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Review article

Targeted cancer therapy through antibody fragments-decorated nanomedicines

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ABSTRACT

Active targeting in cancer nanomedicine, for improved delivery of agents and diagnose, has been reviewed as a successful way for facilitating active uptake of theranostic agents by the tumor cells. The application of a targeting moiety in the targeted carrier complexes can play an important role in differentiating between tumor and healthy tissues. The pharmaceutical carriers, as main part of complexes, can be polymeric nanoparticles, micelles, liposomes, nanogels and carbon nanotubes. The antibodies are among the natural ligands with highest affinity and specificity to target pharmaceutical nanoparticle conjugates. However, the limitations, such as size and long circulating half-lives, hinder reproducible manufacture in clinical studies. Therefore, novel approaches have moved towards minimizing and engineering conventional antibodies as fragments like scFv, Fab, nanobody, bispecific antibody, bifunctional antibody, diabody and minibody preserving their functional potential. Different formats of antibody fragments have been reviewed in this literature update, in terms of structure and function, as smart ligands in cancer diagnosis and therapy of tumor cells.

1. Introduction

Targeted therapy, which improves the interference with specific factors, has been an innovative treatment for cancer. Targeting exclusive molecular mechanisms leads to a local action of active principles and reduces the side effects of conventional treatments on normal cells, thus minimizing the toxicity of chemotherapy. In targeted chemotherapy, the drugs are trained to target varied cellular factors and biologic transduction pathways including signal enzymes, factors involved in angiogenesis and apoptosis induction molecules [1].

In targeted therapy, the use of nanoparticles has provided promising results in delivery of different therapeutic agents and improved their effectiveness with increasing tolerability and bioavailability. The protection of payloads from chemical and biological degradation, development of bioactive macromolecules and capability to endure modification and decoration to be a specific targeting carrier are some of the advantages of therapeutic nanoparticles in drug formulation and delivery [2,3]. Paul Ehrlich magic bullet concept considered drug targeting as an entity of two components with two different roles of recognizing the target and providing a therapeutic action. The revised concept currently includes three components as drug, targeting moiety and pharmaceutical carrier [4,5]. In this way and especially for tumor therapy, various pharmaceutical carriers; such as polymers, liposomes, and micelles, obtained from natural or industrial resources, can be included [6,7]. The targeting moiety that is able to differentiate between tumor and healthy tissues, with greater specificity than the untargeted carrier, can include active targeting ligands with a specific affinity toward the affected zone; such as peptides [8,9], antibodies [9,10], aptamers [11,12] and small chemical entities [13].

On the other hand, there are three main ways for delivery of payloads of nanoparticle drug systems as: i) Passive targeting, when nanoparticles are accumulated in areas with leaky vasculature, as tumors and infarcts via reticuloendothelial system (RES) or enhanced permeability and retention (EPR) effects, ii) Active targeting, that employs the

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Table 1
Main cancer-associated antigens targeted by antibodies and antibody fragments in conjugation with nanoparticles.

Antigen	Full name	Structure	Function	Main type of cancers	Ref(s).
EGFR	Epidermal growth factor receptor	A transmembrane receptor with 4 extracellular domains, a transmembrane domain, an intracellular kinase domain	In epithelial development	Lung, glioma, oral and pharyngeal, liver, head and neck, colorectal cancers	[27,28]
VEGF	Vascular endothelial growth factor	A dimeric glycoprotein	Growth factor for vascular endothelial cells in angiogenesis and vasculogenesis	Ovarian, pancreatic, breast, lung, prostate, colorectal cancers	[29,30]
PLGF	Placental growth factor	A homodimer protein	Similar to VEGF	Pancreatic, prostate, lung, salivary gland cancers	[31–34]
HER2/neu	Human epidermal growth factor receptor 2	A transmembrane receptor with two ligand-binding regions, a short transmembrane domain, and a catalytic tyrosine kinase domain	In development of multiple organ systems	Breast, ovarian, lung, gastric, oropharynx, ovarian, colorectal, bladder cancers	[35]
PSMA	Prostate-specific membrane antigen	A transmembrane glycoprotein	A glutamate carboxypeptidase	Prostate cancer	[36,37]
HGFR/c-Met	Hepatocyte growth factor receptor	A glycosylated polypeptide with an extracellular α-subunit and a transmembrane β-subunit possessing tyrosine kinase activity	In cell migration and growth in embryogenesis	Renal cell carcinoma, lung, head and neck cancers	[38,39]
TfR	Transferrin receptor	A dimer protein with three domains for each monomer	Carrier for transferrin bound to Fe^{3+}	Colorectal adenocarcinoma, liver, leukemia, lung, breast, glioma	[40,41]
CEA	Carcinoembryonic antigen	A glycosyl phosphatidyl inositol (GPI)- anchored cell surface glycoprotein	In cell adhesion as an E- and L- selectin ligand	Colorectal carcinoma	[42]
IGF1R	Insulin-like growth factor 1 receptor	A dimer composed of two extracellular α subunits and two transmembrane β subunits containing the tyrosine kinase domains	In survival or apoptosis, cell migration, proliferation, and differentiation	Glioblastoma, melanoma, neuroblastoma, prostate, colon, lung cancers	[43,44]
EpCAM/CD326	Epithelial cell adhesion molecule	A transmembrane glycoprotein	A cell-cell adhesion molecule as well as in cell migration, proliferation, and differentiation	Breast, colorectal, ovarian cancers	[45]
CA19-9	Carbohydrate antigen 19-9	A glycoprotein	An epitope of sialyated Lewis A blood group antigen, a tumor marker	Pancreatic, colon cancers	[46]
PSCA	Prostate stem cell antigen	A GPI-anchored cell surface protein	In intracellular signaling, much remain unknown	Prostate, bladder and pancreatic cancers	[47]

