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REVIEW ARTICLE

Role of Growth Factor Signaling in Cancer

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ABSTRACT

Growth factors may be defined as any group of protein that stimulate the growth of specific tissues and play an important role in promoting cellular differentiation and cellular division. Growth factors impart one of the important hallmark of cancer i.e sustaining proliferative signaling. They may act through paracrine, autocrine and endocrine signaling to effect growth and proliferation of cancer cells. They may act through various signaling cascades like MAPK, PI3K/AKT, JAK/STAT etc to activate their downstream mediates affecting various pathlogical and physiological functions. Abrupt signaling patterns of growth factors can induce oncogenic transformations. An enhanced understanding of these pathways can help targeting neoplastic transformation at an early stage. This review summarizes various mechanisms for targeted therapeutics against growth factor in cancer and their future prospective.

Keywords: Growth factors, cancer, paracrine, autocrine, signaling, ligands, kinases, inhibitors

1. INTRODUCTION

Growth factors may be defined as any group of protein that stimulate the growth of specific tissues and play an important role in promoting cellular differentiation and cellular division[1]. Growth factors generally act through paracrine and autocrine signaling. Contrary to original belief, they may also act in endocrine manner. Among these autocrine mechanism is thought to play a significant role in growth of cancer cells[2,3]. Growthfactors have diverse mode of action but mostly act through tyrosine kinase receptor pathway. Tyrosine kinase receptors are membrane bound complexes having intrinsic kinase activity on cytoplasmic domain. Upon binding of specific growth factors (ligand) their kinase activity is activated and they phosphorylate their downstream targets on their tyrosine and serine residues to recruit other molecules into signaling cascades[3].

1.1 Growth Factors: Role in Imparting an Important Hallmark of Cancer

Cancer is defined as a cell that grows uncontrollably and hence sustaining chronic proliferation is the most important characteristic of cancer[5]. This excellent proliferative property is imparted largely by growth factors.

Literature suggests link between oncogenes and growth factors[6]:

1. Protooncogene*C-sis* codes for B-chain of PDGF[7]
2. C-erb codes for EGF receptor[8]
3. C-fms oncogene is similar to CSF-1[9].

Secondly, evidences suggest that growth factors can increase transcription of certain proto-oncogene (*myc* and *fos*)[10]. Cancer cells may produce growth factors themselves or may send signals to stimulate normal cells to secrete growth factors[5].

2. CLASSIFICATION OF GROWTH FACTORS

Growth factors are generally classified in following classes[4]:

2.1 Platelet Derived Growth Factor Family

Platelet derived growth factor (PDGF) is initially released from alpha-granules of platelets and act as a chemoattractant for fibroblasts and as mitogenfor these

Table 1. Growth factors are generally classified

S No.	Growth factors
1.	Platelet derived growth factor family
2.	Vascular endothelial growth factor family
3.	Epidermal growth factor family
4.	Fibroblast growth factor family
5.	Transforming growth factor-B family
6.	The Insulin family
7.	Hepatocyte growth factor family
8.	Neurotrophin family
9.	The Ephrin family
10.	Angiopoietins

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cells[11]. PDGF stimulates production of collagenase by fibroblasts causing remodeling of matrix required for tissue repair[12]. It is also released from activated macrophages[13]. Platelet derived growth factor (PDGF) family of growth factor consists of 5 different disulphide linked dimmers PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC and PDGF-DD that act via 2 receptors PDGFRα and PDGFRβ[19]. Platelet derived growth factor receptors (PDGFR) are receptors with intrinsic tyrosine kinase activity that regulates several functions in normal cells[14]. PDGFR play a role in development of lungs, heart, CNS and kidney[15]. Inaddition to physiological functions, PDGF play pathological roles in disease such as atherosclerosis[16], glomerulonephritis[17] and cancer[18].

In context of cancer, PDGF help in blood vessel formation, cell migration and metastasis. Overexpression of V-sis oncogene product PDGF enhances transformation[19]. PDGF signaling is critical for cell-cell communication as PDGF ligands are expressed and secreted by epithelial or endothelial cells to recruit and activate PDGF receptors in stromal components such as smooth muscle cells, pericytes and fibroblasts. Cancer cells express PDGF ligands and its cognate receptors, hence inducing both autocrine and paracrine signaling which helps in cancer progression[18].

