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Review Article

NANO-ANTIANGIOGENESIS IN CANCER THERAPY

Chandana Kamili [a] *, Shafeen Begum [a], Abbulu Konda [a], Ravi Shankar Kakaraparthi [b], Uma Maheshwararao Vattikutti [c]

[a] Department of Pharmacology, CMR College of Pharmacy, Hyderabad- 501401, Telangana, INDIA.

[b] Department of Pharmacology, Sri Sai Aditya Institute of Pharmaceutical Sciences and Research, Surampalem, Andra pradesh, INDIA.

[c] Department of Pharmacognosy, TRR College of Pharmacy, Hyderabad- 500079, Telangana, INDIA.

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ABSTRACT

Cancer angiogenesis is the growth of new blood vessels that tumors need to grow. This process is caused by the release of chemicals by the tumor and by host cells near the tumor. Antiangiogenesis can treat the cancer from the root cause and design of the potent anti angiogenic agents in the nano-form will give a target specific action, decreasing the side effects. In this review, an overview of mechanism of antiangiogenic treatment and role of nanoformulations is being presented. Studies on nano-antiangiogenesis will advance our understanding of the molecular level treatment of tumor angiogenesis and may identify novel and effective targets for the clinical applications of different types of cancers.

KEYWORDS: *Tumor angiogenesis, Cancer, Nanoparticles.*

INTRODUCTION

- The formation of new blood vessels is called **Angiogenesis** (Fig. 1). It is a normal part of growth and healing. But it plays a role in several diseases, including cancer.
- A tumour needs nutrients and oxygen to grow and spread. Blood contains those ingredients. The tumour sends chemical signals that stimulate blood vessel growth. And the blood vessels carry blood to the tumour.
- Prevention of the formation of new blood vessels, esp. the blo od vessels that grow under the influence of malignant tumours is called **Antiangiogenesis** [1].

Anti-Angiogenesis Treatment:

- A cancer needs a good blood supply to provide itself with food and oxygen and to remove waste products. When it has reached 1 to 2mm across, a tumour needs to grow its own blood vessels in order to continue to get bigger.
- Some cancer cells make a protein called vascular endothelial growth factor (VEGF). The VEGF protein attaches to receptors on cells that line the walls of blood vessels within the tumour. The cells are called endothelial cells. This triggers the blood vessels to grow so the cancer can then grow.

*** Corresponding author:**

Dr. Chandana Kamili

Associate professor,

Department of Pharmacology, CMR College of Pharmacy,

Hyderabad- 501401, Telangana, INDIA.

** E-Mail: chandanakamili@gmail.com*

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- Anti angiogenic drugs are treatments that stop tumours from growing their own blood vessels.

Types of Anti- Angiogenesis Treatment:

There are different types of drugs that block blood vessel growth:

1. Drugs that block blood vessel growth factor:

- Some drugs block vascular endothelial growth factor (VEGF) from attaching to the receptors on the cells that line the blood vessels. This stops the blood vessels from growing. **Example: bevacizumab (Avastin).**
- It is a treatment for several different types of cancer. It's also in trials for ovarian cancer and a rare type of cancer of the nerve cells called neuroblastoma.

2. Drugs that block signalling within the cell:

- Some drugs stop the VEGF receptors from sending growth signals into the blood vessel cells. These treatments are also called cancer growth blockers or tyrosine kinase inhibitors (TKIs). Example: **Sunitinib**
- It is used to treat some people with:
- Kidney cancer
- A rare type of stomach cancer called gastrointestinal stromal tumour (GIST)
- A neuroendocrine tumour of the pancreas

3. Drugs that affect signals between cells:

- Some drugs act on the chemicals that cells use to signal to each other to grow. This can block the formation of blood vessels.
- Examples: **Thalidomide and lenalidomide (Revlimid).**

They are used to treat some people with multiple myeloma [2].

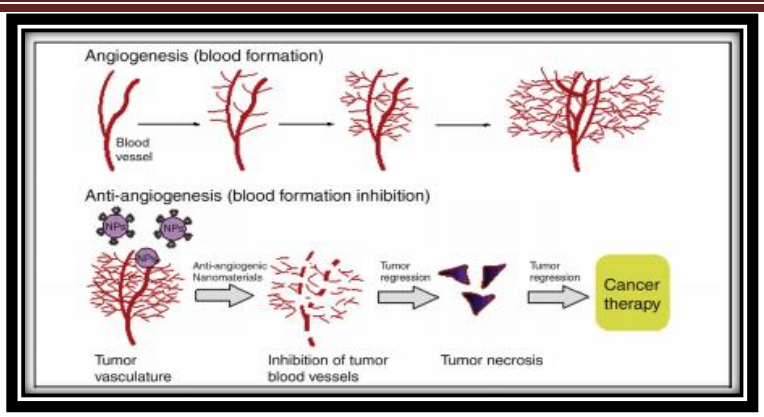

Fig. 1: Angiogenesis Blood formation

Table No. 1: Angiogenic Inhibitors [15-17]

