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The Potential Use of Therapeutic Peptides as Cancer Chemotherapeutic Agents: A Commentary and Prospectus

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Abstract

The use of therapeutic peptides is rapidly becoming more utilized in the field of cancer treatment and therapies. Certain classes of therapeutic peptides belong to a group of pharmaceutical agents termed antimicrobial peptides (AMPs). Such AMPs represent the first immediate line of defense of the innate immune system against microbial infectious agents. It was recently discovered that AMPs possessed the novel property of specifically targeting cancer cells, to which they attach, and penetrate into the cell's cytoplasm. In the present commentary treatise, therapeutic peptides are described concerning their structures, functions, and biomedical applications. In addition, the advantages and drawbacks of the use of therapeutic peptides are introduced and presented. The discussion further advances to the multiple utilizations and optimizations of therapeutic peptides in both basic science and clinical research applications. Finally, the use of a pregnancy-associated AMP is presented as an example in multiple functions and usages in the biomedical field regarding its future chemotherapeutic applications.

Keywords: Alpha-Fetoprotein; Cancer; Peptides; Cell Cycle; Chemotherapy; Chromosome; Instability; Antimicrobial Peptides

Introduction

Certain therapeutic peptides belong to a class of pharmaceutical agents termed antimicrobial peptides (AMPs) which are primarily involved in the innate arm of an organism's immune system [1]. This class of AMPs represents the first line of defense against microbial infectious agents which include bacteria, fungi, and parasites. In recent times, it has been discovered that the AMPs portrayed a unique property that could be employed in the course of cancer therapies. This advantageous trait involved the ability of AMPs to specifically home toward and penetrate into malignant tumor cells while capable of delivering a drug payload (or other cargo) into the cancer cells this tumor-homing property of AMPs is due to their ability to target cells or microbes bearing a net negative charge on the cancer cell's bilayer surface membrane. Compared to other biologics, therapeutic peptides such as AMPs, show little or no immunogenicity, have good targeting abilities, and produce low manufacturing costs [2].

Therapeutic Peptides: Structure, Function, Current Applications

Therapeutic peptides represent a novel class of pharmaceutical (biochemical) substances composed of a sequence series of well-ordered amino acids with overall molecular weights ranging from 500 to 5,000 Daltons. Research into therapeutic peptides originated from multiple biomedical research studies involving the biological activities of natural hormones such as oxytocin, vasopressin, and insulin [3]. The first half of the last century revealed the discovery of life-saving bioactive peptides which were initially researched and isolated from natural sources. Since then, a sophisticated order of peptide developments has been initiated that included novel peptide drug discoveries encompassing novel drug designs, new synthesis methods, adoption of structural modifications, and novel assays for their biologic activity [4]. Analogs of human peptides have now been developed by attaching fatty acids (myristylation) and glutamic acid spacers on lysine residues which were utilized to act as glucagon-like (GLP) receptor agonists for the treatment of type-2 diabetes mellitus [5]. In addition to Type II diabetes, other peptide drugs have since been developed for multiple therapeutic uses in medical areas such as kidney disease involving proteinuria, assay of glomeruli filtration rates, weight loss, cardiovascular disease (heart failure), gastrointestinal obstructions (Crohn's disease), gastric motility disorders, and several different types of cancers [6].

Concerning cancer therapies, peptides have recently been utilized in multiple purposes such as A) imaging probes to detect cell surface proteins expressed in various cancers, B) labeling β-emitters on radiotherapeutic peptides, and C) as cancer antigens to produce vaccines interacting with complexes such as major histocompatibility factors [7]. Such cancer vaccines have been produced by targeting antigens present on cells of the host immune system. Finally, peptides can be utilized as drug carriers to penetrate and deliver cargoes into cancer cells, deposit payloads, and interfere with intra-cytoplasmic protein-to-protein interactions.

