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Is There a Clinical Potential for Antimicrobial Peptides to Serve as a Second Option Treatment for Cancer Therapy? A Commentary/Opinion Paper

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ABSTRACT

Therapeutic antimicrobial peptides (TAPs) are becoming increasingly more utilized in the field of cancer therapies and treatments. Following the first synthesis of the man-made insulin peptide in the early 1920s, the marketplace for peptides has vastly changed. The use of peptides for nutritional supplements, body building regimens, and biomedical and clinical applications has significantly increased. More recently, the therapeutic utilization of peptides in the clinical cancer arena has employed peptides that instinctively home toward and onto cancer cells as their targeted objective. Such peptides are referred to as antimicrobial "tumor-homing" peptides. The many and varied properties and traits of such peptides include cargo-carrying capabilities to deliver drugs, radionuclides, heavy metals, nanoparticles, and exosomes to targeted cancer cells. This paper will review, discuss, and present the above issues concerning mainly the utilization of antimicrobial tumor-homing peptides for cancer treatment and potentially as therapies for other human disorders.

Keywords

Alpha-fetoprotein, Peptides, Growth, Cell cycle, Cell targeting, Antibodies, Small molecules, Cell penetration, Antimicrobial.

Introduction

Historical Background

The study of therapeutic antimicrobial peptides (TAPs) has been one of the most rapidly developing areas in pharmaceutical research and marketing fields in recent times. Early pharmaceutical research efforts in the 20th century originated as a need to search for less expensive small molecules that could behave or mimic the activities of naturally occurring peptide hormones, such as vasopressin, oxytocin, and insulin. In fact, the first successful synthesis of a mammalian peptide with a molecular weight in the range of 500 to 5,000 Daltons was the human insulin peptide, which was synthesized and manufactured in 1921 [1]. In today's marketplace, bioactive peptides in the production pipeline of many pharmaceutical companies can number more than 80 synthetic peptides. Such peptides have now been made available worldwide in a recombinant synthetic version, having replaced the prior animal-derived and isolated forms used in earlier years. At present, a large portion of the therapeutic peptides used in the clinic are directed against type-2 diabetes with peptide drugs known as the semaglutides, which work by mimicking the natural glucagon-like peptide (GLP-1) that regulates insulin secretion. Similar to treatment of type-2 diabetes, newly developed peptides have the potential for multiple applications in multifunctional roles in the clinic [2,3]. However, patients have become more interested in peptides after reading and hearing about peptide benefits for longevity, tissue repair, anti-aging, and energy sources.

The Use of Targeted Antimicrobial "Tumor-Homing" Peptides in Cancer Therapeutics

Objectives

The present report has been directed to the multifunctional applications of peptides in the course of targeted organ/tissue therapies, such as cancer. Although peptides can serve as small molecule and delivery agents, peptides can also be utilized to deliver carrier loads such as nanoparticles and extracellular vesicles (EVs). As drug carriers, peptides can further be conjugated to multiple cargoes such as drugs, radioisotopes, and other small molecules. These antimicrobial peptides can employ several methods of cell surface membrane penetration into target cells; such targeted cells can encompass malignant (cancer) cells, stem cells, and benign tumors [4]. In the course of such activities, peptides can further inhibit or antagonize cell surface receptors and block cytoplasmic signal transductions, receptor-to-receptor cross-talks, and intracellular protein-to-protein interactions. Unlike synthetic pharmaceuticals, peptides are often considered to be naturally recognized by the human body as "self" components. Thus, peptides are often portrayed to the public as natural alternatives to modern pharmaceutical drugs.

Comparison of Small Molecules Compared to Antimicrobial "Tumor-Homing" Peptides

In a comparison of small molecules to that of peptides, one can consider the following points. For example, small molecules can encompass a series of properties and traits which display ease of oral administration, low production costs, rapid cell surface membrane permeability, satisfactory outcomes, and lack of antigenicity. However, the disadvantaged properties of small molecules compared to peptides can include poor *in vivo* stability, lack of flexible molecular backbones, demonstration of low target specificity, and a reduced rate of elimination from the affected target areas (Table-1) [4].

