Angiogenesis Inhibitors for Cancer Therapy

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Abstract

Inhibition of angiogenesis, which refers to blocking the vessel formation from pre-existing blood vessels, has become an attractive target for cancer therapy. Tumors beyond 2-3 mm in size induce the sprouting of new blood vessels from the surrounding vasculature (sprouting angiogenesis). Design and development of new angiogenesis inhibitors has been validated as a target in several tumor types. In this min-review, we will focus on the role of different anti-angiogenesis strategies and inhibitors in treatment of cancer.

Keywords: VEGF: Vascular Endothelial Growth Factor; TGF: Transforming Growth Factor; TNF: Tumor Necrosis Factor; bFGF: Basic Fibroblast Growth Factor; PLGA: Poly Lactic-Co-Glycolic Acid

Introduction

Angiogenesis is a complex process in the body. It is the growth of new blood vessels from pre-existing vasculature systems that occur in both healthy and unhealthy blood vessels [1-5]. There are several systemic chemical signals known as angiogenic activators that are involved in repair of damaged blood vessels and induce new blood vessel formation, but on the other hand there is a type of chemical signal known as an angiogenesis inhibitor that induces removal of existing blood vessels. Keeping balance between angiogenesis inhibitors and angiogenesis activators is important in order to regulate vascular homeostasis (Figure 1) [1]. There are several proteins that control activity of both inhibitors and angiogenesis activators, including platelet-derived endothelial growth factor, vascular endothelial growth factor (VEGF), angiogenin, interleukin-8, hepatocyte growth factor, transforming growth factor -α (TGF)-α, TGF-β, tumor necrosis factor -α (TNF)-α, granulocyte colony-stimulating factor, placental growth factor, basic fibroblast growth factor (bFGF, FGF2), and epidermal growth factor.
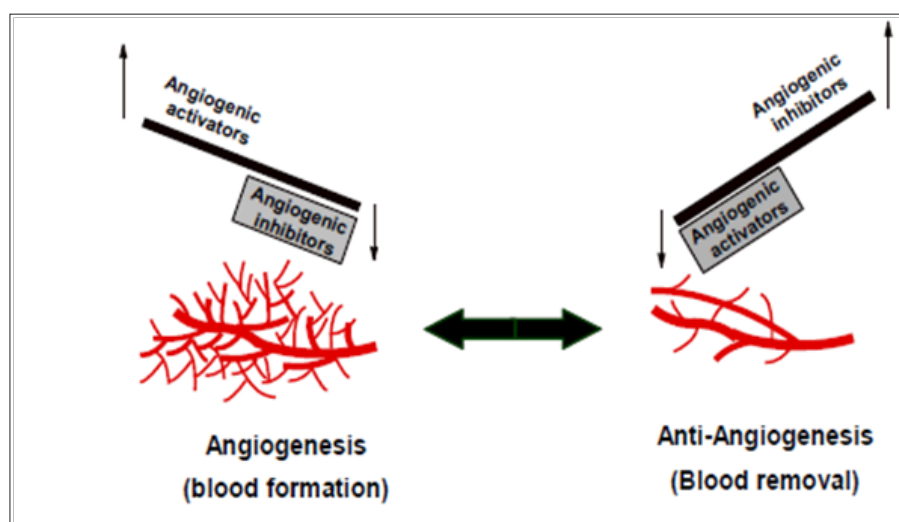

Figure 1: Balance between Angiogenic Inhibitors and Angiogenic Activators in Order to Regulate Vascular Homeostasis.

Examples of Some Angiogenesis Inhibitors for Cancer Therapy

There are two main groups for classification of anti-angiogenesis molecules: direct inhibitors and indirect inhibitors. Direct inhibitors such as angiostatin, endostatin, arrestin, canstatin, and tumstatin target endothelial cells in the growing vasculature. Indirect inhibitors block the expression or activity of pro-angiogenic proteins like EGFR. In Table 1 are listed some approved U.S. FDA angiogenesis inhibitors for the treatment of cancers. Following our interest in searching for new naturally occurring angiogenesis inhibitors, particularly non-protein stimulators of angiogenesis, we previously found that thyroid hormone analogs showed promising pro-angiogenic activity by multiple mechanisms. We reported that tetraiodothyroacetic acid (tetrac), which is a deaminated analogue of L-thyroxine (T4), is able to inhibit the pro-angiogenesis actions of T4 and 3, 5, 3'-triiodo-L-thyronine (T3).