Some Advantages and Drawbacks on the use of Therapeutic Peptides

Therapeutic peptides are further capable of attaching and binding to cell surface membranes in order to interact and trigger downstream intracellular effects. Such peptides have been designed to mimic hormones, growth factors, ion channel components, and anti-infective agents. Peptide binding to cell surface bilayer membranes and intracellular targets can display both high affinity and specificity with modes of action involving various biologics involving proteins and antibodies [7]. However, compared to these latter biological entities, therapeutic peptides exhibit less immunogenicity, higher specific targeting to cells, lower production costs, and low consumer purchase prices [7]. More importantly, peptides can also employ favorable oral (pill) routes of administration to patients. In contrast to small molecules, the physiochemical properties of therapeutic peptides, including their larger size and more flexible backbone, enable them to act as potent cytoplasmic protein--to-protein inhibitors [9]. In clinical environments, such therapeutic peptides can serve as tumor anti-angiogenic agents and can seek out targets such as kinase enzyme receptors, and interactions with serine/threonine receptors; such interactions can result in either cytophilic or cytotoxic result or both [10].

Some, but not all, therapeutic peptides may display some intrinsic limitations, namely, 1) less cell surface

membrane impermeability and 2) reduced in vivo stability. In certain circumstances, such traits could present challenges in further peptide drug developments [11]. In the first instance, certain peptides could display a propensity of weak cell membrane permeability traits which are dependent on both peptide amino acid length and composition. In addition, secondary structure could play an important role with structural compositions consisting of α-helices, and beta sheets, turns, and loops. However, peptides with limited membrane impermeability properties can often target multiple cell surface receptors such as G-coupled receptors, gonadotropin-releasing hormone receptors, and glucagon-like peptide (GLP) receptors [12]. In comparison, many other therapeutic peptides, such as AMPs, are capable of forming pores and channels in cell surface membrane bilayers to overcome this obstacle. In the second instance stated above, some peptides can display poor in vivo stability as a result of vulnerabilities imposed by the effects of amide bond protease degradation and modified secondary and/or immobilized structures [13]. For example, amide bonds are easily hydrolyzed and can be targeted by proteases that attack peptides with improper chemical bond protection. In addition, some peptides lack sufficient secondary/tertiary framework protective structures, which can result in chemically and physically less stable peptides; such peptides can exhibit short half-lives and rapid in vivo elimination [14]. As described below, the presence of asome classes of therapeutic peptides, such as AMPs, can display secondary/tertiary features which can overcome some of the disadvantages described in the previous section.

The Multiple Utilization and Optimizations of Therapeutic Peptides (TP)

A) Therapeutic peptides (TPs) have varied utilizations in the medical field. For example, certain TPs are capable of mimicking hormones albeit they exhibit very short half-lives in vivo. Extensive efforts have been made to modify the structural amino acid sequence that enhances the stability of hormonal-like peptides such as Glucagon-like Peptides (GLP1). The GLP-1 is a 37 amino acid peptide that regulates insulin production and secretion with one such example being Ozempic, a semaglutide [15]. However, an ever-present danger with use of GLPs is the potential of a medically induced annorexin in users. Certain other peptide mimics include leuprolide, a gonadotropin-releasing hormone (GNRH), which is used as a GNRH receptor agonist for treating endometriosis, uterine fibroids, and precocious puberty [16]. Octreotide is another PT which is a somatostatin mimic drug utilized for the treatment of excessive growth hormone levels as found in acromegaly [18]. Additional natural bioactive peptides have been derived from other biologic forms such as bacteria, plants, and animal secretions such as disintegrins in snake venoms [3] (Table-1).

