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INHIBITION OF ANGIOGENESIS BY TARGETING DIFFERENT CELLS: A REVIEW

[1]Soumya R. Khuntia*, [2]Gunjan Raj, [2]Sanjeev K. Majhee, [2]M. Saquib Hasnain, [2]Ram K Singh

[1]Department of Pharmaceutics, Seemanta institute of Pharmaceutical sciences, Jharpokharia, Mayurbhanj, Orissa-757086, INDIA.
[2]Department of Pharmaceutical chemistry, Seemanta institute of Pharmaceutical sciences, Jharpokharia, Mayurbhanj, Orissa-757086, INDIA.

ABSTRACT

Angiogenesis indicates process of growth of blood vessels and an imbalance leads to melignancy, infections, ischaemia etc. In angiogenesis, the vascular network expands by sprouting and remodels to several organized system of large vessels and smaller ones. Vascular and lymphatic EC sprouting can be regulated by VEGF and PIGF (a homologue of VEGF). Now-a-days angiogenesis can be inhibited by targeting different cells like mural, stromal, endothelial and haematopoetic cells. Some anti-angiogenic agents like VEGF antibody "AVASTIN" and RTKIs Which targets the VEGFR like receptors and arrests EC proliferation and prevents vessel growth. Sometimes combination of VEGF inhibitors with other inhibitors of distinct targets can increase the efficacy. When the mural cell and stromal cells are targeted, local release of VEGF and angiopoetin 1 occurs, and that may leads to tumor growth when PDGF signaling is over expressed. Therefore PDGFRβ signaling is inhibited and tumor vessels are dilated and EC apoptosis increased. These PDGFRβ inhibitors also destabilize SMCs which supply bulk flow to tumors making them susceptible to EC inhibitors. On the other hand PDGF-BB antagonists lower the intestinal fluid pressure & improve drug delivery through the tumor vasculature. In the recent future, the treatment of cancer will involve the use of cytotoxic radiation to destroy the malignant cells. Tumor cell angiogenesis may also be inhibited directly by targeting cells and it may lead to vessel decompression resulting in increased perfusion & drug delivery.

Keywords: Angiogenesis, VEGF, PDGF, mural and stromal cell, neurodegeneration.

Introduction

Angiogenesis is the process of growth of blood vessels. It is necessary for organ growth and repair of damaged tissues in adults [1]. An imbalance of angiogenesis leads to melignancy, infections, ischaemia and immune disorder. In embryo, blood vessels provide the necessary oxygen for the organs to develop and also provide instruction tropic (growth promoting) signals. In angiogenesis, the vascular network expands by sprouting and remodels to several organized system of large vessels and smaller ones unexpectedly. New endothelial cells are internally covered by pericytes and smooth muscle cells, than stromal and mural cells. Vascular and lymphatic EC sprouting can be regulated by VEGF and homologues VEGF-C. Mural cells around endothelial channels and recruited by PDGF-BB, (platelet derived growth factor) and angiopoetins[2]. Angiogenesis is related to neural brain stem cells and learning [3]. Hence an imbalance of VEGF causes neurodegeneration [4], respirating distress and possibly cardiac-failure. VEGF, the protein is thus found in all states (normal and diseased) hence when this is inhibited, apart from diseased cells, normal cells also get damaged. PIGF (a homologue of VEGF) is only found in diseased cells hence the inhibition of PIGF will prevent the disease and at the same time no normal cells death occurs. So anti-angiogenic drugs are manufactured targeting PIGF [5].

***Corresponding Author Soumya R. khuntia Email:- srkhuntia.pharma@gmail.com**

Inhibition of angiogenesis by targeting endothelial cells:

The best and most advanced anti-angiogenic agent is VEGF antibody "AVASTIN", a VEGF aptamer (MACUQEN, EYETECH) and RTKIs which targets VEGFRs and other receptors. Other compounds targeting VEGF family members include VEGF trap (REGENERON) and antibodies VEGFR-2 or VEGFR-1 (INCLONE) and against the VEGFR-1 ligand PIGF (THROMBOGENICS, Ltd. And BIOINVENT INTERNATIONAL).