Comparison of Antibodies to the Antimicrobial "Tumor-Homing" Peptides

Antibodies have long been employed in the clinic to treat many and varied types of medical conditions. The main reason for their usage, among others, is their high concentrations of binding affinities (picomolar, nanomolar concentrations) of the antibody to its targeted antigen, often being cell surface receptors [5]. In comparison, advantages of antibodies over antimicrobial peptides can encompass; a lesser capacity for molecular degradation, longer half-lives, slower blood clearance, proclivity for cell culture, ease of injection delivery into patients, and competitive production costs; such traits are especially true with the utilization of both neutralizing and monoclonal antibodies [6]. In contrast, the disadvantages of antibodies in comparison to peptides can include longer half-lives, slower target areas of accumulation, larger molecular size (150KDaltons), less capability for cell internalization, difficulties in quality control in post-manufacturing processes, high immunogenicity, increased cell toxicity, and increased.

Therapeutic Antimicrobial "Tumor-Homing" Peptide (TAPs) Traits and Properties

As compared to the above properties of small molecules and antibodies, therapeutic antimicrobial peptides (TAPs) can exhibit rapid elimination from the target areas, lower binding concentration affinities, decreased production costs, and shorter half-lives. In contrast to antibodies, TAPs further demonstrate higher efficiency in targeting cells and tissues, rapid cell membrane penetration and pore-forming ability, and ease of intracellular incorporation [7]. Furthermore, therapeutic TAPs have been utilized as tumor-homing vehicles for delivering various payloads or cargoes such as drugs, small molecule, nanoparticles, and extracellular particles and vesicles into target cells, tissues, and organs. As additional factors, TAPs exhibit low immunogenicity and can bind and antagonize cell surface receptors and associated proteins; furthermore, such peptides are able to interfere and/or block intracellular protein-to-protein interactions [8]. Finally, TAPs that carry cargoes could also transport cytotoxic peptides, radioisotopes, and short peptides containing tri-amino acid sequence stretches. An example of a classical TAP molecule is the alpha-fetoprotein derived "Growth Inhibitory Peptide" found only in the fetus during pregnancy; this peptide will be described below in more detail [9,10].

Table 1: Comparison Among Small Molecules, Antibodies and Therapeutic anti-microbial Tumor-Homing Peptides.

Properties	Small Molecules	Antibodies	Tumor-Homing Peptides
Affinity	None	Higher (pM-nM)	Lower (nM-µM)
Stability	Highly vulnerable to degradation	Less vulnerable to degradation	Moderately vulnerable to degradation
Body clearance and half-life in the blood	Rapid decrease, very short half-lives	Slower clearance and longer half-life (~3 weeks)	Moderately fast clearance with short half-lives (6-8 hours)
Target tissue accumulation	Rapid	Slower	Fast
Size (molecular weight)	Very small, less than 100kd	Large (150kDa)	Small 2-5,000 Daltons
Cell/tissue penetration	Rapid in most cases	Perivascular and slower	Extra cell matrix, rapid
Internalization into cells	Very efficient	Less efficient	Several minutes
Controlled chemical modification	Easily achieved	More difficult to achieve	Moderately efficient
Immunogenicity and toxicity (liver, bone marrow)	No immunogenicity, less toxicity	Less immunogenicity, low to moderate toxicity	Lack of immunogenicity, low toxicity
Production, quality control (QC), and cost	High quality control, low cost	Cell culture or animal, more difficult QC, and higher cost	Peptide synthesizer instrumentation, usage, and moderate cost easy quality control

Legend: NM= nanomolar; µM= micromolar; PM=picomolar

A Comparison of Therapeutic Antimicrobial (Tumor-Homing) Peptides to Those of Cell Penetrating Peptides (CPPs)

