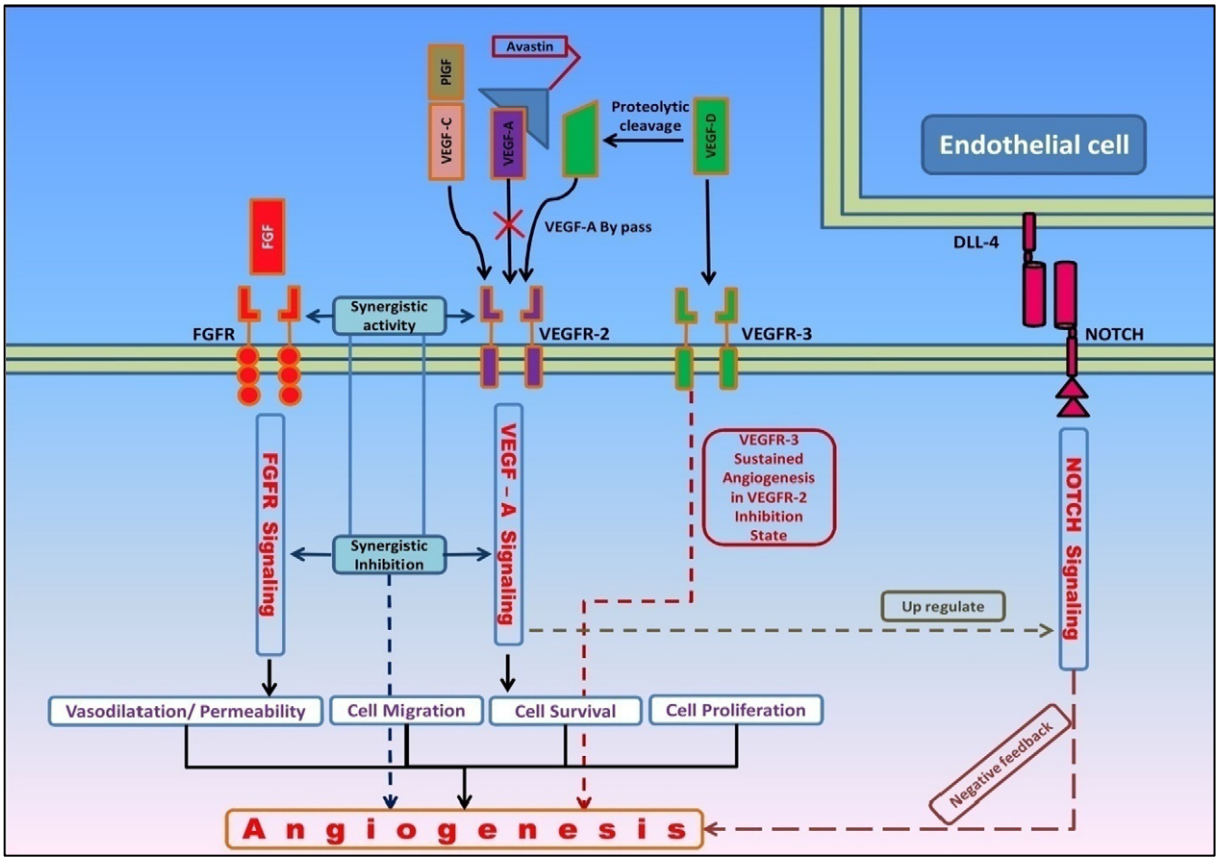

Fig. 3. Diagramatic representation of mechanisms of resistance to anti-angiogenic therapy.

combined action of Dll4 and Notch is reported to be involved in anti-angiogenic resistance in VEGFA targeted therapies [155,283]. Activity of VEGFA up-regulates the Dll4 and Notch axis; however, under physiological conditions Dll4 and Notch act as a negative feedback mechanism for angiogenesis [283]. The pro-angiogenic role of Ang–Tie signaling pathway is well established. It is reported that the binding of Ang1 with Tie 2 results in vessel maturation, reduces the vascular permeability and promotes vessel stabilization. On the other hand, antagonization of Ang1 by Ang2 leads to the formation of new blood vessels, by destabilizing the junctions of pericytes-endothelial cells and also promotes cell proliferation, migration and survival [51].