INHIBITORS	TREATMENT
Axitinib (Inlyta)	Kidney cancer
Bevacizumab (Avastin)	Colorectal, Kidney, Lungscancers
Cabozantinib (Comtriq)	Medullary thyroid & Kidney cancer
Everolimus (Afinitos, Zortress)	Kidney cancer, Breast cancer, Pnets, subpemdymal gaint cell astrocytoma
Lenalidome (Revlimid)	Multiple myeloma tumours
Pazopanib (Votrient)	Kidney cancer & advanced soft tissue sarcoma
Ramucirumab (Cyramza)	Gastro-oesophagal juntion, adrenocarcinoma, a cancer located ehere stomach joins oesophagus, non-small cell lung cancers
Regorafenib (Stivarga)	Colorectal cancers, gist
Soarafenib (Nexavar)	Kidney, liver and thyroid cancers
Sunitinib (Sutent)	Kidney cancer, gist
Thalidomide (Synovir, Thalomide)	Multiple myeloma
Vandetenib (Caprelsa)	Medullary thyroid cancer

Mechanism of Action of Various Angiogenic Inhibitors:

Axitinib:

Its primary mechanism of action is thought to be vascular endothelial growth factor receptor 1-3, c-KIT and PDGFR inhibition, this, in turn, enables it to inhibit angiogenesis (the formation of new blood vessels by tumours).

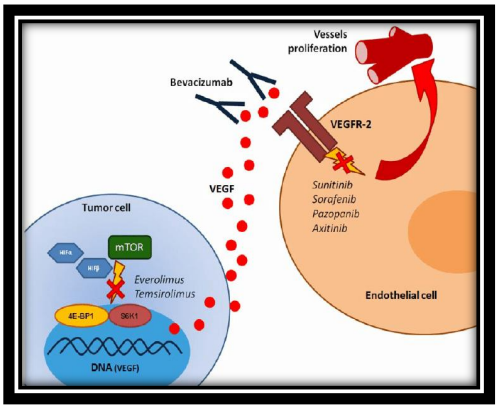

Fig. 2: Mechanism of action of Axitinib [3]

Bevacizumab:

Avastin is designed to directly bind to VEGF extracellularly to prevent interaction with VEGF receptors (VEGFRs) on the surface of endothelial cells, and thereby may inhibit VEGF's angiogenic activity.

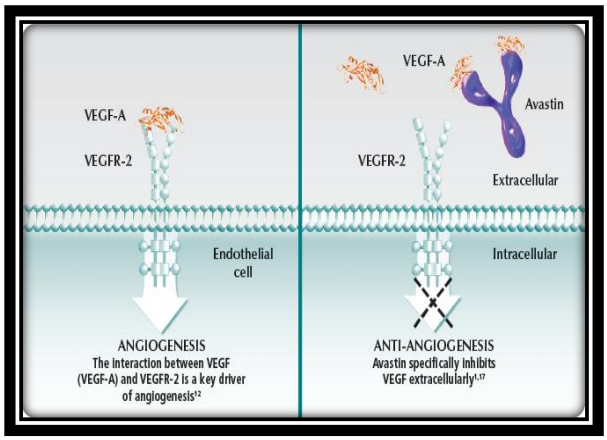

Fig. 3: Mechanism of action of Bevacizumab [4]

Everolimus:

By inhibiting mTOR, AFINITOR blocks the effects caused by the loss of the *TSC1/TSC2* genes and reduces cell growth, proliferation & angiogenesis.

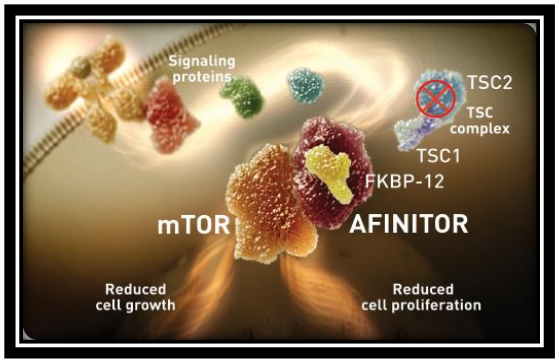

Fig. 4: Mechanism of action of Everolimus [5]

Sunitinib:

It inhibits cellular signaling by targeting multiple receptor tyrosine kinases (RTKs).