The cell penetrating peptides (CPPs) represent small molecular weight peptides that mimic a type of peptide sequence derived from an HIV-1 protein termed the "transactivator of transcription (TAT) Peptide"; this specialty derived type of peptide can penetrate into cells and deliver cargoes to cancers and dysfunctional and/or distressed cells [11]. The CPPs represent potent multi-cargo peptide carriers that can passage into and through cell membranes. In comparison to the TAPs, the types of peptides that represent the CPPs consist of full-spectrum antibiotic peptide agents that can attack microorganisms such as bacteria and fungi. Some CPPs, such as the "matrikines", are capable of participating in cellular biological activities such as cell growth/proliferation, differentiation, migration, adhesion, and apoptosis. In contrast, the tumor-homing TAPs differ from the CPPs in their main purpose, utility, amino acid composition, and biological activities. However, in contrast to other larger peptides, CPPs can induce the opening of small transient cell membrane pores resulting in membrane cytolysis and leakage, while subsequently delivering small drug cargoes into cancer and other distressed, dysfunctional cells [12]. In comparison, TAPs are able to destabilize and disrupt the cell surface membrane bilayer, partition into the cell surface membrane bilayers, induce formation of transmembrane channels and/or pores, and aid in enhancing the host innate immunity [11,12]. However, the prime targeting objective of the CPP is the cell surface bilayer membrane, which induces small pores for intracellular entry. They can also penetrate cytoplasmic organelle membranes, disrupting signal transduction pathways. The TAPs, in comparison to CPPs, focus on drilling or permeabilizing into the cell surface bilayer membrane to partition membranes into their phospholipid headgroup layers; this ultimately influences cell penetration and downstream cellular activities. There exists in CPPs, an abundance of positively charged amino acids (AA) together with the presence of a significant number of hydrophobic AAs [13]. In contrast to the CPPs, the TAPs comprise mostly amphipathic properties; these include a notable number of hydrophobic AAs in conjunction with lesser amounts of positively charged AAs. As candidates for cancer therapeutic agents, the TAPs are superior to CPPs in that the TAPs affect cell membrane channels and pore formation which results in stabilization of the cell membrane electrical potential (Table 2).

Comparison of The Growth Inhibitory Peptide (GIP) with CPPs and the Tumor-Homing TAPs

As mentioned above, the pregnancy Growth Inhibitory Peptide (GIP) resembles a TAP molecule, which constitutes a peptide derived from the fetal AFP polypeptide during mammalian pregnancy. In contrast to CPPs, GIPs are capable of not only creating pores but also inducing channel formation within the cell surface bilayer membranes; these channels are often localized near clusters of cell surface receptors together with associated chemokines and cytokines in a signal complex grouping cluster [14]. The antimicrobial-like "tumor homing" GIP peptides can also function to disrupt and destabilize cell membranes and bind to the cell surface bilayer membranes by means of their α-helix contents, AA composition, and amphipathic features. Peptides such as GIP and the TAPs are attracted to and bind only to net negative charged cell surface membranes; such negative charged membranes are also displayed on bacteria, fungi, and transformed cancer cells together with population of tumor stem cells. In summation, the GIP cell homing attraction to cancer cells depends entirely on the electrostatic cell surface net negative charge displayed on the surface of cancer and tumor stem cell membranes [15]. This latter electrical charge property stands in contrast to the positive charge present on normal, non-distressed, non-malignant, and highly growth regulated cells (Table 2).

GIP Could be Considered as a Hybrid Peptide Form by Possessing Properties Shared by both CPPs and the Tumor-Homing TAPs

The hybrid properties and traits of CPPs and TAPs are not always equally shared with the GIPs. Thus, examples of compliance and

Table 2: Comparison of Cell Penetrating Peptide (CPP), tumor antimicrobial peptides (TAP), and AFP-derived growth inhibitory peptide (GIP) according to their biochemical and biophysical properties.

