IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN: 2278-3008, p-ISSN:2319-7676. Volume 7, Issue 4 (Sep. – Oct. 2013), PP 52-54
www.iosrjournals.org

Angiogenesis Inhibition – A promising approach to combat Cancer

Sanjib Ghosh

Abstract: *To combat cancer angiogenic pathway is targeted by many workers worldwide. A number of anti-angiogenic drugs have been used to treat cancer patients for several decades. Imatinib, Bevacizumabetc are the widely used drugs that are used to treat cancer by inhibiting angiogenesis. It is notable that the use of various natural health products like curcumin, quercetinetc are increasing.*
Keywords: *Angiogenin, FGF, Imatinib, Bevacizumab, curcumin, quercetin.*

I. Introduction

Angiogenesis is the process of formation of new blood vessels. It begins *in utero* and occurs throughout life. All metabolically active tissue in mammals and others require continuous supply of oxygen and nutrients for their survival. For this purpose new blood vessels are required in newly formed tissues and angiogenesis is the process that recruit new blood vessels signaled by pro-angiogenic molecules. Without blood vessels tumors can neither grow beyond a critical size nor metastasize to another organ[1]. On the other hand, without an efficient blood supply it is impossible to deliver anti-cancer drugs to all regions of a tumour.

Types

The Scotishanatomist John Hunter (1794) provided the first recorded scientific insights about angiogenesis. It is of two types.

- Sprouting angiogenesis : it is characterized by sprouts composed of endothelial cells, which usually grow towards an angiogenic stimulus such as VEGF-A. It adds blood vessels to the portions of tissues that previously devoid of blood vessels.
- Intussusceptiveangiogenesis : it forms blood vessels by a splitting process in which elements of interstitial tissues invade existing blood vessels.

A brief history of Angiogenesis

- The term 'Angiogenesis' was introduced by Dr. John Hunter to describe the formation of blood vessels in the reindeer antler in 1787.
- In the year 1935, Dr. Arthur TremainHertig reported angiogenesis in the placenta of pregnant monkey
- In 1971, Judah Folkman first described that tumour growth is dependent upon angiogenesis.[1].
- The first pro-angiogenic factor b-FGF was discovered by Yuen shing and MichealKlagsbrun in 1984.
- In 1989 Dr. Nepoleone Ferrara discovered vascular endothelial growth factor or VEGF.
- In 1992, the first clinical trial of an anti-angiogenic drug (TNP-470) begins in cancer patients.
- After 1999, a massive revolution in the world of Cancer research through angiogenesis began

Regulation of Angiogenesis

- Increasing metabolic activity may stimulate blood vessel growth[2]
- Long term increase in blood pressure lead to vascularization.
- Oxygen is the master regulator of angiogenesis[3]. Many pro-angiogenic factors and their receptors can be activated directly or indirectly by Hypoxia. These include –
  (a) VEGF – A and its receptors – VEGFR-1 & VEGFR-2
  (b) FGF2
  (c) TGF-betas

Oxygen also regulates expression of the transcriptional regulator such as Hypoxia inducible factor-1 (HIF-1) and inducible nitric oxide synthase (iNOS).

- Adenosine is a metabolic regulator of angiogenesis. It is thought to serve as a negative feedback signal to maintain tissue oxygenation within a normal range.[3]

Angiogenic growth factors :

Table 1 : A list of Angiogenic Growth Factors[4]

1.	Angiogenin
2.	Angiopoietin-1
3.	Del-1
4.	Fibroblast Growth Factors : a-FGF &b-FGF
5.	Follistatin
6.	Granulocyte colony stimulating factor
7.	Hepatocyte Growth factor
8.	Interlenkin – 8
9.	Leptin
10.	Midkine
11.	Placental Growth factor
12.	Platelet-derived endothelical Growth Factor
13.	Platelet derived growth factor- BB
14.	Pleiotrophin
15.	Proliferin
17	Transforming Growth factor-alpha
18	Transforming Growth factor-beta
19	Tumour necrosis factor – alpha
20	Vascular endothelial Growth Factor