Table 1: The Classical Antimicrobial Therapeutic Peptides (AMP) are Composed to the GIP-34 Peptide and Listed According to their Biochemical and Biophysical Characteristics, Traits, and Properties

Characteristics, Traits, Properties	Antimicrobial Peptides (AMP)	AFP-Derived Growth Inhibitory Peptide (GIP)	References
1) Cell membrane penetration effects	Forms transmembrane pores and/or ion channels, stabilizes the cell membrane potential	Interacts potentially with transmembrane channels and is a cell membrane disruptor	[1, 9]
2) cell method internalization	Transmembrane channel, and pore forms, pinocytosis	Interacts with membrane channels, as a pore-forming and displays non-receptor endocytosis mechanism	[2, 4]
3) Cell-specific targeting	Microbial cell wall/membrane, plasms membranes of vertebrate (mammals), transformed cancer cells	Plasma bilayer negative cell membrane; of target cells, transformed cancer cells, stem cells, and bacterial membranes	[6, 10]
4) Cell cargo delivery and associated properties	Contains low cargo delivery capability, binds metals, dimerizes with peptides and proteins, binds nanoparticles	Transmembrane passage of small ligands, binds dyes, metals, and promotes protein/peptide interactions	[11, 13]

5) Cell toxicity	Cytostatic and/or cytolytic	Cytostatic only	
6) Number of AAs in lengthAmino Acid (AA) Composition	Largely amphipathic-containing both positive and negative charged AAs and hydrophobic AAs second structure	Amphipathic forms containing positive and negatively charged, and hydrophobic AAs in secondary structure	[23, 25]
7) Peptide secondary structure	Displays alpha-helix, beta sheets, beta hairpin loop structures	Displays alpha-helix, Beta sheets, β-hairpin loops, and disordered structures	[32, 33]
8) Effect of host immunity	Promotes and enhances the innate immune response of host organism, initiates immunomodulation	Synergistic with cytokine/chemokine receptor activities, binds secondary targets sites	[35, 36]
9) Angiogenesis responsiveness	Modulates angiogenesis and related factors	Blocks/inhibits angiogenesis-associated factors	[36]
10) Cytokine/chemokines interaction	induces cytokine/chemokine production pro-inflammatory reactions	Synergistic and regulate chemokine with activities	[37]
11) Metastasis, cell spreading and migration	Neither enhances nor inhibits metastasis	Inhibits cell spreading/migration and inhibits metastasis	[40, 41]
12) Effects on platelet aggregation	No effect	Inhibits platelet aggregation	[43, 45]

GIP= growth inhibitory peptide; AMPs= antimicrobial peptides

Rational Design of Peptides Based on Protein--to-Protein Interactions

The rational design of TPs can involve discovery technologies based on the known crystal structure of targeted proteins [14]. Such rational designs of TPs have included computer-assisted bioinformatics technology comprised of computational analysis of major and minor binding pocket sites located on proteins [19]. Such technologies have involved the identification and location of the molecular surfaces of two interacting proteins. One such computational technology has involved the Root-Bernstein method of amino acid pairing interactions [20]. Further TP development has comprised structural optimization methods such as peptide cyclization, myristylation and backbone modifications intended to improve biological activity, storage stability and physiochemical properties [21]. The optimization modifications of the peptide secondary structure can encompass sequence modifications to stabilize the peptide secondary structure which involves structures such as α-helices, beta turns, beta loops, and beta hairpin conformations which enhance and improve cellular intake bioactivity, availability, and physiochemical properties of the therapeutic peptide [22]. Finally, identification of non-essential versus essential amino acids in the peptide sequence could constitute a first step in such modifying endeavor.

The Chemical Synthesis of Therapeutic Peptides

The chemical synthesis of TPs has utilized the development of solid phase synthesis technology by a procedure developed in 1963 [22]. This method of modern-day peptide synthesis is accomplished by combining a series of sequential steps involving amino acid compiling of consecutive amide bond formations with each subsequent step of amide bond protection followed by a deprotection step method. This type of peptide synthesis is accomplished by multi-step reactions within an instrument called an automatic peptide synthesizer. The impurities produced via the final solid phase procedures are mainly derived from incomplete side reactions during the overall synthesis procedure [23]. Solving the elimination of the synthetic side reactions has made the chemical synthesis of therapeutic peptides a relatively uncomplicated commonly used methodology [23, 24]. In summary, the solid phase synthesis of peptides consists of a cycle of coupling the carboxylic group of amino acids to a solid polymeric resin, and the liberation of amine

groups from a chemical protection group [24].