Expression of PDGFRα has been reported in breast carcinoma. According to clinical studies on human breast cancer samples 39.2% of invasive ductal carcinoma PDGFRα is present which attributes aggressiveness as it metastasizes to lymph nodes and shows HER2 and Bcl2 expression[19]. Simultaneous expression of PDGF-A and PDGFR-α in epithelium, stroma and endothelium of invasive breast carcinoma suggests possibility of autocrine and parcrine signaling which promotes angiogenesis. Hence PDGFα has emerged as a potential target of breast cancer[20]. PDGFRβ is upregulated and activated in prostate cancer of which it is overexpressed in 88% of primary prostate cancer and 80% of metastasized bone lesions[21]. PDGF-D was identified as a ligand for PDGFRβ and the serine protease matripase as its extracellular proteolytic activator in prostate cancer[22]. PDGF-BB isoform promotes growth of human oseophageal carcinoma cell lines and prevents apoptosis of cancer cells[23]. Additionally overexpression of PDGFRβ is associated with tissues of esophageal cancer[24]. PDGF-C and PDGF-D ligands play a role in development of brain tumor and PDGF autocrine signaling regulates survival and mitogenic pathway in glioblastoma[18]. In coordination with these studies it has also been found that antitumor effect of chemotherapeutic agents can be enhanced by inhibiting PDGF receptor signaling in tumor stroma.

2.2 Vascular Endothelial Growth Factor Family

Humam vascular endothelial growth factor (VEGF) family consists of VEGF-A,VEGF-B, VEGF-C, VEGF-D and Placental Growth factor[25]. There are 3 receptor which are regulated by protein kinase for VEGF family of ligands: VEGFR1, VEGFR2, VEGFR3. And two non-enzymatic receptors: Neuropilin1 and Neuropilin-2[26]. VEGF is secreted by any cell that encounters hypoxia[27]. VEGF acts as a mitogen thereby being important survival factor for endothelial cells and monocyte motility[28]. VEGF changes permeability of endothelial cells by causing injury to help angiogenesis[29].

Major factors regulating VEGF includes growth factors, local environmental hypoxia, hormones and cytokines[30]. The key regulator of hypoxia induced angiogenesis is transcription factor Hypoxia-induced-Factor (HIF-1)[31]. It was very early proposed that inhibiting angiogenesis can be effective antitumor strategy because tumor growth required for blood vessel formation[32]. VEGF mRNA is expressed in neoplastic cells where as endothelial cells express VEGFR1 and VEGFR2 mRNA and proteins[33]. The increase in blood vessel formation helps tumor to gain necessary oxygen and nutrient. Tumor angiogenesis is a hall mark of cancer which supports tumor growth and metastasis[34].

VEGFA binds to progenitor cells which express VEGFR1 and induce suppression of NF-κB activation and signal transduction pathway[35]. In Breast cancer, VEGF-A expression is associated with increase in microvessel density[36]. Clinical trials confirm that VEGF expression is an indicator for relapse –free survival[32,37]. It has also been found that VEGF is essential for initial subcutaneous growth of breast carcinoma cells[38]. Recent studies also suggest that upregulated VEGF-A is associated with poor prognosis in non-small cell lung carcinoma[39]. Low VEGF-D to VEGF-C ratio in tumors correlates with both lymphnode metastasis and lymphatic invasion by cancer cell[40]. In colorectal cancer, VEGFA expression is stepwise upregulated for MVD and VEGF-C correlates with extent of lymph node metastasis[36,40]. In prostate cancer VEGFA expression is reported to play a role in advancing focal carcinoma, invasion and metastasis[32].