Table 1: Examples of Some FDA-Approved Inhibitors.

Generic Name	FDA-approved Indication
Everolimus	Kidney cancer, advanced breast cancer, pancreatic neuroendocrine
	tumors (PNETs), and sub-ependymal giant cell astrocytoma
Vandetanib,	Thyroid cancer
Cabozantinib	
Bevacizumab	Colorectal, non-small-cell lung, and glioblastoma multiforme
Thalidomide	Myeloma
Lenalidomide	Myeloma (myelodysplastic syndrome (MDS))
Ramucirumab	Stomach cancer and gastroesophageal junction adenocarcinoma
Regorafenib	Colorectal cancer and gastrointestinal stromal tumor
Ziv-aflibercept	Colorectal cancer
Sorafenib	Renal cell and hepatocellular carcinoma
Sunitinib	Renal cell and gastrointestinal carcinoma
Temsirolimus and	Renal cell carcinoma
Axitinib	
Pazopanib	Renal cell carcinoma, kidney cancer, and advanced soft tissue
	sarcoma

Tetrac also has high affinity for the integrin -αvβ3 receptor, which is important for its interactions with extracellular matrix proteins and other growth factors. Due to huge application of nanotechnology in different biomedicine fields [6-9], and in order to limit the action of tetrac to the integrin -αvβ3 receptor, we conjugated it to poly(lactic-co-glycolic acid) (PLGA) from its outer ring hydroxyl without any change on the carboxylic acid group in the inner ring [10-12]. We also presented a new pro-angiogenesis modulator called MR-49 by deiodination of tetrac, which showed significant pro-angiogenic rather than anti-angiogenic activity of tetrac (Figure 2) [13].
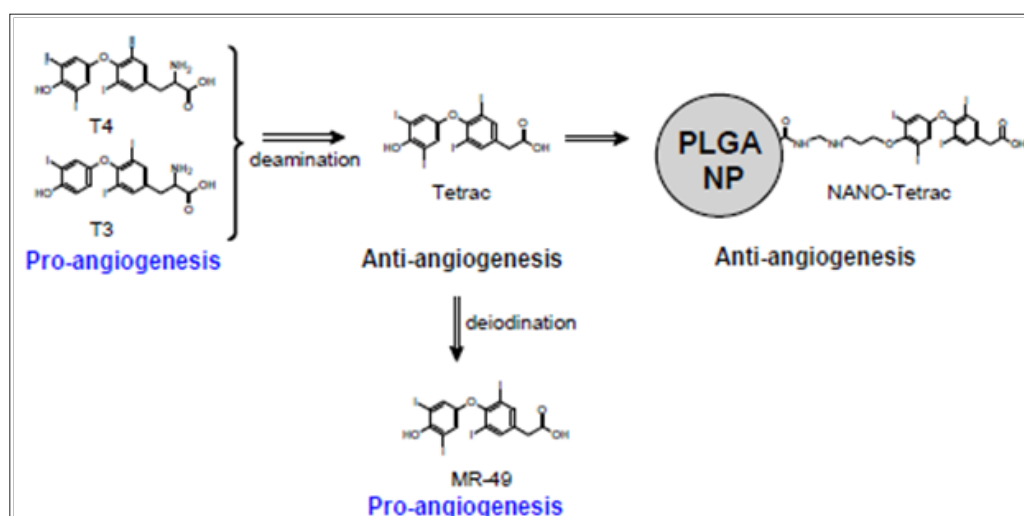

Figure 2: Chemical Structure of Thyroid Hormone Analogs.

Conclusion

Angiogenesis, the formation of new blood vessels, plays a significant role in tumor development and might be arrested by effective inhibition of tumor angiogenesis and thereby the growth of tumors may be decreased or stopped. There are two main way including direct or indirect method for designing new angiogenesis inhibitors and sometimes the combination of this anti-angiogenesis agent with some chemotherapy agents, might be essential for effective management of tumor.

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