The Growth Inhibitory Peptide: An Example of a Therapeutic Antimicrobial Peptide

A) Alpha-fetoprotein as the Origin of the Growth Inhibitory Peptide (GIP)

Human alpha fetoprotein (HAFP) is tumor-associated pregnancy protein present during both ontogenic and oncogenic growth phases. The HAFP protein has recently been shown to provide the source of an intrinsic peptide, as described below. In the clinical laboratory, HAFP has long been employed as a tumor and gestational age-dependent fetal defect marker with dual utility as a screening agent for both neural tube defects and aneuploidies [25]. HAFP has further been utilized as a serum tumor biomarker for liver, yolk sac, and germ cell cancers. In recent years, AFP has been determined to be a growth regulatory factor for both fetal and tumor cells in which HAFP enhances the growth in both cellular types [26, 27]. In contra-distinction to its growth promoting features, HAFP is also able to undergo a molecular conformational change that converts the entire growth promoting HAFP molecule into a temporary transitional form that displays growth inhibiting properties. This temporary growth inhibiting form derived from HAFP has been termed "Transformed AFP." This HAFP intrinsic-derived peptide has been isolated, purified, and characterized as a 34 amino acid peptide fragment and has been termed the "Growth Inhibitory Peptide" (GIP). The GIP peptide has since been classified an antimicrobial peptide due to its similar structure and properties to the AMP (Table-1).

B) The HAFP-derived Growth Inhibitory Peptide

Growth Inhibitory Peptide (GIP) is a "novel" peptide derived from HAFP which is present in fetal and maternal blood during pregnancy [28]. The free isolated 34-mer peptide is capable of targeting, blocking, and suppressing unwanted, non-regulated growth spontaneously arises in the human fetus [29]. Regardless of whether these unregulated growths are caused by cellular genetic miscues or by environmental mutations, the GIP fragment for HAFP produces a temporary pause in fetal growth in causal aberrant entities conditions that arise during pregnancy [30, 31]. In later studies, isolated GIP has been reported to inhibit and prevent malignant cell growth in nine different types of cultured cancers, including breast, prostate, colon, ovarian cancer, and others [32] (Table-2). GIP can further assist in preventing blood clotting, reducing growths of uterine endometriosis, and can aid in the alleviation of fatigue caused by fibromyalgia [33, 34].

C) The encrypted and concealed growth inhibitory peptide (GIP) site on HAFP is not detectable using present day commercial polyclonal or monoclonal antibodies [29]. This hidden site has been shown to be revealed by partial unfolding of the native full-length HAFP protein following exposure in the fetus to internal intra-and extra cellular stress/shock pregnancy environments [30, 31]. As discussed above, 34-amino acid sequence of this occult segment has been identified and produced as a synthetic peptide [35-37]. The major trait of the 34-mer synthetic peptide was found to exhibit a growth suppressive activity in both neonatal and tumor cells; hence the name, Growth Inhibitory Peptide (GIP).

D) Some of the most potent growth inhibitors have been discovered as peptide fragments derived from abundant plasma or extracellular matrix (ECM) proteins that themselves do not inhibit growth [38]. The containment of a class of growth modulatory peptide segments within the structure of various circulating proteins (their intrinsic peptides) appears to be a recurring theme in the field of signal transduction and growth regulation. Another recent literature example of this type of activity was the discovery of an occult (cryptic) binding site for tenascin on the fibronectin molecule [39]. The encrypted and concealed tenascin binding site was only detectable as a proteolytic fibronectin fragment and/or when fibronectin was in an extended linear configuration.