Because of above vital roles VEGF plays in cancer via upregulating angiogenesis there is lot of focus on targeting VEGF for advanced anti-cancer strategies. Antibody based strategies to target VEGF are extensively being studied. Currently more than 20 monoclonal antibodies are approved by FDA for therapeutic use[41]. Example:

1. Monoclonal antibodies
    a. Rituximab against CD20 for non-hodgkin lymphoma[42]
    b. Trastuzumab for breast cancer[43]
    c. Cetuximab for metastatic colorectal cancer and head and neck cancer[44]
2. Antibodies with fusion protein
    a. Bevacizumab for metastatic colorectal cancer and non-small cell lung cancer and metastatic breast cancer[45].

2.3 Epidermal Growth Factor Family

Epidermal growth factor family (EGF) is a complex network that modulates growth of cells. EGF is released by cells and then either by autocrine signaling i.e. stimulates its own growth or paracrine signaling i.e. stimulate growth of neighboring cells[46]. Ligands known to bind to EGFR are Epidermal growth factor (EGF), Transforming Growth Factor-α (TGF-α), amphiregulin, heparin-binding EGF-

like growth factor, Betacellulin and Epiregulin[47]. EGFR are Receptor tyrosine kinases and they belong to ErbB family which consists of Erb-1 (EGFR), ErbB-2 (HER2 or Neu), ErbB-3, Erb4[48]

EGF has been known to be mitogenic for mesenchymal and epithelial cells[49]. EGF stimulus to normal cells causes them to transform into neoplastic cells by increasing the level of phosphotyrosine in proteins[50] and increase in sugar and aminoacid metabolism. Expression of *c-fos* and *c-myc* is upregulated by EGF[51]. EGF has also been found to play a vital role in viral carcinogenesis as it enhances viral transformation of cells[52]. Chemical carcinogenesis of methylcholantherene in skin is enhanced by EGF[53]. EGF phosphorylates tyrosine residues of src, erb, abl, yes, fgr, ros, fes (fps) and fms[54].

Human breast cancer cell line like MCF-7 was found to synthesize and secrete EGF-like immunoreactive factor in culture[55]. Prostate cancer cell lines DU-145 were also found to secrete EGF-like polypeptides into serum-free culture medium[56]. Overexpression of TGF-α and EGFR by carcinomas are correlated to chemotherapeutic resistance, metastasis, and poor prognosis[57]. EGF-like peptides and erbB receptor induce transformation of cells in transgenic mice models. Evidences support that expression of rodent p-185c-neu and EGFR in Nh-373 cells is necessary for neoplastic transformation[58]. EGF overexpression has been found in metastatic breast cancer and aggressive form of uterine cancer[59]. Erb3 is associated in human mammary cancers. ErbB1/EGFR cases have accelerated intraepithelial proliferation[48,60].

Therapeutic interventions against EGF includessuramine which inhibits the binding of EGF to its recetor[61] and gefinitib which targets ErbB1 tyrosine kinase activity which causes inhibition of autophosphorylation[62]. Cetuximab, a monoclonal antibody which prevents ErbB1 signaling by binding to the ligand binding domain is now being clinically used[63].

2.4 Fibroblast Growth Factor Family

In humans, FGF family has 23 polypeptide encoding genes. Fibroblast growth factor family includes FGF1 i.e. acidic FGF, FGF-2 i.e. basic FGF and FGF-6 and FGF8. FGF receptors comprises of FGFR1-4 which are involved in both autocrine and paracrine signaling[64]. FGF are mitogenic for epithelial and mesenchymal cells. FGFs were first angiogenic factors to be indentified[65] and hence posses high angiogenic activity[66] in addition to enhancing motility and invasiveness of cells[67].

FGF signaling is a must for sustained self-renewal and pluripotency of human embryonic stem cells (HESCs)[68]. During haematopoiesis, FGF stimulates growth of progenitor cells[69]. FGF-2 stimulus leads to neoplastic transformation of cells[70]. Elevated levels of FGF2 in micro-environment of metastatic prostate cancer help cells to evade the anti-proliferative effect of chemotherapy[71]. Myeloma-associated oncogene FGFR3 is upregulated in cancer cells from patients with Chronic Myeloid leukemia (CML)[67,72].