These agents not only arrests EC proliferation and prevent vessel growth but also leads to EC death. Immature pericyte devoid cells are most susceptible. VEGF inhibitors also restrict the movement of endothelial progenitor cells (EPCs) from the bone marrow. Anti-VEGF treatment improves the architecture of tumor vessels by reducing vascular permeability and the interstitial fluid pressure, thereby improving the delivery of cytotoxic drug to tumor vessels hence increasing the efficacy of chemotherapeutics [6]. Besides anti-endothelial cell activity they are cytotoxic directly to malignant cells (which require VEGF for growth) and suppress the proangiogenic activity of haematopoetic cells and activate antitumor immune attack. A continuous low dose [7,8] of chemotherapeutics targeting dividing cells may also inhibit EC growth. The combination of VEGF inhibitors with other inhibitors of distinct targets remains largely untested, which is applied can very well increase the efficacy and decrease the inhibition to angiogenesis inhibition.

Inhibition of Angiogenesis by Targeting Mural and Stromal Cells:

Tumor vessels are covered by PCs [9]. Bone marrow mobilizes $cKit^+$ $sca1^+$ $VEGFR^+$ perivascular progenitor cells which differentiate mural cells and the whole process is a result of the signals of PDGF-BB [10] to the bone marrow. Local release of VEGF (an EC survival factor) and angiopoetin 1 (which tightens vessels by means of a matrix and cell-cell contacts) leads to an increase of mural cells tumor vessel stabilization, and hence of tumor growth [9]. All of these occur when PDGF signaling is over expressed. Therefore, if PDGFRβ signaling is inhibited, fewer PCs are recruited, tumor vessels and dilated and EC apoptosis increased. Use of combined administration of RTKIs, targeting VEGFRs and PDGFRβ, increased anti-angiogenic effect even in an uncontrollable late stage of solid tumors [12]. PDGFRβ inhibitors also destabilize SMCs which supply bulk flow to tumors making them susceptible to EC inhibitors.

In 1989, Paget said that tumor from metastatic deposits only in a particular place where they get the necessities for growth. Tumor stroma is an active contributor to tumor progression. It contains inflammatory infiltrates, an increased microvessel density and, day's functional lymphatics, a different and denser extra cellular matrix (ECM) and carcinoma activated fibroblasts (CAFs). The cell (CAF) expresses the receptor (PDGFRβ) which grows the tumor by the release of angiogenic factors such as VEGF and PIGF in response to PDGF-BB [9].

Therefore we can say that CAFs accelerates tumor by growth of pericytes and increase the malignancy. On the other hand suppressing angiogenesis, PDGF-BB antagonists lower the intestinal fluid pressure & improve drug delivery through the tumor vasculature.
Stromal fibroblasts also require EPCs by releasing stroma-cell derived factor 1α (SDF-1α) [12]. Inhibition of this chemokine inhibits tumor growth. Whether stroma cell renders ECs resistance to chemotherapeutics through cell-adhesion mediated drug resistance (CAM-DR) [13] stem cell are still unanswered.

Inhibition of Angiogenesis by targeting haematopoetic cells:

Inflammation stimulates progression of cancer. Tumor cells produce various cytokines and chemokine that attracts macrophages, dendritic cells, mast cells, T-cells and haematopoetic progenitors. Tumor derived VEGF & PIGF also stimulates the growth of some of the above cells. Inflammatory cell also causes lymph (angiogenesis) in tumor [14]. For instance tumor associated macrophages (TAMs) accumulate in hypotoxic regions & produce lymph (angiogenic) factors such as VEGF, VEGF-C and VEGF-D [15]. Certain leukocyte attracting chemokines such as IL-8 directly stimulate EC growth. Blocking the signals that promote leukocyte infiltration and survival may thus inhibit tumor angiogenesis.

In embryo the hematopoietic stem cells (HSCs) moves to the avascular areas for endothelial cell sprouting and release angiogenic factor like angiopoetin. In adults bone marrow derived HSCs like c-Kit and VEGFR-1 become recruited aften together with EPCs to tumor in response to VEGF & PIGF [12, 16, 17]. The angio competent cells circulate around nascent oxygen which is retained by $SDF_{1\alpha}$ and increases the growth of residing vessels by releasing angiogenic factors such as VEGF, PIGF and angiopoetin. However the PIGF release from tumor cell signals $VEGFR\text{-}1^+$ haematopoietic bone marrow progenitors to recruit the tumor cell and EPCs [18]. Anti VEGFR antibodies prevent the formation of such metastatic by interfering with SDF-1 and PIGF. RTKIs, which block c-Kit, may also have similar effects.