These include all receptors for platelet-derived growth factor (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs), which play a role in both tumour angiogenesis and tumour cell proliferation. The simultaneous inhibition of these targets therefore reduces tumour vascularization and triggers cancer cell apoptosis and thus results in tumour shrinkage.

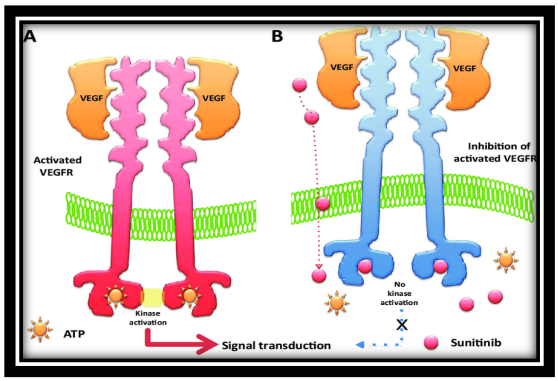

Fig. 5: Mechanism of action of Sunitinib [6]

Thalidomide:

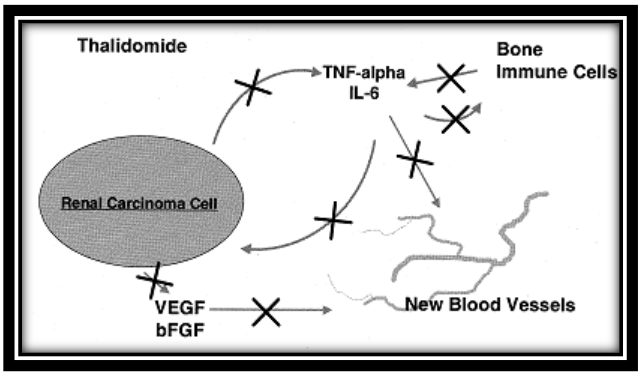

Fig. 6: Mechanism of action Thalidomide as angiogenic inhibitor

Side Effects of Angiogenesis Inhibitor:

- High blood pressure
- A rash or dry, itchy skin
- Hand-foot syndrome. This causes tender, thickened areas on the palms and soles. Sometimes, it causes blisters.
- Diarrhoea, Fatigue, Low blood counts
- Problems with wound healing or cuts reopening

Rare side effects are:

- Serious bleeding
- Heart attacks, Heart failure
- Blood clots
- Holes in the intestines, called bowel perforations

Nanotherapeutics as Effective Angiogenic Inhibitors:

Among several pro-angiogenic factors secreted by a variety of tumours, VEGF is a highly overexpressed and well-characterized tumour-derived pro-angiogenic factor. During its action, the anti-angiogenic Nano therapeutics attach to VEGF and prevent its binding with the respective receptor, thus avoiding the initiation of new blood vessels. Based on this concept, a variety of NPs with anti-angiogenic properties have been developed by researchers around the world in the past decade.

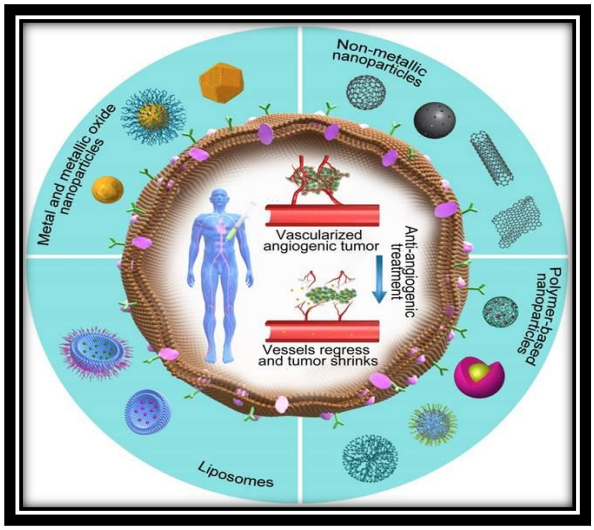

Fig. 7: Different nanoparticles in the treatment of anti-angiogenesis [7]

Targeting Tumour Abnormalities & Anti-Angiogenic Limitation by Nanotherapeutics:

- The main mechanism involved in the nontherapeutic approach to anti-angiogenesis activity is the prevention of binding of pro-angiogenic factors to their respective receptors.(Fig-8A)
- Since the ECs of tumours and normal tissues have different features, targeting the vasculature with therapeutic NPs can be optimized by the conjugation of antibodies/ligands, such as the anti-VEGFR-2 antibody, that are capable of binding these overexpresse antigens/receptors.
- These receptors stimulate gene expression and intracellular signalling that are involved in vital and critical cellular processes, such as cell growth, apoptosis, survival, metastasis, invasion, and tumour cell motility [8].
- Therefore, the binding of these antigens/receptors to functionalized NPs offer opportunities for tumour targeting and attack [9].
- For instance, after the specific binding between angiogenic growth factors and their relevant receptors, ECs are activated and release several proteases that can effectively degrade the basement membrane and ECM [10].

- Based on this fact, researchers have developed anticancer strategies that target the related proteolytic enzymes participating in the angiogenesis cascades. Such targeting can be considered to be another important mechanism of anti-angiogenesis *via* a nontherapeutic approach to inhibit the activity of ECM proteolytic enzymes.(Fig-8B)

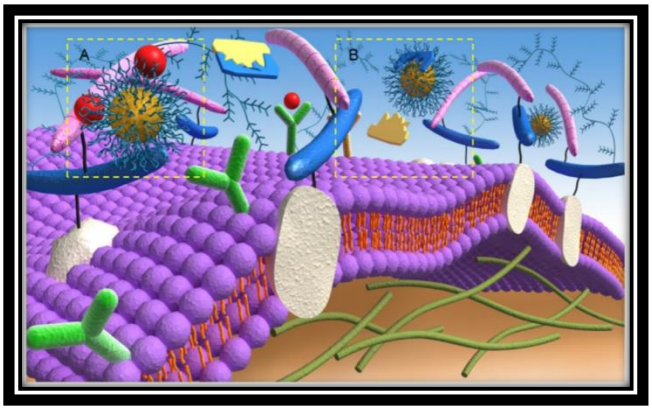

Fig. 8: Anti-angiogenic mechanisms of targeting A) angiogenic growth factors &

B) Proteolytic enzymes of the extracellular matrix by Nano therapeutics: [8-10]

Inherent Resistance Against Anti-Angiogenic Therapy:

- Cancer resistance remains the major obstacle in angiogenesis treatments of many cancer types and requires to be addressed cautiously.
- The development of tumour resistance towards anti-angiogenic agents can be either inherent or acquired.
- It is imperative to understand why most patients stop responding, or do not respond at all, to angiogenic drugs and how such limitations can be overcome [11].
- Progress in Nano medicines based on NPs is anticipated to overcome drug resistance [12]. For example, the size of NPs, which can easily be controlled in different ways, allows them to intrinsically approach the metastasized tumours*via* enhanced permeability and retention (EPR) effects without being recognized by the main target in drug resistance, P-glycoprotein [13].
- Recently, studies have shown that poly (ethylene oxide) (PEO)-poly caprolactone (PCL) NPs successfully co-delivered paciltaxel and ceramidedrugs to the target site to overcome MDR in breast cancer cell lines [14].

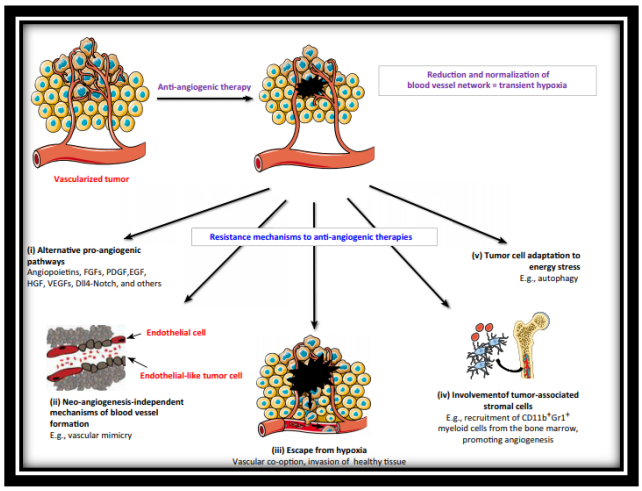

Fig. 9: Resistance mechanisms to anti-angiogenic therapies [11]

Table No. 2: Mechanism by which Tumours acquires Resistance towards Anti-Antiogenic therapies [18]

MECHANISM OF RESISTANCE	PREDECTIVE MARKER	CLINICAL EVIDENCE
Up regulation of compensatory pro-angiogenic signals.	FGFs	Induction of FGF2 in patient's serum that progressed on anti-VEGF therapy.
Increase in pro- angiogenic factors by stromal cells.	TAFs	Tumors resistant to anti- VEGF therapy produce TAFs which support tumor growth and angiogenesis.
Recruitment of bone marrow derived pro-angiogenic cells.	CECs	Increased after AZD2171 and sunitinib treatments of renal cell cancer patients.
Over expression of vascular pericytes coverage.	PDGF	Targeted tumor vasculature pericytes may lead to disturbance of vessel integrity and metastasis.
Induction of hypoxia	HIF-1	Increased the circulating levels of basic FGF and stromal cell- derived factor 1 alpha (SDF1α) that controlled by HIF-1 after VEGF blockade.