Transgenic mice with both epithelial FGF3 overexpression and FGFR1 activation lead to epithelial proliferation and invasion of lesions[73]. FGFR2IIIb knockout mice fail to develop branching morphogenesis in breast which suggests that FGFR2 expression predisposes to breast cancer[74]. Single Nucleotide Polymorphisms occurring in FGFR2 and FGFR4 have been linked to their critical role in pathogenesis of breast cancer[75]. FGFR2 amplification occurs both in breast cancer and gastric cancer and is associated with poor prognosis[76]. Evidences indicating FGFR activating mutations specifically in FGFR2 are found in endometrium cancer[77] and in FGFR3 are present in bladder cancer[78].

FGF2 is present at increased levels in prostate cancer. FGF1 is found to be upregulated in 80% of prostate cancer which can be confirmed from IHC[79]. FGF1 has also been found to increase in prostatic intra-epithelial neoplasia (PIN)[80]. Transgenic mice with activated FGFR1 kinase develop PIN[81]. FGFR4 plays a significant role in prostate cancer initiation as confirmed by the presence of homozygozicity for FGFR arg388 is associated occurrence of prostate cancer[82].

A lot of efforts are being put to FGF/FGFR inhibitors. Data from phase I/II clinical trial proved that FGFR inhibitors exhibit antitumor activity. For example:

1. Nonselective FGFRTKIs-Donovitinib[83] inhibits FGFR, PDGFR and VEGFR.

   Nintedanib[84] potentially blocks VEGFR, PDGFR, FGFR. And also targets SRC, LYN,LLK.Poratinib, an oralmultikinase inhibitors inhibits BCR-ABC[85].
2. Selective anti-FGF-TKIs- AZD4547[86] pan FGFR selective causes desregulation of FGFR expression and hence shows anticancer response.BGJ398 selectively inhibits FGFR1-3 and is in phase I clinical trial[87].

2.5 Transforming Growth Factor-β Family

Transforming growth family –β is a secreted cytokine that critically influences proliferation and cellular differentiation. It plays an important role in immunity, cancer, bronchial asthma, lung fibrosis, heart diseases, diabetes etc[88]. Ligands of TGF-β family are bone morphogeneic proteins (BMPs), growth and differentiation factors (GDFs), anti-mullerian hormone (AMH, activin, Nodal and TGF-β, TGF-β includes- TGF-β1, TGF-β2, TGF-β3[89].

There are 8 types of SMAD proteins divided in 3 classes[90]:

i. Receptor regulated SMAD (R-Smad) –Smad 1,2,3,5 and 8.
ii. Co-mediator SMAD (Co- Smad) – smad 4
iii. Inhibitory SMAD (I-smad) – smad 6,7.

TGF-β signaling negatively regulates growth and inhibition of this pathway contributes to tumorigenesis[91]. As TGF-β negatively regulates growth, inactivating mutations in TGFBR1, TGFBR2, SMAD2, SMAD4 are commonly found in human cancers. In addition to this there is also loss of expression of TGF-β and Smad in many cancers. Disruption of TGF-β activated Smad pathway is sufficient to change gene expression which accelerates tumor formation. SMAD proteins play important role in TGF-β

associated growth inhibition and apoptosis. Rho proteins and PI3K regulate cell shape, loss of adherens junction and motility[92]. Colon, gastric, billary, pulmonary and ovarian cancer witness biallelic inactivation of TGFBRIII, which leads to inhibition of kinase domain of the receptor[93]. Some proteins called as 'ligand traps' trapTGF-β family members so that their membrane access can be stopped. Example Folistatin trap BMPs and it is found to be overexpressed in hepatocarcinoma[94] and breast cancer bone metastasis[95]. Germin-1 dysregulated expression is associated with skin and other cancer[96].

Intragenic mutation in SMAD4 occurs in colorectal cancer[97]. Gastric cancer and T-cell lymphoblastic leukemia has been *characteris*ed by Loss of Smad3 expression[93]. Smad2 and Smad3 protein expression is decreased in epithelial human cancers and rat prostatic carcinomas[98] and expression of Smad6 and Smad7 is increased[99].