Anti-Angiogenic Therapeutic Drugs :

- A number of inhibitor of tumour vasculature have been identified which are able to block tumourgrowth and metastasis. These are used as anti-angiogenicdrugs in *invitro* and *invivo*. Anti-angiogenic drugs may act by any of the following ways –
  (a) Inhibiting synthesis of angiogenic proteins by cancer cells
  (b) Neutralizing the angiogenic proteins
  (c) Inhibiting the receptors of endothelia for angiogenic proteins
  (d) Directly inducing endothelia cell apoptosis

Small molecule Inhibitors : There are some tyrosine kinase receptors that play important role in the angiogenesis of tumours. These receptors are the targets of some small-molecules that inhibit angiogenesis. Imatinib is such an agent that targets bcr-abl proteins (it is a tyrosine kinase fusion protein that causes chronic myelogenous leukemia or CML)[5]. It was introduced in 1990 and approved in 2001 for the treatment of CML.

Table 2 : A list of Small-Molecules serving to resist angiogenesis

Sl. No.	Molecular Target	Small-Molecule drugs	Current Status	Reference
1	Growth Factor Receptors	Iressa	FDA approved	(6)
2	VEGFR	Vatalanib	Under Phase II trial	(7)
3	Multiple growth factor receptor	Imatinib	FDA approved	(8)

Monoclonal antibodies : The use of monoclonal antibodies is an promising approach to treat cancer targeting angiogenesis. Monoclonal antibodies can be designed to target the tumour cells only. They kill the tumour cells directly or activate immune system to kill the tumor cells. Several anti-angiogenic monoclonal antibodies have been approved by FDA till to date. Bevacizumab is such an agent that acts as a potential angiogenic inhibitor. It was approved by FDA in 2004 for the treatment of metastatic colorectal cancer[9].

Use of natural health products as anti-AngiogenicAgent :

Most anti-angiogenic drugs have cytotoxic affects that may lead to the destruction of functionally important cells along with the tumour cells. To overcome these problems, there is an restless search for a way that can ensure minimum harm with maximum benefit. It seems to be true the search for the weapon against cancer. Several outstanding discoveries have revealed that the weapon may be hidden in the world of herbs and phytochemicals.

In 1990, Ingber*&et al* isolated fumagillin from the fungus *Aspergillusfumigatus* and suggested that fumagillin have anti-angiogenic properties[10]. It was apioneering discovery that opened a new window in cancer research.

In the following paragraph, few interesting informations about natural products having anti angiogenic properties are discussed.

Curcumin : It was isolated from turmeric (*Curcuma longa*). It is reported from several studies that curcumin inhibits the transcription of two most critical angiogenesis factors – VEGF and b-FGF[11]. CD-13 is a membrane bound enzyme found on actively growing blood vessels. Curcumininhibits CD-13 activity[12].

Resveratrol : It is a phytolexin found in grapes and wine. It inhibits VEGF- induced angiogenesis by disruption of reactive oxygen species – dependent src kinase activation and VE-cadherin tyrosine phosphorylation[13].

Epigallocatechin-3 gallate : It is extracted from green tea (*Camellia sinensis*). From rodent studies, it is reported that the compound have inhibitory effect on the transcription of VEGF[14]

Quercetin : It is found in apples, onions, red grapes, citrus fruits, cherries, broccoli and leafy greens. It has anti-angiogenic effects.[15]

II. Conclusion :

Managing cancer is the biggest challenge for the biologists of this century. In every corner of the world thousands of scientists are engaged for searching a weapon to defeat this dangerous enemy. Though it is the fact that 'We have miles to go' to get the ultimate success. The scenario of cancer research since last 25 years shows that biologists have already discovered various target points to attack by chemical or phytochemical products to destroy the cancer cells or to activate systems that inhibit their growth or regulate their death. But there are many difficulties to send the drug at the proper location to interact with the target component. Now, efforts are required to cross this barrier.

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