Inhibition of Angiogenesis by neoplastic cells:

The treatment of cancer will involve the use of cytotoxic radiation or tumor cell targeted biological tools to destroy the malignant cells. Tumor cell destruction will

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lead to vessel decompression resulting in increased perfusion & drug delivery. Thus HERCEPTIN(GENENTECH), an anti EGER antibody block neoplastic cells and act as an anti-angiogenic by lowering the angiogenic factors and upregulating endogenous anti-angiogenic inhibitors [19]. While SORAFENIB or SUTENT inhibit both EC and tumor cell division makes them useful as monotherapy in renal cell carcinoma & gastrointestinal stromal tumors, respectively [20].

Figure 1 shows strategies targeting endothelial and non-endothelial cells to inhibit tumor angiogenesis.

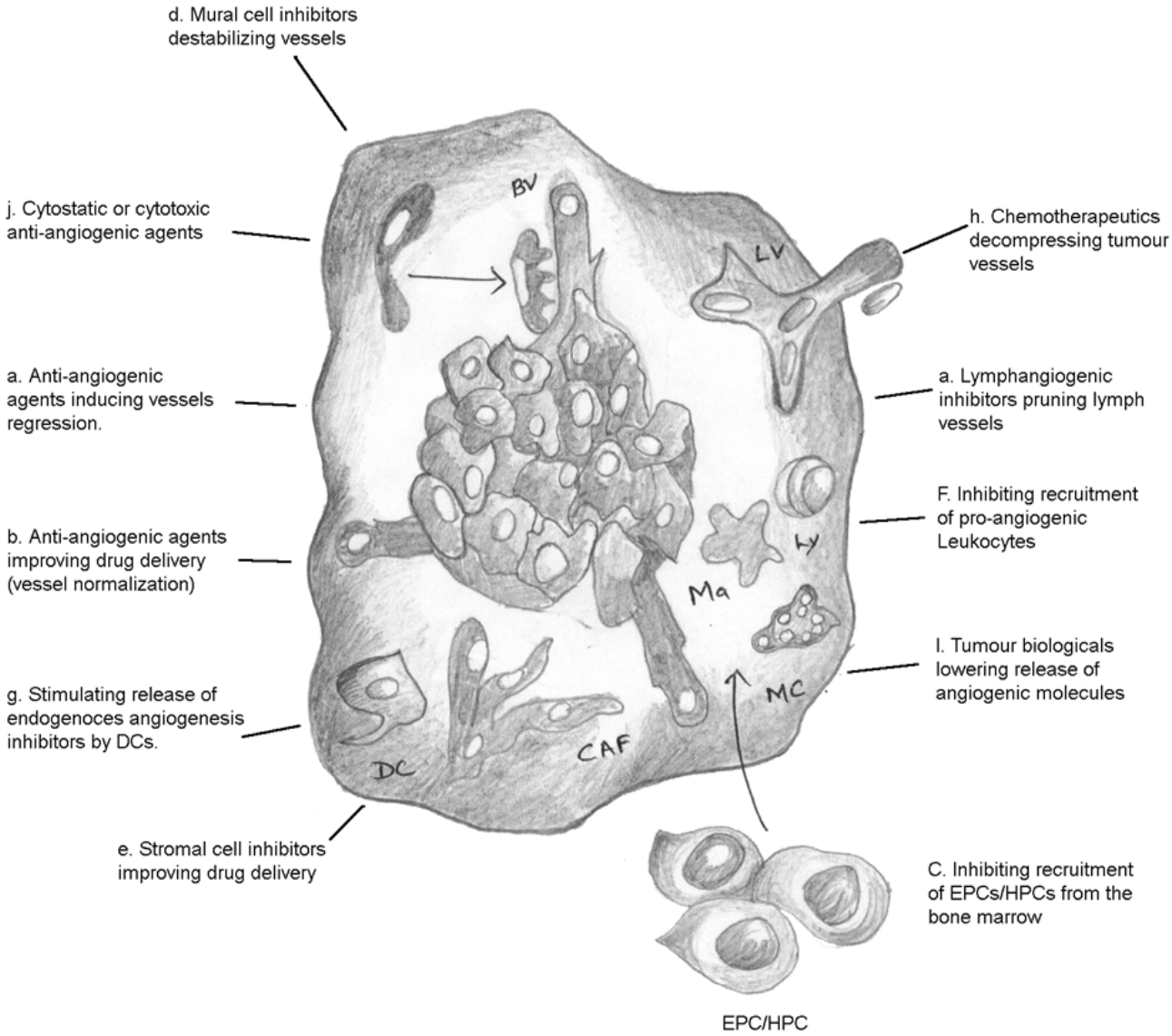

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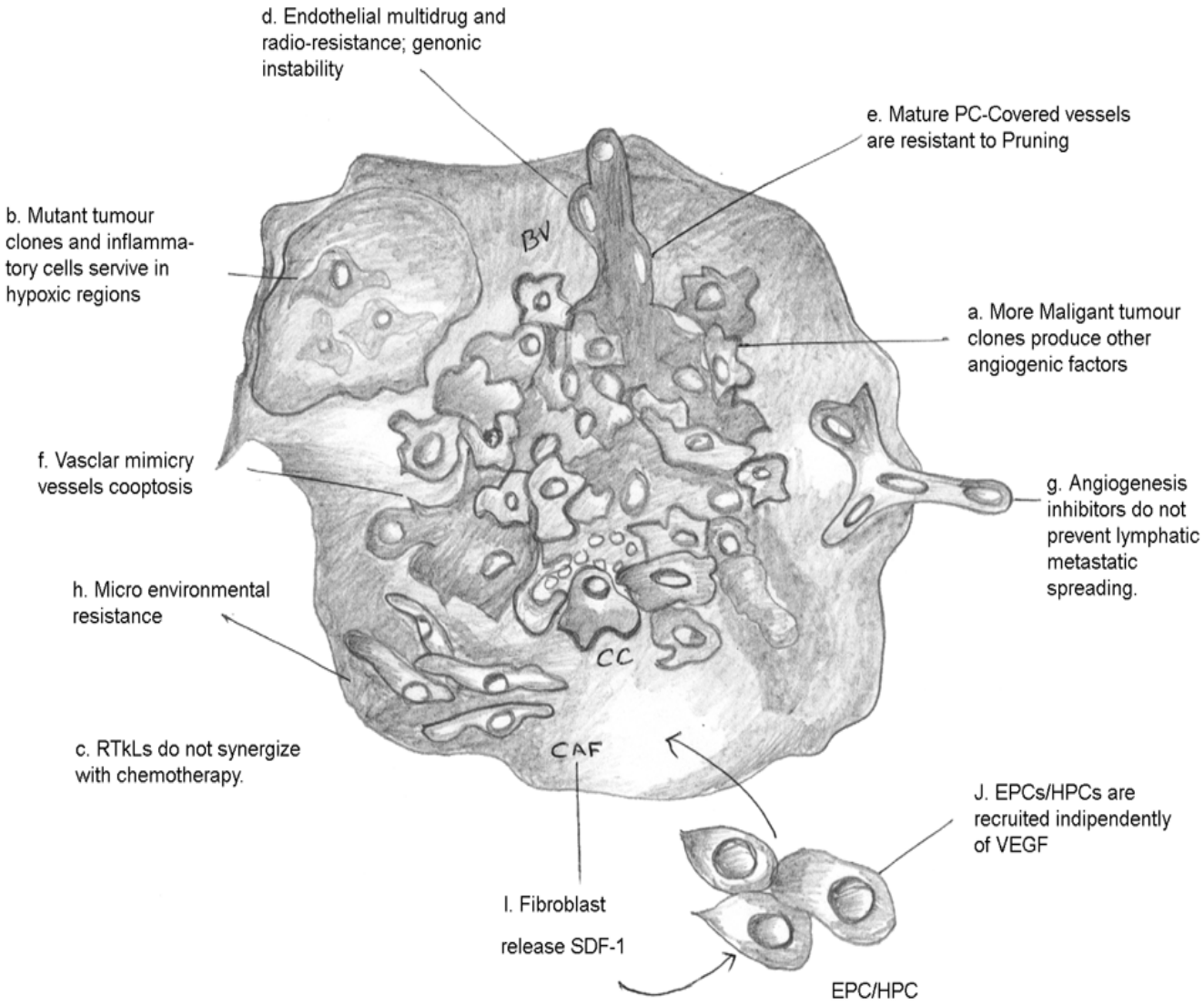
Figure 2 shows Mechanism of acquired resistance to anti-angiogenic agents.



Conclusion:

There is now proof that an anti-angiogenic approach, when combined with chemotherapy, results in increased survival in patients which advanced malignancies. It called be argued if the therapy were initiated at earlier stages of malignancy. However, lengthy clinical trials will be required to test the hypothesis. Combing traditional anti-angiogenic agent with inhibitors of lymphangiogenesis may provide a powerful anticancer approach.

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