2.6 Insulin-like Growth Factor Family

Insulin-like growth factors are associated with regulation of metabolism, growth and survival[101]. The signaling pathway utilized by IGF includes phosphoinositide-3-kinase (PI3K) and Akt or Ras and MAPK, which mediates response to many stimuli[102]. IGF family is constituted of two polypeptide ligands (IGF-1 and IGF-2), two membrane bound receptors (IGF-IR, IGF-IIR) and six binding proteins (IGFBP-1,2,3,4,5,6)[103]. IGF-I increases cellular uptake of amino acids and glucose and stimulates glycogen and protein synthesishence exerting a anabolic effect on protein and carbohydrate metabolism[104]. IGF-I plays role in cell proliferation, differentiation and apoptosis. IGF-1 stimulates expression of Bcl proteins and hence blocks the initiation of apoptosis[105]. IGF-II has mitogenic and anti-apoptotic action and also regulates cell proliferation and differentiation[106].

IGFBPs have both IGF-dependent and IGF-independent functions. When IGFBPs bind to IGFs, they help in transporting IGFs, protecting IGFs from proteosomal degradation, and regulate the interaction between IGFs and IGf-IR[107].

IGF-I and IGF-II are associated with variety of cancer like sarcoma, leukemia, prostate, breast, lung, colon, stomach, esophageal, liver, pancreas, kidney, thyroid, brain, ovary and uterus[108]. Cancer cells having high metastatic potential have higher expression of IGF-II and IGF-IR. IGF-IR elimination from cell inhibits the signal transduction, abolishing the mitogenic activation of IGFs in cancer cells[109]. IGF-IIR antagonizes effect of TGF-II and loss of function of IGF-IIR is associated in cancer and cancer cells which lack IGF-II degrading ability have good growth profile[110]. The action of IGFs is regulated by IGFBPs in cancer[111].

Oh[112], *et al.* found that IGFBP-3 inhibits breast cancer cell growth and induces apoptosis in both breast cancer and prostate cancer[113]. This happens because of presence of IGFBPs proteases. It was emphasized that increased levels of IGF-I is associated with increased breast cancer risk[114]. Increased levels of IGF-I and II are reported in colorectal cancer and hepatocarcinoma[115,116]. In pancreatic cancer pathway, mTOR is the point intersection, which allows IGF-IR/GPCR interaction to potentiate cell growth and proliferation[117]. IGFs can cause direct HIF-1α expression through MAPK/PI3K pathway and IGF-IR synthesis occurs during hypoxia leading to neoangiogenesis[118].

IGF pathway is an interesting target for cancer therapeutics. The mainstay of IGF target therapy is:

1. Small molecule inhibitors which inhibits tyrosine kinase domain of IGF-IR. (eg. Tyrophosphins, Picropodopyllins, INSM-18, BNS-754807[119].
2. Monoclonal antibodies (mAb) directed at IGF-IR. (eg. Ganitumab, AVE-1642, MK-0646, cixutumunab)[120].

OS7-906 is a small molecule TKIs that attaches to ATP binding site of tyrosine kinase receptor and causes dual inhibition of IR and IGF-IR[121]. Picropodophyllins inhibit IGF-IR. Exelixis are multitarget TKIs inhibit IGF-IR and Bcr-abl kinase[122]. Epigallocatechins is a catechinpolyphenolic component of green tea. It phosphorylates and activates TK and activates TK and inhibits IGF-IR by autophosphorylation of IGF-IR tyrosine kinase which causes cell cycle arrest[123]. Ganitumab is monoclonal antibody with IgG1 back bone and inhibits ligand binding of IGF-1 and-2 which inhibts IGF-IR phosphorylation[124]. AVE-1642 bind to IGF-IR and inhibits binding of IGFs. Cixutumunab is a fully humanised antibody blocking IGF-Rs and is in clinical trial phase II for breast cancer[125].

