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Review

Vascular-homing peptides for cancer therapy

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ABSTRACT

In the past 30 years, a variety of phage libraries have been extensively utilized to identify and develop tumor homing peptides (THPs). THPs specifically bind to tumor cells or elements of the tumor microenvironment while no or low affinity to normal cells. In this regard, the efficacy of therapeutic agents in cancer therapy can be enhanced by targeting strategies based on coupling with THPs that recognize receptors expressed by tumor cells or tumor vasculature. Especially, vascular-homing peptides, targeting tumor vasculature, have their receptors expressed on or around the blood vessel including pro-angiogenic factors, metalloproteinase, integrins, fibrin–fibronectin complexes, *etc*. This review briefly summarizes recent studies on identification and therapeutic applications of vascular-homing peptides targeting common angiogenic markers or with unknown vascular targets in some certain types of cancers. These newly discovered vascular-homing peptides are promising candidates which could provide novel strategies for cancer therapy.

Contents

1. Introduction

Tumorigenesis is a complex process resulting from genetic changes and malignant transformation of normal cells. A summary of common characteristics in most cancers includes uncontrolled cell proliferation, loss of apoptosis, uncontrolled in metastasis as well as angiogenesis. Angiogenesis is an essential process that

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facilitates tumor growth and survival [1–5]. The tumor vasculature which is structurally leaky, tortuous and fragile expresses a set of molecules and markers which are distinct from the normal blood vessels [3,6]. All these abnormalities contribute to tumor growth and cancer cell migration leading to uncontrolled metastasis which is the major complication and cause of death in cancer patients. So it is envisaged that effective cancer therapies should be targeting cancer cells as well as tumors vasculature. Moreover, blood vessels are more genetically stable and unlikely to acquire multidrug resistance which cancer cells often induce during the course of cancer therapies.

Vascular endothelial growth factor (VEGF) is a major stimulator in angiogenesis [7,8]. Although anti-VEGF therapies have been reported extensively, many problems exist with VEGF inhibition therapy such as acquired resistance and negative effects, due to the requirement of VEGF in non-angiogenic normal tissue function. Anti-angiogenic therapies also involved various membrane receptors and components of the extracellular matrix important in angiogenesis such as fibroblast growth factors (FGFs), platelet derived growth factors (PDGFs), placental growth factor (PlGF) and angiopoietins *etc*. Many of the strategies in inhibiting protein interactions targeting those factors mainly focus on human blocking antibodies and most of them have been clinically used or were undergoing clinical trials.

Monoclonal antibodies have been clinically used for Non-Hodgkin lymphoma, breast cancer and colorectal cancer, *etc* [9,10]. In recent years, especially the last five years, novel THPs especially vascular-homing peptides showed huge therapeutic importance as vascular-targeting vectors to deliver anticancer drugs and imaging agents in cancer therapy and diagnosis. Whole cells, tissue samples and live animals have been widely used as baits to obtain feasible binding peptides from a variety of phage libraries [11,12]. Many vascular-homing peptides could bind to multiple types of cancer, not to a specific one, which is based on the fact that molecular markers expressed on the surface of endothelial cells of tumor blood vessels are always shared or over-expressed in several cancer types [13,14]. This review briefly summarizes recent progress in clinical studies about some classical vascular-homing peptides like NGR and RGD and preclinical research for newly emerged novel vascular-homing peptides.

2. Vascular-homing peptides targeting common vascular molecular addresses

2.1. Peptide targeting CD13 (NGR)

Aminopeptidase N (CD13), a membrane-bound metalloproteinase, has been demonstrated to be involved in the regulation of cell proliferation and migration, antigen presentation, and angiogenesis [15–18]. It is mainly expressed by endothelial cells and pericytes in tumor vasculature, but also expressed in normal tissues, including mast cells, keratinocytes, myeloid cells, proximal renal tubules as well as epithelial cells [19–22]. In the 1990s, The NGR motif was isolated by *in vivo* phage display in nude mice bearing human breast tumors [23]. It was found that the motif could specifically bind to the blood vessel expressing CD13 which was barely expressed on normal blood vessels. The NGR peptide now serves as an important drug vehicle to deliver anticancer drugs and imaging agents for cancer therapy and diagnosis, showing high affinity to molecular markers expressed on the surface of endothelial cells of tumor blood vessels [23,24]. The NGR peptide-directed vasculature targeting aimed to increase neovasculature-homing attributes. In this regard, a broad spectrum of chemicals have been conjugated synthetically to NGR peptides, including cytotoxic drugs, therapeutic proteins, proapoptotic peptides, viral particles, imaging agents and DNA complexes [18,23,25–41].

