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Review

Structure-based design for binding peptides in anti-cancer therapy

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ABSTRACT

The conventional anticancer therapeutics usually lack cancer specificity, leading to damage of normal tissues that patients find hard to tolerate. Ideally, anticancer therapeutics carrying payloads of drugs equipped with cancer targeting peptides can act like "guided missiles" with the capacity of targeted delivery toward many types of cancers. Peptides are amenable for conjugation to nano drugs for functionalization, thereby improving drug delivery and cellular uptake in cancer-targeting therapies. Peptide drugs are often more difficult to design through molecular docking and *in silico* analysis than small molecules, because peptide structures are more flexible, possess intricate molecular conformations, and undergo complex interactions. In this review, the development and application of strategies for structure-based design of cancer-targeting peptides against GRP78 are discussed. This Review also covers topics related to peptide pharmacokinetics and targeting delivery, including molecular docking studies, features that provide advantages for *in vivo* use, and properties that influence the cancer-targeting ability. Some advanced technologies and special peptides that can overcome the pharmacokinetic challenges have also been included.

1. Introduction

The global market of cancer drugs in 2015 amounted to $107 billion [1]. Annual global growth in the market is expected to be 7.5–10.5% through 2020, reaching a total of $150 billion [1]. Recent progress in the identification of new cancer targets has widened the scope of anti-cancer therapeutics from conventional chemotherapy or radiotherapy to molecularly targeted drugs. However, without a "guiding missile" for cancer targeted delivery, many of such anti-cancer therapeutics lead to damage of normal tissues that patients find hard to tolerate. The explosion of genomic data has uncovered a plethora of genes available to be exploited as therapeutic targets with anti-sense oligonucleotides, siRNAs, etc. But, targeted delivery of these DNAs and RNAs to avoid interference with the functions of these genes in normal cells remains to be a bottleneck. In this regards, immunotherapy with monoclonal antibodies against cancer cell surface antigens has greatly improved cancer specific delivery, although some normal tissues expressing the same antigens are inevitably affected, albeit to a lesser degree. Since the approval of Rituximab for the treatment of non-Hodgkin's lymphoma in 1997 [2], immunotherapies have achieved considerable success in cancer therapy. The recent approval of bispecific antibodies [3,4], and CAR-T [5,6] have further fueled the therapeutic potentials of cancer immunotherapeutics (Fig. 1). However, the number of the available cancer surface antigen targets is still quite limited; and the current immunotherapeutics often do not possess ability to target a broad spectrum of cancers, thus requiring identification of expression of cancer surface antigens for selection of suitable monoclonal antibodies for particular cancer types. The development of immune checkpoint blockade by monoclonal antibodies has led to a new era in cancer immunotherapy, making cancer cure a realistic possibility. However, it may unleash immune system to attack normal cells, causing autoimmune phenomenon. Thus, cancer site specific delivery of these immune checkpoint inhibitors may confine the activation of immune system around the tumor site. Ideally, anticancer therapeutics carrying various payloads of drugs equipped with cancer-targeting peptide (CTP) can act as "guiding missiles" with the capacity of targeted delivery toward many types of cancers (Fig. 1). Henceforth, future development of novel "one for all" anticancer therapeutics for smart and targeted delivery to many different types of cancers is eagerly awaited.

In order to attain selective drug delivery, cancer biomarkers that are exposed exclusively on the surface of cancer cells may serve as

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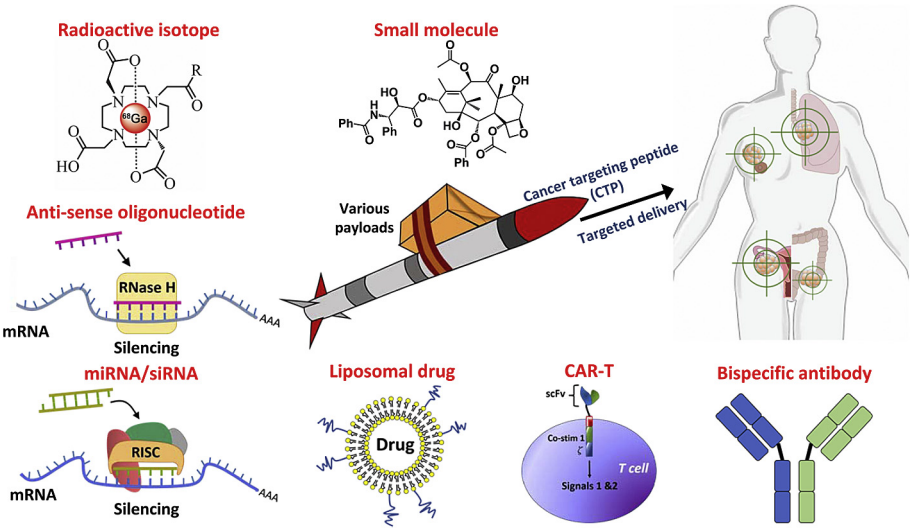