2.7 Hepatocyte Growth Factor Family

Hepatocyte growth factor (HGF) is also known as Serum factor (SF, HGF mediates its action through binding to a specific receptor site c-Met[126]. HGF binds to extracellular α-chain of c-Met receptor leading to tyrosine phosphorylation of terminal kinase domain and progression of downstream pathways[127]. HGF is expressed mainly by mesenchymal cells. Activation of HGF includes Hepatocyte growth factor Activator (HGFA)[128]. Matriptase, matrix degrading serum protease converts pro-HGF to biologically active HGF (also Heparin, Factor XIII, tissue plasminogen activator (t-PA) and Urokinase Plasminogen activator (u-PA))[129].

HGF is a mitogenic regulating cell growth and death[130]. HGF functions includes inhibition of apoptosis[131], angiogenesis[132], morphogenesis[133] and regulator of organ development[134].

Met is mainly expressed in epithelial cells whereas HGF is predominantly secreted by mesenchymal cells. This represents a cross-talk between epithelial cells and stromal cells[135,136]. The autocrine activation of Met occurs in osteosarcoma and glioblastomas. In breast cancer, it is activated by paracrine signaling[137]. Many carcinomas overexpress met as it is required for tumor growth and survival[138]. In hepatocytes, Met binds to Fas and inhibits Fas-induced apoptosis. Mutations in Met have been evident in juxtamembrane in gastric and lung cancer[139,140]. Interaction between c-Met and RTKs is linked to development of resistance to cancer therapies[141]. C- Met interacts directly with epidermal growth factor (EGFR), allowing activation of c-Met after stimulation of cells with EGFR

ligands EGF or TGF-α[142]. Mutation in c-Met kinase domain were reported in human renal papillary carcinomas[143]. Genetically transmitted cancers might be due to presence of heterozygous mutations in c-CBL binding site[144]. Hypoxia, a usual oxygen deficient state in tumors activate c-Met transcription via HIF1α stabalisation[145].

HGF has emerged as potentially good therapeutic target against cancer and following anti-cancer strategies have been devised:

(a) Against HGF: neutralizing antibodies, anti-sense oligonucleotides, ribozyme siRNA and HGF regulators[146].
(b) Against c-Met: HGF antagonist, antibodies, small molecule inhibitors, antisense oligonucleotides, ribozymes, siRNA as non-specific inhibitors[147].
(c) Against c-Met signaling events[148].
(d) HGF activation inhibitors[149].
(e) SRC inhibitors have also shown good primary results in treatment of cancer cells.
(f) HIF can also be good target as its stabilization leads to transcription of c-Met[150].

2.8 Neurotrophin Family

It was found in 1990 that some secreted proteins were important to normal growth of neurons and dendritic cells. Later they were named as neurotrophins[151]. The first neurotrophin discovered was NGF (Nerve growth factor)[152]. And next was brain derived neurotrophic factor (BDNF, In mammals two more neurotrophins were discovered, neurotrophin 3 and neurotrophin 4 and 5.

Receptors for Neurotrophin are transmembrane receptor of two different classes i.e. Trks and neurotrophin receptor P75. The cell survival is mediated by Trk receptor whereas P75 induces cell death. Trk i.e. (tropomyosine receptor kinases) are receptor tyrosin kinases and they are further categories into 3 types receptor types, TrkA[153] TrkB and TrkC. The preferred ligand for TrkA is NGF, where as for TrkB preffered ligand is BDNF and NT4/5 and TrkC binds preferentially to NTB[154]. P75 is a bundle of six short α-helixes spanning of 90 amino acids forming a fold but do not posses any intrinsic catalytic activity[155].

Spingomyelin is hydrolysis to ceramide by P75[156] and after ligand binding causes dopamine release[157]. P75 interacts with caveolin following TNF-α and NFKβ activation[158]. NFG was discovered from sarcoma while human colon cancer biopsy revealed TrkA and P75 was isolated from human melanoma cell lines[159]. In breast cancer there is increase in NGF expression leading to phosphorylation mitogenesis, invasion, metastasis and angiogenesis via activation of all the three pathways i.e MAPK, PI3K/AKT and PLCγ[160]. In melanomas, NGF-mediated paracrine signaling promotes proliferation and invasion[161]. In prostate cancer there is loss of P75 protein in basal epithelium cells due to mRNA instability. Loss of function of P75 leads to cell survival, proliferation and metastasis[162]. In pancreatic cancer NGF expression is increased which enhances proliferation, invasion and tumorigenicity[163].