Table No. 3: Promising Solutions by Nanoparticles to Overcome the Barriers of Cancer Therapy [19-21]

BARRIERS FOR CANCER THERAPY	PROMISING SOLUTIONS	EXAMPLES OF USED NPs	OUTCOME
Poor oral availability , short half-life and continuous parenteral administration	Increase intestinal absorption and drug selectivity	Nano polymeric Lodamin [TNP - 470 conjugated to mono methoxy poly ethylene glycol/ polylactic acid]	Selectively inhibited tumour growth and metastasis without any side effect
Multidrug – resistant [MDR] & drug efflux pumps	Stimuli – responsive drug release	Mesoporous silica nano particles [MSNs]	Increase intracellular uptake and enhanced ability to overcome MDR

Elevated interstitial fluid pressure	Increasing interstitial transport of drug	Intermediate – sized nano particles [20 – 40nm] targeting VEGFR-2	Decrease the interstitial fluid pressure and enhanced drug delivery
Reduce vascular density & perfusion rates	Reducing the interstitial fluid pressure in solid tumours	Combination of Taxane therapy with NPs are using a Hedgehog inhibitor [IPI-926]	Improve the functional vascular density and enhance drug delivery to tumour
Irregular vessel permeability	Activate the target by covalent conjugation of antibodies to NP surfaces	Immunoliposomes [Anti – HER2]	Increased drug uptake and facilitated intracellular drug delivery
Abnormal vessel porosity	Prolong drug systemic circulation	Liposomes, PEG NPs	Improved drug availability and leading to superior tumour uptake
Hypoxic micro enviornments	Induced drug delivery	Hypoxia – sensitive polymeric micelles encapsulating DOX	Effectively deliver the drugs into hypoxic cells
Acidic micro enviornments	PH -sensitivity NPs	-Poly his containing nanogel and hydrogel NPs. gelatin NPs	Speedup drug release kinetics and increase drug efficacy
Reduce the apoptotic threshold in MDR	Increase the apoptotic activity	Combination therapy of tamoxifen and paclitaxel NPs	Significant enhancement in antitumour efficacy without any toxicity

Design Consideration of Nanotherapeutics:

A sufficient concentration of a therapeutic drug must reach the target cancer cells for maximumefficacy, but at the same time, the drug should behighly selective in its action without exerting adverse effects on normal tissues.

A logical method for efficient cancer drug delivery and targeting can be obtained by the association of anti-cancer drugs with functionalized NPs.

However, many factors can affect NP distribution, including size, chemical modification, surface properties, and shape.

Among these, the size of NPs remains a vital factor in the normalization of tumour vessels and the approach to the tumour sites.

For highly and poorly permeable tumours, the optimal diameter size for enhanced accumulation in the tumour site can vary.

The diameter range should be <100 nm for tumourswith dense stroma. As such, NPs in the range of 10-200 nm are more appropriate for cancer treatment.

Generally, NPs ≤10 nm can easily be filtered out through the kidneys, whereas NPs ≥200 nm are primarily accumulated within the extracellular.

The main consideration in the development of anti-tumour drugs is to target specific proteins/cellular receptors that are expressed excessively in tumours and/or angiogenic blood vessels. Thus, the design of Nano therapeutics for such applications should be carried out carefully and must possess the following features:

- Competent differentiation between normal and cancerous cells and between the forms of proteins and cellular receptors that are involved in the respective signaling pathways.
- The ability to quantitatively determine the expression level of multiple tumour types, and
- The ability to block the activity of tumour angiogenic vessels and thus be utilized as a therapeutic intervention.

CONCLUSION

Nanotechnology has already revolutionized cancer therapy in many aspects and is radically changing the treatment pattern.

Using nanotechnology the drug can be targeted to a precise location which would make the drug much more effective & reduce the chances of possible side effects.

More specific targeting delivery.

Reduction in toxicity while maintaining therapeutic efficiency.

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