Table 2: The Growth-Suppressive (Cytostatic) Screening Results* of Human AFP Derived Growth Inhibitory Peptide (GIP) for Multiple Types of Human Tumor Cell Cultures*. Cells Were Exposed to the Peptide for Six Days, Fixed, and Stained With Sulforhodamine-B. None of the Cells' Lines Were Dependent on Estrogen for Growth

Human Tissue or Origin	Cell Line Designation	Tumor Tissue Type	% Growth Inhibition	Growth Response Degree
Colon	KM-12	AC	75	Suppression
	HCC-299	AC	80	Suppression
	Colo-205	AC	10	Slight Suppression
	HCT-116	AC	75	Suppression
Ovary	OVCAR-3	AC	80	Suppression
	SK-OV-3	AC	60	Suppression
	IGROV1	AC	75	Suppression
	OVCAR-4	AC	85	Suppression
Breast	MCF-7	AC	80	Suppression
	MDA-MB-231	AC	80	Suppression
	MDA-MB-435	AC	70	Suppression
	BT-549	AC	25-40	Moderation Suppression
	T-47S	AC	25	Slight Suppression
Prostate	PC-3	AC	80	Suppression
	DU-145	AC	90	Suppression
Non-small cell lung	HOP-62	CA	75	Suppression
	NCI-H226	CA	05-Oct	Slight Suppression
	NCI-H460	CA	80	Suppression
Melanoma	UACC-62	Epithelial	80	Suppression
	SK-MeL-28	Squamous	35	Mild Suppression
	SK-MeL-5	Squamous	10	Slight Suppression
	SK-MeL-2	Squamous	50-75	Moderate Suppression
	UACC-257	Squamous	75-80	Suppression
Central Nervous System	SF-295	CA	80	Suppression
	SF-539	CA	15-20	Slight Suppression
	U-251	CA	45	Moderate Suppression
	SNB-75	CA	50	Moderate Suppression
Kidney	TK-10	Renal CA	85	Suppression Moderate Suppression

RXF-393	Renal CA	45-50	Suppression
A498	Renal CA	75	Suppression
ACHN	Renal CA	80	Moderate Suppression
CAK-1	Renal CA	50-75	

Legend: AC= Adenocarcinoma, CA= Carcinoma

*National Cancer Institute Therapeutics Screening Program, Bethesda, MD, used with permission.

Data derived and extracted from Ref. 15,16,20

The Multiple Functions of the 34-Mer Growth Inhibitory Peptide (Gip)

A) In further studies of human cancer growth, GIP was found capable of: A) inhibiting estrogen-dependent and independent breast cancer growth; B) blocking growth of tamoxifen-resistant breast cancer cells; C) Suppression of cell-to-cell contact inhibition in breast cancer cells [40-43]; D) inhibition of cancer growth studies in 38 of 60 different cultured cell lines including breast, prostate, ovarian, central nervous system cancers, melanoma, kidney, lung, and colon [32] (Table-3). Growth suppression in multiple breast cancer cell cultured lines were discovered including MCF-7, T-47D, Bt-547, and in vivo sarcoma isografts via mouse 6WI-1 in vivo hollow fiber cancer assays; and F) inhibition of platelet aggregation [33, 34]. The remarkable aspect of all in vivo assays was the total lack of any GIP-induced harmful and/or toxic side effects. Finally, as a cell surface membrane disruptor, GIP has been demonstrated to inhibit and suppress cancer cell spreading, migration, cell-to--cell contact, cell-to-extracellular matrix, and cancer metastasis in various animal models [32, 34, 40-43].

Table 3: GIP Microarray Data: Transcripts of PCR Displaying 1.0 or Larger Log Fold (Log Base 2.0) Decrease for Genes Associated with Cell Division and Proliferation Processes*, Ubiquitin, and Ion Channels