In neuroblastoma TrKAIII isoforms potentiates survival via activation of PI3K-AKT pathway[164]. Whereas in glioblastoma NGF induces causes cell death by autophagy[165] and in medulloblastoma TrkA expression has good prognosis[166]. TrkA signaling can be inhibited by tyrosine kinase inhibitors such as indocarbazole[167]. Tamoxifen inhibits NGF mediated TrkA phosphorylation independent of its action on estrogen receptor[168].

In phase I clinical trial neurotrophin receptor-linked tyrosine kinase receptor inhibitor, CEP-701 was found to be orally safe and has entered phaseII clinical trial[169]. The selective Trk inhibitorAZ613 was found active against neurotrophin factor- mediated proliferation and signaling of neuroblastoma cells[170]. The Trk tyrosine kinase inhibitor CEP-701 exhibited anti-tumor efficacy in xenograft models of human pancreatic ductal adenocarcinoma[171]. It has found that Lestaurtinib enhances the anticancer efficacy of chemotherapy in murine xenograft model of neuroblastoma via inhibition of TrkB activation and has promoted the clinical trial of Lestaurtinib[172].

2.9 The Ephrin family

Ephrin expression play regulatory role in development and tissue homeostasis, along with the formation of tissue boundries, assembly formation of neuronal mesh work, remodeling of blood vessels and organ size[173]. Eph receptors are largest family of receptor tyrosine kinase. They bind GPI-linked and transmembrane ephrin ligands, generating bidirectional signaling at site of cell-cell contacts. Eph receptors are divided into two groups EphA and EphB, depending on two types of ligands that bind. EphA are further divided into 10 sub- groups EphA (EphA1-10) and EphB kinase (EphB1-6,Similarly there are two types of ephrin ligands: EphrinsA (A1-A6) and EphrinsB (B1-B3,EphrinA ligands are tethered to the cell membrane through glycosyl phosphotidyl-inositol (GP1) anchor. Whereas EphrinB ligands are transmembrane proteins possessing a cytoplasmic region and a PDZ-binding motif[174].

Expression of Ephs and Ephrins is frequently altered in human cancers. Eph receptors promote both tumorigenesis and tumor suppression[175]. EphA2 overexpression has been found to cause oncogenic mutations and promotes metastasis in murine breast cancer models[176]. EphB2 provides survival advantage to breast cancer by attenuating the inherent cell death pathways and upregulated anti-apoptotic proteins. EphB4 knockdown inhibit breast cancer cell viability, migration and invasion[177]. EphA1 is elevated in colorectal cancer cases. It is mostly detected in stage II[178]. Signaling EphA2 and EphrinA1 were more common in early stages of cancer. High expression of EphA3 is associated with lowersurvival rate[179]. It has been found that EphA2 is overexpressed in human prostate cancer and it is linked with metastasis[180]. EphA2 overexpression in associated with invasiveness in glioblastoma and is now important in targeted therapeutics against glioblastomas[181]. That overexpression of EphA4 enhances cell migration and proliferation through promoting the FGF signaling pathway[182]. EphB2 expression is higher in

invasive glioblastomas[183]. Metastatic melanoma cells are characterised by EphA2 expression[184]. EphrinA1,serves as growth factor, angiogenic signal and chemoattractant for melanoma cells but also angiogenic and chemoattractant for epithelial cells[185]. EphA2 promots angiogenesis[186].

Therapeutic targets against ephrins and Ephs are classified as :

(i) Inhibition of receptor-ligand interactions[187]:
Eg a) EphA2-Fc, EphB3-Fc are used in breast cancer and pancreatic cancer that targets ephrinA.
b) 2,5-dimethyl pyrrolyl benzoic acid derivatives target EphA4 to inhibit angiogenesis.

(ii) Activation of Eph forward signaling[188]: Eg EA2, B233 antibody against EphA2 in breast cancer.