Characteristics, Traits, Properties	Cell Penetrating Peptides	Anti-microbial tumor-homing Peptides	AFP-derived GIP peptides
1. Stability	Highly vulnerable to degradation	Moderately vulnerable to molecular degradation	Slow to moderate molecular degradation
2. Body clearance half-life	Rapid clearance 4-6 hours	Moderate clearance, 6-8 hours	Moderate clearance, 5-6 hours
3. Cell membrane penetration	Forms transient pores, penetrates cell membrane bilayers	Forms transmembrane pores and cell membrane channels	Interacts with cell surface membranes forming pores and channels
4. Cell-specific targeting	Bacterial cell wall of fungi, virus, and mammalian cell membrane	Microbial cells walls, mammalian cell membranes	Mammalian cell membrane, cancer and cancer stem cell membranes
5. Cell cargo delivery	Transports microorganism and carries bound drugs, chemical, small molecules	Cargo drug carrier that binds metals, fuses with peptides/proteins	Transmembrane passage of small ligands, binds dyes and heavy metals
6. Peptide secondary structure	Disordered in free solution, mostly lacks secondary structures	Displays alpha helix, beta sheets and turns, hairpin loops	Displays α-helix, beta sheets, hairpin loops, low-disordered structures
7. Number of amino acids	6-10 amino acids	12-50 amino acids	8-36 amino acids
8. Cell toxicity	Cytolytic, cytotoxic	Cytostatic, cytolytic and cytotoxic	Cytostatic only
9. Cytokine chemokine effects	No effect on cytokines, chemokines	Induces cytokine and chemokine production interaction	Regulates and is synergistic with chemokines and cytokines

AFP= alpha-fetoprotein; AA=amino acid.

non-compliance sharing traits among the receptor peptides are discussed below. For example, both GIP and TAPs do not require binding as a cell surface interaction in order to penetrate through the cell membrane and gain intracellular entrance. In contrast, CPPs interact with a cell membrane energy-dependent clathrin/caveolae-mediated endocytosis system to accomplish cell entry [12,13]. In contradistinction, all three peptides can and do employ attraction to an energy-independent electrical net surface charge interactions, specifically with a net negative-charged cell surface membrane as discussed above. However, only CPPs require a guanidinium group interaction for cell surface membrane penetration working together with the clathrin/caveolae interaction process mentioned above [13]. It is interesting that CPP and TAP peptides are both mechanistically cell cytotoxic, cytostatic, and cytolytic, while GIP is solely cytostatic. It is further known that CPPs consist of a total length of only 6-10 amino acids, while TAPs and GIPs can range from 8 to 40 AAs in length [14]. Regarding secondary structure, CPPs are largely disordered in solution and mostly lack a significant secondary structure, while both TAPs and GIP display alpha-helix, beta sheets, and hairpin loop secondary structures together with a small proportion of disordered structures [15]. Finally, CPPs display a lack of biological activity for the angiogenesis process as well as the cytokine/chemokine interaction events. However, both TAPs and GIP show numerous cytokine/chemokine interactive cell surface events and synergistic biological activities [16]. Thus, GIP has been shown to display multiple TAP-like effects, but lesser but still present CPP properties in the presently proposed TAP/GIP model of a hybrid molecule comprising some of both peptide properties.

Therapeutic Antimicrobial "Tumor-Homing" Peptides in the Delivery of Nanoparticles

TAP peptides have been utilized as dronelike molecules for the delivery and transportation of nanoparticles. Nanoparticles themselves are defined as extremely small particles with dimensions ranging from 1 to 100 nanometers, while providing a large surface area-to-volume ratio. This size-to-volume ratio provides a property favorable for multiple applications in medicine, electronics, and environment sciences. The binding of nanoparticles to peptides can increase the contact affinities of the peptide to bind to cancer cell surface membranes. In addition, the peptide-nanoparticle complex further protects the peptide from protease-mediated degradations [8]. One of the best-known peptides employed as tumor-homing peptide is the tri-amino acid sequence of RGD found imbedded within an 11 amino acid peptide with the single letter code of ACDCRGDCFCG (termed RGD-4C peptides) [17]. This RGD-4C peptide has been reported to bind to a cell surface membrane containing an overexpressed αVβ3 integrin molecule which participates in angiogenic blood vessel formation at the surface of tumors. The attachment of the RGD-4C peptide not only binds to the tumor cell surface membranes but also enhances the cell penetration of peptide-bound drugs being delivered into tumor cells. Overall, the binding of RGD-4C peptide to the cell surface integrin as discussed above, can affect the targeting of the RGD-4C peptide to different types of cancers including melanomas, and colon, ovarian, lung, and glioblastoma brain tumors. Again, as in many cases, the cell surface αVβ3 integrin molecule plays a significant role as a cell surface membrane target [18].