Gene Title	Fold Decrease (-)	Cell Function
I. Cell Cycle Regulation		
1. Calpain (LOC 441200)	-32.5	Cell cycle progression
2. F-box/Wd40, Domain-10 (FBXW10)	-14.9	P27 degradation pathway
3. Establishment of Cohesion-1, Homolog (ESC02)	-9.2	DNA replication
4. Checkpoint Suppressor-1 (CHES1) (FOXN3)	-9.2	S-phase checkpoint
5. Cyclin- E**	-4.6	Regulates G-S transition
6. SKP2	-4.3	Mediates p27 degradation
7. Transcription Dp-1 (TFDP1)	-4.3	Binds E2F-1; G1 to S
8. CDC20 Cell Division Homolog	-4.3	Activates ubiquitin
9. Histone-1, H4g (HIST1H4G)	-3.2	DNA repair/replication
10. Fanconi Amenia-D2 (FRANCD2)	-2	DNA repair/synthesis
II. Ubiquitin-associated Proteases		
1. Tripartite Motif-containing-62 (TRIM62)	-3	Finger ligase
2. SH3 Domain Protein (EVE1)	-2.3	ADAMS regulation
3. SUMO1/Sentrin/SMT3 Specific Protease (SENO3)	-2.1	Lysine targeting ubiquitin

4. Ubiquitin Specific Protease-49 (MGC20741)	-2.1	Ubiquitin enzyme
5. Ubiquitin Ligase Protein Complex (KIAA0804)	-2.1	Protein degradation
III. Channel Associated Proteins		
1. Potassium voltage-gated channel (KCNB2)	-8	Shab ion channel
2. Transmembrane Channel Like 5 (TMC5)	-5.2	Ion transporter
3. Potassium voltage-gated channel, KQT-like (KCNQ3)	-4	Cation signaling

*Expression of 716 transcripts was significantly altered after 8 days of treatment with GIP as compared to treatment with the scrambled peptide. Four hundred thirty were downregulated, while 286 were up regulated.

**=real time PCR

B) The Mechanism of Action Concerning the Growth Inhibition By GIP: The Cell Growth Cycle

The mechanism of action of the growth inhibition and cell membrane disruption of GIP-34 has been discovered and reported and is now well-understood [45, 46]. Overall, the growth suppression of GIP-34 involves interference with the cell growth cycle itself, multiple cells signaling transduction cascades, and protein-to-protein crosstalk interactions. Blockage of the interval stages of cell growth cycle results in: 1) cell cycle "phase G1-to-S phase" arrest; 2) prevention of p27 and p21 cyclin inhibition of ubiquitin degradation; 3) protection of p53 from inactivation of phosphorylation [47]; 4) blockage of K^+ ion channels and transient receptor potential channels induced by estrogen and epidermal growth factors [48]. Additionally, acting as a chemotherapeutic adjunct agent, GIP-34 was found capable of alleviating the side effects of: A) tamoxifen resistance; B) Uterine hyperplasia; C) Herceptin antibody resistance; D) radio-resistance and chemo-resistance of drugs; E) cardiac arrythmias; and F) doxorubicin bystander cell toxicity.

GIP-34 could further serve as a cancer preventative and therapeutic agent by: 1) acting as a decoy ligand for the CXCR4 chemokines receptor for cancer metastasis [49]; 2) mimicry of a disintegrins by inhibiting cancer cell growth, migration, angiogenesis, and platelet aggregation; 3) blocking circulating tumor cells from initiating metastatic migration [49, 50]; 4) disabling cell-to-stromal cell communication by inhibiting of cytoskeletal factor activities required for cell migration [47-50]; 5) serving as an antimicrobial peptide for cell entry, drug delivery, and pore channel formation [51]. See Table-4 for a GIP microarray analysis of RNA associated with cell division, ubiquitin activities and ion channel activities.

Additional Uses and Biological Activities of Growth Inhibitory Peptide (GIP)

The GIP-34 peptide itself exhibits long storage shelf-life, and the GIP lyophilized powder can be stored in a dry state, or at room temperature in the dark for extended periods of time [37]. The peptide has been found to be well--tolerated in the mammalian body and is non-toxic in all animals studied to date GIP, it is mechanistically novel, and can be used in combination with therapies such as radiation and with chemotherapeutic drugs such as tamoxifen and doxorubicin [42]. A major advantage of using GIP peptide is that no toxic side-effects have ever been observed or reported in over 2,000 animals utilized in pre-clinical trials, even at high doses. Some of these effects could be explained by itscytostatic nature rather than the cytotoxic activity of the GIP-34 peptide [45].