(iii) Kinase inhibitors: E.g. Dasatinib against EphA2 in prostate cancer.

(iv) Inhibition of Eph expression: E.g. EphA2 siRNA against pancreatic cancer and ovarian cancer[189].

2.10 Angiopoietins

Various growth factors are linked to physiological as well as pathological angiogenesis[190]. Angiopoietin family of growth factor is composed of four members that bind to same TIE-2 tyrosine kinase receptor leading to different consequences. Angiopoietins was discovered by Davis et al., in 1996[191]. On the basis of structure Angiopoietins (ANG) are classified as[192]:

1. ANG-1
2. ANG-2
3. ANG-3
4. ANG-4.

ANG-1 function is to stabilise and mature the blood vessels[193]. Whereas ANG-2 is produced by endothelial cells at the site of vascular remodeling and destabilizes the vessel by lossening the endothelial cell junctions. ANG-2 acts as antagonist of ANG-1 because they compete with each other for TIE-2 receptor binding site[194]. ANG-3 acts in a similar way as ANG-1 promoting phosphorylation of TIE-2 receptortyrosine residues. ANG-4 effects are similar to ANG-2 acts as a antagonist of ANG-1[192]. Upregulated ANG-2 is correlated to metastasis in breast cancer and lung cancer[195]. Apart from cancer, ANG-2 upregulation is frequently found in diseases such as macula degeneration, rheumatoid arthritis[196], osteoarthritis[197], and psoriasis[198]. Major therapeutics targeting ANG-2 in clinical trial are:

(i) AMG-386: which is Fc-fusion protein blocks interaction between ANG-1 and ANG-2 and TIE-2 receptor. It is proposed to be effective in multiple cancers like ovarian, breast, fallopian tube cancer[199].

(ii) CVX-060: it selectively blocks ANG-2 and TIE-2 interaction and has a very long half-life. It is in trials in combination with sunitinib, sorafenib, bevacizumab and irinotecan[200].

(iii) CEP-11981: it is found to inhibitor of both VEGF and TIE-2 receptor tyrosine kinase[201].

(iv) MED13617: it is human anti-ANG-2 mAb. It has been shown to decreases angiogenesis and retard tumor growth in mouse models in combination with mAb bevacizumab[202].

3. PERSPECTIVE

Growth factors are necessary for normal growth of non-transformed cells. Theses cells perform their committed physiological functions via availability of growth factors. But the signaling in normal cells is limited as the growth factors are depleted at the site by various degrading pathways. But as discussed by Hanahan and Weinberg, the first hallmark of cancer is self-sufficiency of growth signals, which has two advantages. Firstly, because of continued availability of growth factors the check points of cell cycle can be overcome. Secondly, the growth suppressor signaling is bypassed. Hence abrupt signaling can induce oncogenic transformations. An enhanced understanding of these pathways can help targeting these neoplastic transformation at an early stage.

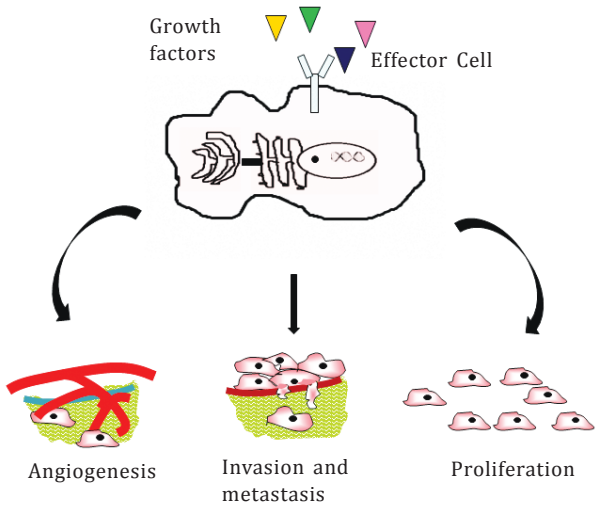

Figure 1. Schematic representation of Growth factor mediated signaling leading to malignant transformation of non-malignant cell.

Conflict of Interest : None

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