Fig. 1. Therapeutic payloads that can be carried by peptides for cancer-targeted therapy and imaging. Ideally, anticancer therapeutics carrying various payloads of drugs can be like "guided missiles" with the capacity of targeted delivery toward many types of cancers. In other words, novel "one for all" anticancer therapeutics that target against many different cancers will await further development of "universal" cancer targeting technologies. Cancer-targeting peptides (CTP) can guide various types of therapeutics to attack cancer cells. In addition to small molecules and radioactive isotopes, therapeutics such as anti-sense oligonucleotides, miRNA/siRNAs and liposomal drugs are all able to conjugate with cancer-targeting peptides. Immunotherapies like bispecific antibodies and CAR-T cells can also have cancer-targeting peptides.

valuable tools for achieving improved drug-delivery in cancer-targeting therapies. As "guiding missiles" to target cell surface biomarkers in cancer, CTPs are preferable to antibodies since sequence and conformation diversity may be more readily optimized for high specificity; peptides are also easier to synthesize and produce. Therefore, binding peptides are favorable for conjugation with many other therapeutic agents or delivery systems [7], especially using the CTPs which can target a broad spectrum of cancer types [8,9].

Peptides are a kind of aptamer which can be used to target a specific protein because unique amino acid sequences and conformations required for molecular recognition are usually achievable in peptides. Compared with traditional small molecule drugs, protein-binding peptides have not been widely developed for clinical use due to several disadvantages, including short half-lives in the circulation, indefinite cell permeability, poor oral bioavailability, and complicated conformations [10]. Nevertheless, the high potential value of peptides has led investigators to develop chemical or biological strategies for overcoming these natural disadvantages in pharmacokinetics, and binding peptides are, therefore, more likely to be widely developed for future *in vivo* use.

Most known peptide drugs are derived from fragments of natural proteins [11] or were discovered by screening a random peptide library, such as a phage-display [12]. The use of *in silico* strategies to design new peptide sequences based on the structural features of target proteins remains a great challenge. Difficulties with structure-based approaches to peptide design arise from several features of peptides, including exceptional flexibility of structure, indeterminate effects of secondary conformations, and a high number of potential molecular interactions that make optimization highly time consuming. Nevertheless, computer-aided methods play a useful role in the rational design of peptides [9,13]. Many tools for protein structural modeling and molecular docking have been successfully developed. Novel scoring algorithms, such as HotLig [14], are also proposed to improve the prediction of molecular docking [14]. To date, more than 127,000 structures of biological macromolecules have been collected and are available in the Protein Data Bank (PDB, http://www.rcsb.org). The abundance of these resources makes structure-based strategies applicable in peptide design. In this review, the development and application of strategies for structure-based design of targeting peptides will be discussed, especially the use of our recent studies on the optimization of the GRP78-binding peptides for enhancing the efficacy of cancer imaging and therapy [9].

In addition to issues regarding *in silico* methods for structure-based design for binding peptides, this review will also cover topics related to peptide pharmacokinetics and targeting delivery, including molecular docking studies, features that provide advantages for *in vivo* use, and properties that influence the cancer-targeting ability of peptides.

2. *In silico* strategies of structure-based design for binding peptides

Computer modeling can help to annotate and compile complex structural features of a protein. Furthermore, interactions between a protein and its binding peptides can be modeled by molecular docking strategies as an aid to understanding the factors influencing the formation of protein-peptide complexes and how to improve binding affinities through optimization of amino acid sequences in the peptides. Moreover, understanding the conformation of a peptide within the binding site of the protein is helpful for optimization of peptide structures. For example, cyclic or stapled peptides often have improved binding affinities when compared with highly flexible peptides. On the other hand, modification of peptide structures, without disrupting binding affinities, can also be useful in improving the solubility, bioavailability, biostability or other physicochemical/pharmacokinetic properties of peptides.

A scheme for designing peptides using molecular docking procedures is shown in Fig. 2. Briefly, the energy-optimized conformations of proteins and peptides are first required to perform molecular docking studies (Fig. 2). Only high quality structural data on the protein will enable reliable prediction of the molecular docking. In combination with the protein structural data, a known binding peptide can be used as a lead peptide for derivation of optimized structures (Fig. 2). For most applications, it would be time-consuming to use molecular docking to perform *de novo*