The GIP peptide also has the advantage of being both a cell penetrating peptide (CPP) and a channel blocker depending on the peptide concentrations used as demonstrated by prior electrophysiologic studies [52]. The CPPs are known to gain entrance into cancer cells by disrupting or disturbing the lipid bilayer surface and corkscrewing itself into the plasma bilayer membranes of cells displaying a net negative cell surface charge as displayed by cancer cells. Hence, cells destined for apoptosis including cancer cells, are known to undergo a cell surface membrane lipid inversion by switching the sphingomyelin outer layer cell mem-

brane with phosphatidylcholine or phosphatidylserine, thus shifting the internal bilayer negative charge to the outer surface of the cancer cell membrane and transposing the net position charge to the inner bilayer [53, 54]. This phenomenon provides a basis for target cell specificity in searching out and homing onto cancer cells, and not to bystander positively charged normal cells [53, 54]. The ion channels affected by CPPs (GIP) are largely voltage-dependent and are selective for cation such as Ca^{++}, Mg^{+}, Mn^{++}, and Na^{++} ions (Table-3). In contrast, GIP has been confirmed to be a tumor-homing peptide seeking out tumor cells that over-express Transient Receptor Potential (TRP) non-selective calcium channels. Thus, GIP may prove to be efficacious as a tumor homing agent for a variety of cancers. Additionally, GIP can also be used as an inhibitor of platelet aggregation during the process of metastasis to aid in preventing blood clots as observed in human patients undergoing chemotherapeutic drug treatments. Thus, GIP could be effective as an anti-metastatic agent due to its ability to inhibit cell spreading and migration, platelet aggregation, and cellular adhesion to extra-cellular matrix proteins [32, 33].

Concluding Statements

It can be concluded from the above treatise that therapeutic peptides could possibly represent the next generation of emerging chemotherapeutic adjunct agents. Similar to bacterial cells, cancer and stem cells display a net negative cell surface charge which distinguishes them from non--malignant (normal) cells of all mammals including man. This distinguishing feature forms the basis that provides the therapeutic peptides, such as AMPs and GIP, to specifically home onto and penetrate into cancer cells and not normal mitotic dividing cells. Thus, the therapeutic AMP peptides like GIP possess an enormous advantage of cell target homing specificity over those of present-day heterocyclic benzene-based chemotherapeutic drugs.

More precise future applications could further involve the clinical potential for antimicrobial peptides to serve as a second option treatment for cancer therapeutics. Present day use of chemotherapy in the clinic involves the use of heterocyclic benzene hydrocarbon derivates that attack all mitotic dividing cells in the body. These could include both nonmalignant and malignant tumor cells. Such deleterious examples of chemotherapy could include hair follicle growth, cell lining the entire gastrointestinal tract, stem cells of the bone marrow, and liver cells. Such effects could encompass hair loss, nausea, vomiting, depletion of bone marrow cells, and liver dysfunction. In contrast, the use of AMPs as a second option treatment for cancer therapy might involve AMPs either as an adjunct to classical present day chemotherapy to serve as the primary first option for such therapies.

The hesitancy and avoidance of big Pharma to adopt the use of peptides as therapeutic agents involves the cost, production, and profit of using heterocyclic benzene-based drugs instead of peptides. The recent surge in the use of diabetic-associated semaglutide peptides debunks this argument. In summary, the present review and commentary of this report have first introduced, discussed, and displayed the properties and traits of therapeutic AMPs. This initial introduction was followed by describing a pregnancy-derived example of an AMP-like therapeutic peptide (GIP) which was derived from the well-studied alpha fetoprotein polypeptide as a birth defect biomarker. Finally, it is conceivable that an AMPL peptide GIP could someday find a place in the therapeutic toolbox of drugs utilized for clinical cancer therapies.

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