A stromal cell-dependent mechanism of resistance is attributed with involvement of variety cells, including Flk1 + endothelial progenitors and other pro-angiogenic tumor infiltrating immune cells in the tumor stroma, having pro-angiogenic functions in neovascularization [101,42]. It is experimentally proved in animal model studies that paralyzing the functions of endothelial cell progenitor (ECP), leads to reduced angiogenesis and thereby extending the survival of the animal [116,43]. Evidence to this fact was demonstrated in murine model studies, wherein the treatment of anti-VEGFR2 monoclonal antibodies reduced the number of ECPs and arrested the tumor growth [261,44]. Therefore it was believed that suppression of ECPs might be one of the possible mechanisms in imparting resistance to anti-VEGF therapies. Apart from ECPs, the secreted cytokines such as Granulocyte colony-stimulating factor (G-CSF), PLGF, stromal derived factor (SDF) 1α, also recruit distinct immune cells in the tumor microenvironment. The pro-angiogenic factors secreted by these cells, may be recurring the neovascularization and thereby acting as potential factor in resistance to anti-VEGF therapies [101,260,269]. Recently, a glycosylation-dependent lectin–receptor interaction pathway is implicated in conferring resistance to anti-VEGF refractory tumors. It was experimentally demonstrated that glycosylation-dependent binding of Galectin-1 to ECs, mimics VEGF-A function. The authors also suggest that targeting glycosylation-dependent lectin–receptor interactions may circumvent the problem of resistance and increase the efficacy of anti-VEGF treatment [67].

6.3. Non-availability of valid biomarkers

Biomarkers are the indicators of normal physiological or pathogenic processes and also furnish information about pharmacologic responses towards a specific therapeutic approach. In brief, biomarkers play a crucial role in judging the efficacy and dosage of specific therapeutic regime, at the same time play an important role in the overall management of a disease. In clinical practice, generally there are four categories of biomarkers such as prognostic, predictive, pharmacodynamic and surrogate biomarkers. Biomarkers that inform on the progression of disease (i.e. over-all outcome of cancer) regardless of treatment being used, are termed as prognostic biomarkers [322,151]; at the same time a predictive biomarker present clues on the effect of a therapeutic mediation [219]. An ideal pharmacodynamic biomarker should indicate an appropriate change or alteration in a biological process or target. This can only be observed, if a biomarker is absolutely coordinated with the treatment outcome. In this way, it is one of the predictive biomarkers. It is to be noted that classification of biomarkers should be coupled with context, since their identification is carried out through the major multidisciplinary areas of the biomedical field and hence categories of biomarkers can be overlying/overlapping in nature [207]. On the other hand, surrogate biomarkers are defined on the concept of surrogate endpoints. Surrogate biomarkers are based on fundamental relationship between treatment effects on the biomarker, and on the clinical endpoint [145]. For example, Jain et al. [151] tried to define and validate surrogate biomarker on the basis of relationship between development of bevacizumab induced dose-limiting toxicities and normalization of tumor vasculature via radiation and chemotherapy [302].

The importance of valid biomarkers in cancer therapy is indispensible as the classification of cancer cells is based on the presence of specific biomarkers [228]. With the advancement in bio-analytical technology and clinical biochemistry, a series of potential biomarkers belonging to physiologic, genetic, circulating, tissue, and imaging class of biomarkers for antiangiogenic therapy (for colon, breast, renal, thyroid, and liver) have emerged from the recent clinical investigations [109,153,177,187,262,286,300]. However, no validated or cancer-specific biomarkers exist in the current clinical practices, which may guide for selecting the specific cancer patient, for specific anti-angiogenic therapy. Moreover, the biomarkers that could identify the escape pathways, which can be possibly targeted after the development of resistance to anti-angiogenic therapy, are also not developed in the current mainstream of clinical diagnosis [151,300].

Jain et al. [151] have very extensively reviewed the need of biomarkers for anti-angiogenic therapy, by raising a series of rational clinical questions addressing the need of development of valid biomarkers for increasing the efficacy and impact of anti-angiogenic therapy. The authors have also highlighted the possible challenges that may arise in developing and validating the biomarkers for anti-angiogenic therapy. Pharmacodynamic biomarkers can be conveniently used as a marker to ascertain whether the treatment induced biochemical change has any outcome in the form benefits to patient; however, this is only possible, if the used biomarker coincides with the treatment regimen. It is a well-known clinical observation that hypertension is a general side effect of anti-VEGF therapy, and it is commonly used as pharmacodynamic biomarker in anti-angiogenic therapy [146]. Non-validation of this biomarker in the context of anti-angiogenic therapy, limits its usage in clinical practice, as Hurwitz et al. have reported that the increase in blood pressure may not be induced by Bevacizumab, nevertheless, the clinical observations clearly indicate that hypertension cannot be considered as prognostic biomarker for advanced cancer patients [147].