targeting moieties coupled to nanoparticles for delivery of nanoparticles in affected zones as it is the case for the active targeting of angiogenesis, uncontrolled cell proliferation and tumor cells and iii) Physical targeting, which is another way of delivery of nanoparticles, based on abnormal physiological conditions as pH and temperature in the pathological zone [3,5].

The conventional targeted therapies show poorly understood effects in some of the tumors due to restricted availability of tissue or lack of an appropriate targeting agent with strong affinity to the intended location. Although this challenge might have failed, the changes in the targeting therapies have made notable advances in effective targeted treatments based on the use of small molecule inhibitors, antibodies or small molecules with high-affinity binding [14].

2. Antibody-decorated nanoparticles and novel ligand formats

Monoclonal antibodies (mAbs) have been successfully used at the experimental and clinical scale to target cancer-specific antigens [15,16]. Antibodies possess high specificity and a vital role in modern cancer therapeutics as ligands for nanosized drug delivery vehicles. Antibody-targeted nanoparticles can ideally act on specific cancer cells without significant side effect and adequate plasma half-life [17]. Furthermore, antibodies show suboptimal structural characteristics, especially in complex with nanoparticles, and thus the strategies over time move toward minimization the use of full antibodies. These strategies led to development of nanoparticle-antibody fragment conjugates which provide important biomedical tools in diagnostic and therapeutic fields [18]. In this category, there are arguments about the choice of different nanoparticles and questions concerning the development of complex and cellular interaction and uptake.

There are many types of nanoparticles, whether synthetic or natural, with a wide range of biomedical applications [2,19,20]. The polymeric nanoparticles are attractive drug carriers because of their great efficacy and reduced cytotoxicity on peripheral healthy tissues. The specific size and shape for tissue penetration and biodegradability allow them to be used notably for active and passive targeting [21]. Some polymeric nanoparticles are prone to facile chemical modifications which could enhance the binding specificity [19]. Polymeric micelles with a micellar core are also promising carriers to deliver chemotherapies to tumor cells due to their various molecular interactions. It can help to the efficient incorporation of different therapeutic molecules as hydrophobic or charged ones into the micellar core. They have an excellent stability as well as some nanocarriers formulations have a controllable size distribution [22]. Liposomes seem to be first carriers in drug delivery systems for the transition from bench to real use. Ease of synthesis, low batch-to-batch variability, biocompatibility, and steric stabilization lead to the superiority of liposomes compared to other nanoparticle carriers in the field of clinical manufacturing requirements. Moreover, liposomes are surface-functionalized in similar ways to other carriers to selectively target tumor cells. Galactosylated liposomes have been bound efficiently to asialoglycoprotein receptors expressing on the surface of hepatocytes for delivering the therapeutic agents. However, there are limitations in association with engineered liposomes in delivery systems; such as accelerated clearance and non-specific binding of serum proteins. The successful delivery of some ligand-targeted liposomes against some antigens is highly dependent on tumor development stage [23]. Nanogels or hydrogel nanoparticles with a highly hydrated structure were shown that can deliver the anticancer drugs with help of a biomolecular coating. The controllable swelling, viscoelasticity and other advantages related to these nanocarriers make them favorable candidates for drug targeting and stimuli-responsive formulations. Nanogels are flexible and versatile nanocarriers and therefore are offered as targeted drug delivery vehicles [24]. Carbon nanotubes are another ideal carrier for target drug delivery systems. They are huge cylindrical large molecules with unique physicochemical properties as large surface areas that, after appropriate