Therapeutic Peptides in the Delivery of Exosomal Vesicles (EVs)

Exosomal vesicles are endogenous cytoplasmic microparticles which are secreted from various cells into the blood circulation. Exosomes are technically defined as tiny, intracellular derived vesicles (round sacs) that can serve as intercellular transductor messengers because they are able to transport proteins, RNA, and DNA cargoes; hence, such biological compounds can be transported by therapeutic antimicrobial tumor-homing peptides as cargoes to be delivered into cells [19]. Exosomes range in size from 30 to 160 nm and can be utilized in multiple therapeutic applications such as wound healing, tissue repair, and inflammation. Such EV particles are also capable of transporting nucleotides, proteins, and lipids for deposition into multiple types of target cells. Tumor-homing peptides loaded with surface bound exosomes, when taken into tumors cells, have been reported to decrease adverse side effects which occur during and after applied chemotherapeutic treatments [20]. The surface modifications of exosomes can be performed using genetic engineering of immune-associated dendritic cells that have been previously modified to contain exosomes expressing LAMP2, a cell membrane protein fused to an RVG-10 amino acid peptide. Furthermore, RVG peptides bound to exosomes have also been utilized to deliver short interfering RNAs into neurons, microglia, and oligodendrocytes in the brain. This type of peptide brain delivery has been accomplished by specifically targeting the exosomes onto the brain-derived gamma-aminobutyric acid (GABA) receptor, which can induce target gene knockdowns [21]. Finally, exosome surfaces have been modified to employ lipid-based membrane anchors, electrostatic interactions, and ligand-receptor interactions. Tripeptides with RVG and RGD AA sequences have further been directed against targeted tumor cells located in the brain, breast, melanoma, and lung tumors [22].

Additional Functions of the Tumor-Homing Peptides

Tumor-homing peptides can further bind to cell surface receptors and penetrate through cell membranes to deliver their cargoes (see below). Alternatively, other similar peptides can serve as antagonists to target cell surface receptors and/or accessory proteins whose TAPs serve as interference peptides. Once within the cell cytoplasm, such peptides can bind to their intracellular targets and inhibit the interactions between the target and a binding partner which is involved in blocking intracellular protein-to-protein interactions [23-26].

Peptide-guided Delivery of Cells

Tumor-homing of peptides bearing cytotoxic T-lymphocytes directed to cancer have also been developed which take advantage of the "chimeric antigen receptor" (CAR)- T cell technology employed to enhance T cell- to- tumor interacting properties [27]. The CAR-T cell technology was designed and developed to express three biologic components composed of: 1) A dual chimeric receptor composed of an anti-tumor antibody, 2) a cytoplasmic zeta chain from the T-cell receptor, and 3) these are

together with a co-stimulator domain segment [28]. Such CAR-T engineered cells have demonstrated enhanced tumor-homing and anticancer growth properties.

Peptide-Targeted cytotoxic Peptides

Cationic amphipathic peptides with cytotoxic properties demonstrate an ability to reduce multidrug resistance regarding tumor cells and to display broad-spectrum anti-tumor activities [29]. However, as disadvantaged affects, such cytotoxic peptides possess poor cell membrane penetration, weak therapeutic activity, and a lack of structural stability. In posing positive advantaged affects, such cationic peptides can trigger mitochondrial membrane disruption, release of Cytochrome-C, and induction of cell apoptosis [30]. Other such peptides are capable of inducing mitochondrial swelling leading to programmed cell death. Similar types of cytotoxic and lytic peptides are part of the components found within the human defensin peptide family of AMPs.

Peptide Targeted Receptors Combined with Radionucleides (PRTR)

The TAP "tumor homing" peptides that target receptor combine the tumor-homing properties with their ability to bind and deliver radionuclides (radioactive isotopes) into cancer cells [31]. However, radioactive toxic side effects to neighboring healthy cells remains a confounding factor especially regarding bone marrow cells. Such peptides can selectively target endocrine-associated cell receptors in the treatment of neuroendocrine tumor cells [32]. Such TAP peptides can also affect the development of nearby blood vessels, which are engaged in the angiogenic formation response. Digestive tract cell receptors can further be affected by such peptides targeted to the cell surface receptor response and these are being exploited to target tumors such as human colon, colorectal, and pancreatic cancers [33].