Doxorubicin is the first anticancer drug coupled to an NGR peptide (CNGRC). Compared with unconjugated doxorubicin, the conjugate exhibits enhanced antitumor efficiency and decreased toxicity [25–27]. CNGRC-coupled proapoptotic peptide D (KLAKLAKKLAKLAK) specifically induced apoptosis of angiogenic endothelial cells [28]. NGR peptides have been delivered virus and DNA polyplex for gene therapy. Recombinant NGR-containing adeno-associated virus preferentially transduces CD13 expressing cells [40]. A novel NGR containing system, CNGRC-polyethylenimine-DNA polyplex, is developed for specific gene delivery [41].

Table 1
NGR peptides under clinical evaluation (http://clinicaltrials.gov/).

Condition	Status	Intervention	Phase	Year
Solid tumors	Ongoing	NGR-hTNFα	I	2007
Small cell lung cancer	Ongoing	NGR-hTNF: iv q3W 0.8 mcg/sqm NGR-hTNF; Doxorubicin: iv q3W 75 mg/sqm doxorubicin 60 min after NGR-hTNF infusion	II	2007
Ovarian cancer	Ongoing	NGR-hTNFα; Pegylated liposomal-doxorubicin; Doxorubicin	II	2011
Ovarian cancer	Ongoing	NGR-hTNF: 0.8 mcg/m^2 as 60-min intravenous infusion every week until confirmed evidence of disease progression or unacceptable toxicity occurs; Doxorubicin: 60 mg/m2 every 3 weeks, until cumulative dose of 550 mg/m^2	II	2011
Non-small cell lung cancer	Ongoing	NGR-hTNFα; Cisplatin; Gemcitabine; Pemetrexed	II	2010
Soft-tissue sarcoma	Ongoing	NGR-hTNFα; Doxorubicin	II	2007
Malignant pleural mesothelioma	Ongoing	NGR-hTNFα plus best investigator choice	III	2009
Malignant pleural mesothelioma	Recruiting	NGR-hTNFα	II	2007
Solid tumors	Completed	NGR-hTNFα: iv q3W escalating dose up 1.6 mcg/sqm	I	2007
Solid tumors	Completed	NGR-hTNF:iv q3W escalating dose NGR-hTNF up to 1.6 mcg/sqm; Cisplatin: iv q3W 80 mg/sqm 30 min after NGR-hTNF infusion for a maximum of six cycles	I	2007
Solid tumors	Completed	NGR-hTNF: 0.2, 0.4, 0.8 and 1.6 μg/m^{2}as 60-min intravenous infusion every 3 weeks; Doxorubicin: 75 mg/m^2 intravenous infusion over 15 min (starting 1 h after the end of NGR-hTNF infusion)	I	2007
Colorectal Cancer, Head and Neck Cancer, *etc*.	Completed	CNGRC peptide-TNF alpha conjugate	I	2006
Colorectal cancer	Completed	NGR-hTNFα: iv q3W or q1W NGR-hTNF 0.8 μg/m^2	II	2009
Colorectal cancer	Completed	NGR-hTNFα; Oxaliplatin; Capecitabine	II	2008
Malignant pleural mesothelioma	Completed	NGR-hTNFα: iv q3W or q1W 0.8 mcg/sqm NGR-hTNF	II	2004
Hepatocellular carcinoma	Completed	NGR-hTNFα: iv q3W or q1W 0.8 mcg/sqm NGR-hTNF	II	2007