As of today the most extensively explored biomarker in anti-angiogenic therapy is VEGF [38,151]. Besides the significant importance of VEGF as biomarker, its non-validation has created a chaotic situation in using it as a predictive circulating biomarker for ascertaining the efficacy of anti-angiogenic therapy. Many clinical investigations have shown that the baseline levels of VEGF are not in tune with the response of anti-angiogenic regimen. In one of the phase III clinical trial designed for analyzing the combined effect of Bevacizumab and anticancer agent mCRC, it was observed that the VEGF levels in primary tissue cannot be correlated with the response [154]. More or less similar kinds of confusions are associated with a series of biomarkers (VEGFRs, PLGF, ANG-2, SDF, IL-6, IL-8, CECs, Vascular cell adhesion protein or VCAMs, MMP-9, etc.), that have potential to be explored in determining the efficacy of anti-angiogenic therapy [204,300]. Therefore, on the eve of emerging acquired drug resistance, the validation of cancer-specific biomarkers responding to anti-angiogenic therapy is indispensable for increasing the efficacy of this therapeutic regime.

7. Challenges and future prospectus of the anti-angiogenic therapy

Successful clinical attempts of anti-angiogenic agents in increasing therapeutic index of anti-tumor drugs, either alone or in combination, and the emerging clinical limitations reported in recent years, clearly warrant a designing of some novel strategies to circumvent the aforesaid problems, which *per say* are the challenges for increasing efficacy of anti-angiogenic therapy. The first important priority is the development of targeted anti-tumor agents discriminating the tumor cells and their normal counterparts through intervention of agents/tools having potential to regulate the 'angiogenic switch' positively and negatively towards physiological and pathological angiogenesis respectively. Low efficacy of anti-angiogenic agents, aggressive recurrence, rapid metastasis of tumor after withdrawal of anti-angiogenic drugs, and acquired drug resistance are still promising challenges and certainly, opportunities for the clinicians and researchers to unlock the mysteries

underlying these adverse clinical manifestations. More precisely, future settings of antiangiogenic therapies should capitalize more on understanding the compensatory angiogenesis pathways, along with identification of molecular signatures, which can delineate sensitivity to anti-VEGF treatment [67].

As a part of describing the solutions to challenges in anti-angiogenic therapy, Ebos and Kerbel [85] have given more stress on designing suitable cancer models for evaluation of anti-angiogenic therapy at various stages of tumor development. According to the authors, the most appropriate model studies may uncover the unknown differential activity of the therapeutic agent in different settings and possibly such attempts might be useful in evaluating the toxicity of anti-angiogenic agents [85]. Jain et al. [151] have described a series of challenges in identifying biomarkers for anti-angiogenic therapy, which includes defining adequate criteria of response, heterogeneous and dynamic nature of cancer, inability to perform repeated biopsies (before and after antiangiogenic therapy), inherent design of clinical trials, unpredictability of response or toxicity, resistance by activation of tumor VEGF-independent angiogenic pathways, optimization and standardization of various biomarker assays [151]. Besides the previously mentioned challenges, it is very important to translate the candidate biomarkers of anti-angiogenic therapy into valid biomarkers, for increasing the efficacy, personalization of medicine and for improving the overall marker guided therapeutic index of this regimen.

The future of any therapeutic regimen is strongly influenced by the related technological advances. Nanotechnology in specific has made a significant impact on clinical therapeutics, diagnosis and being, constantly updated to meet the requirements of the present day clinical practices. Anti-angiogenic therapy is also not an exception to this ongoing trend. Sufficient literature has been cited in the recent past, describing the advances in nanoscale delivery of anti-angiogenic agents [57,122,131,258]. Administration of anti-angiogenic drugs using nanoparticle mediated drug delivery (NPDD), is of immense importance from a clinical point of view, as it is already validated that NPDD has longer circulation half-lives of drugs, enhances the therapeutic efficacy, marginalizes the side effects of the drugs, selective targeting of the tumor tissue/vasculature and improves the overall pharmacokinetics [20,71,230,314].

In recent years, combination or synergistic therapy and NPDD have a significant impact on improving the efficacy of anticancer drugs. In the current clinical practices, mostly the anti-angiogenic therapy is prescribed as combination therapy (www.clinicaltrial.gov). It is also reported that the combination of two or more drugs has synergistic effect on target, which may improve the therapeutic index and also help to suppress drug resistance through multiple mechanisms [143]. Perhaps the rational linking of NADD with anti-angiogenic therapy might be a potential area of research to circumvent the present challenges of anti-angiogenic therapy.

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