Tumor-Homing Peptides as Drug Conjugates

Peptides conjugated to small molecule drugs require the constituents of three basic elements. First, a TAP tumor-homing peptide is required to provide the foundational base molecule; secondly, a chemical "linker" bond agent must be supplied; and thirdly, a cytotoxic drug is the effector factor to be added [34]. The delivery of this triad group into tumor cells can produce a toxic effect by the interaction and contact with intracellular targets. Lastly, intracellular enzymes present within the cytoplasm are able to break the drug linkage bond connected to the peptide and release the drug into the target cell cytoplasmic compartment [35]. Thus, the peptide-drug conjugate can bestow a cytotoxic effect on the cancer cell without harming normal bystander cells in order to increase their therapeutic efficacy. In summation, the use of the peptide-drug conjugate provides a safe advantage to bystander cells within the patient due to the rapid clearance of the drug conjugate, its low immunogenicity, and lack of liver organ induced damage.

Tumor-Homing Peptides as Antagonists of Kinase Enzymes Directed to Receptors and Relevant Proteins

Tumor cell surface membranes display an abundance of various growth factor receptors which can be utilized as anticancer target agents. One such receptor is the c-Met receptor for a tyrosine kinase enzyme which binds to the hepatocyte growth factor (HGF) [36]. It is the HGF that is involved in the initiation of both tumorigenesis and the metastatic processes. Thus, such peptides have been designed to bind c-Met with a high affinity which is intended to inhibit tumor cell migration and cell proliferation. As a second example, a genetic splice variant of the CD44 lymphocyte cell surface receptor that binds c-Met has been exploited to inhibit tumor growth in preclinical pancreatic cancer models [37]. Thus, peptides that act as cell surface receptor protein antagonists have the capability to serve as potential therapeutic agents for inhibiting cancer cell growth, progression, and metastasis.

Tumor-homing Peptides as Antagonists of Hormone Receptors

Blocking or inhibiting the actions of hormones in malignant endocrine organs is a process capable of slowing or downregulating the growth of cancer cell. This type of hormone therapy in reproductive organs, applied to breast and prostate cancers, has been utilized as a standard of treatment to decrease tumor size and cell volume [38]. Therapeutic peptides directed against such hormone receptor targets (i.e., gonadotrophin-releasing hormone) can downregulate and desensitize the hormone receptor in pituitary cancer target cells. Other such therapeutic peptide serving as a receptor antagonists have been employed against ovarian, prostate, and breast cancers; these actions have proven effective due to the use of non-peptide hormone antagonists displaying short half-lives [38]. Finally, a therapeutic "tumor-homing peptide" has been developed against the receptor for Somatostatin, which is a hormone produced by paracrine cells throughout the gastrointestinal tract [40]. Thereby, the inhibition by tumor-homing therapeutic peptides has been directed against the somatostatin receptor which has resulted in blockage of both insulin secretion and glucagon metabolism.

Concluding Statements

It is evident from the above discourse, that therapeutic peptides will predictively be a wave of the future regarding novel cancer treatments and perhaps other ancillary disease. In the current market, peptide-based therapeutics have largely included diabetic drug peptides and peptide-based hormone analogs such as octreotide, leuprolide, and goserelin. In future years to come, an increasing number of peptide therapeutics will have been developed, especially regarding the field of cancer therapies; these could serve as an adjunct or second option cancer chemotherapy agents. In cases other than cancer, therapeutic peptides have become or are in the process of becoming an important source as alternative or secondary options for present day maladies, such as various sicknesses, diseases, and disorders. For example, the FDA has approved a number of peptides as drugs, such as insulin in diabetes that do not naturally synthesize sufficient amounts of such peptides for the patient. As an example, the human growth hormone peptide has been supplied to children with developmental disorders and delays caused by low levels of the growth hormone peptide. In the long run, the major factor in selecting peptide medications for patients has remained depending whether such medications are safe and effective in long term treatments.

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