

Progressive Advances in Anti-Cancer Studies of an Alpha Fetoprotein-Derived Antimicrobial Peptide: A Review and Meta-analysis

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Abstract

The present review and meta-analysis presents the progressive tracking and advances following the discovery of an alpha-fetoprotein derived antimicrobial peptide, named the Growth Inhibitory Peptide (GIP). The discovery of a concealed GIP epitope on Human AFP has given rise to multiple potential medical peptide applications related to cancer detection, therapy, and treatments. GIP has been demonstrated to possess the capacity to inhibit the growth and proliferation of multiple cancer cells both in cell culture and in animal models. GIP was further found to inhibit cancer growth in nude mice implanted subcutaneously using the GI-101 human breast cancer cell line. GIP was also utilized to study mouse mammary tumor growth and induced ascites fluid production; both metrics were similarly inhibited. Microscopic tracking of GIP by immunohistochemical methods determined that GIP entered tumor cells by pore formation, became distributed diffusely throughout the cytoplasm, and eventually accumulated in a perinuclear fashion surrounding the nucleus. Overall, GIP was found to inhibit the unregulated growth of both malignant and benign tumors after homing onto cancer cells and penetrating into their cytoplasmic interior.

Keywords

Alpha-fetoprotein, Peptides, Cell growth cycle, Instability disorder, Breast cancer, Malignancies, Antimicrobials, Cell cultures.

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Introduction

Historical Remarks

Alpha-fetoprotein and its Peptide Fragments

Alpha fetoprotein (AFP) is a type of plasma protein produced primarily by the fetal liver, yolk sac, and gastrointestinal tract during development [1]. In adults, AFP levels are typically in the nanogram range, but can become elevated in certain pathologies, including liver cancer and germ cell tumors [2]. Thus, AFP has been utilized as a biomarker for oncologic cancers and to aid in early

tumor detection, diagnosis, and monitoring of tumor treatment responses. In addition, AFP has also served as a pregnancy biomarker for fetal defects such as open neural tube anomalies and cranial anencephaly in the fetus and in newborns [2].

The AFP Molten Globule Form

Interestingly, the Molten Globule Form (MGF) of a protein has been proposed as a natural existing form of a protein localized within the cell cytoplasm [4,5]. Further research suggested that the protein secondary structure of AFP is controlled and regulated

predominantly by the interaction and binding of AFP with multiple types of ligands [6,7]. Release of these ligands from AFP results in a MGF, and this functional form of AFP was reported to be reversible under certain natural conditions [7,8]. Thus, the molecular conformation of the entire AFP molecule can be modified following exposure to various microenvironmental states causing a shock/stress induced unraveling and exposure of a concealed peptide site on the AFP molecule [9,10]. The MGF of AFP has been implicated in a variety of physiological activities and has been found in normal, cancerous and fetal conditions. Within the native form of AFP, a hidden peptide segment is present; however, when subjected to stress and shock conditions, the MGF form of AFP can undergo a conformational transformation and expose a concealed peptide segment [4]. The AFP molecule with an exposed peptide site has been utilized as a pregnancy biomarker for third trimester perinatal distress and as a fetal growth restriction/retardation marker in late pregnancy [11].

The Potential Use of Antimicrobial Peptides as an adjunct Cancer Therapeutic Agent

Characteristics of Antimicrobial Peptides

The antimicrobial peptides (AMPs) constitute the innate host defense arm of the immune system of mammals including man. The AMPs serve as potent, broad spectrum antibiotic-like agents found in many eukaryotic animals [12]. Due to their ability to target negatively charge cell surface membranes of microorganisms, AMPs have the ability to home onto, and target negatively charged membranes of cancer cells; after cell membrane attachment, such peptides can then penetrate into the cancer cell cytoplasmic interior [14]. The AMP-like (AMPL) peptides display amphipathic secondary structural traits, which usually consist of 10-50 amino acids in length. The AMPs further contain two or more cationic amino acids, a large proportion of hydrophobic amino acids, and some anionic amino acids [15]. The AMPs also contain many dipolar ions (Zwitterions) and constitute further amphipathic traits which include secondary structures consisting of: 1) alpha-helices, 2) beta strands, 3) beta hairpin loops, and 4) one or more disulfide bonds (2). The amphipathic nature of these peptides allows them to partition into and/or interact with cell surface membrane-embedded channels through electrostatic attractions [44]. It is of interest that most, if not all, of the above secondary structural properties of the AMPL peptides are present in the GIP-34 peptide.

Revealing a Hidden AMPL- Peptide Sequence Derived from AFP During Pregnancy

Human AFP, in its native full-length form, displays mostly fetal growth enhancing properties consistent with its role as a growth factor and a major serum transport protein during pregnancy [1,2]. Molecular variants of the AFP molecule have long been reported in the literature [16] and the molten globular form (MGF) of AFP was discovered in 1994 [6]. Later in 1996, a new novel fetal peptide was discovered as a 34 amino acid segment in the AFP third domain; this peptide was present as a concealed growth inhibitor peptide within the molecular folds of AFP during pregnancy [17]. This growth inhibitory peptide (GIP) encompasses a 34 amino acid

sequence which is concealed and hidden in a molecular cleft which lies imbedded within the native form of AFP [18]. This hidden peptide segment (GIP) on the AFP molecule was discovered following an amino acid search for matched binding partners of the heat shock protein-70 (HSP-70) protein [17]. The GIP segment is not detectable using present day conventional and/or commercial antisera produced against the full-length AFP [16].

The discovery of the hidden GIP-34 epitope on human AFP have given rise to multiple publications and applications relating to tumor diagnostics, detection and treatment. Purified GIP peptides have been synthesized by F-MOC chemistry using an Applied Biosciences 431A peptide synthesizer and purified by chromatography on reverse phase HPLC, lyophilized to a powder, and stored at 4°C [19]. Thus, GIP-34 has been synthetically produced and purified, bioassayed, and characterized. All such assays revealed a beta-sheet/turn peptide as a secondary structure [20]. The synthesized and isolated GIP segment demonstrated notable cytostatic antigrowth activity against multiple tumor types. In addition, GIP can be incorporated into a variety of diagnostic, therapeutic, and preventative strategies for cancer treatments in the clinic.

The Tumor Cell Growth Inhibition Property of GIP

Growth Inhibitory Peptide-34 (GIP-34) is a novel hidden peptide derived from alpha fetoprotein first discovered by Mizejewski, et al. [17]. The significance of this anticancer peptide lies in its unique properties and potential therapeutic applications in the field of oncology. GIP-34 has demonstrated a capacity to inhibit the growth of multiple human tumor types and to alleviate symptoms of other diseases, making it a promising candidate for a diverse array of clinical treatments [21]. The discovery of GIP-34 peptide originated from investigations concerning the multifaceted roles of AFP, especially focusing on the regulation of cancer growth. Following further research and experimentation, this hidden peptide segment was identified as part of the amino acid sequence of the AFP molecule itself. This peptide (GIP-34) has been demonstrated to exhibit inhibitory effects on cancer cell cycle growth, cell migration, adhesion, metastasis, and angiogenesis all of which can impact a variety of malignant and benign disorders [22]. These latter observations were deemed as highly significant, offering new insights into how AFP-derived peptides could be harnessed for multiple clinical cancer purposes [22].

GIP-34 Studies Employing Growth and Proliferation Assay Procedures and Results

The growth regulatory capabilities of the GIP have been further elucidated via cell proliferation assays employing both *in vitro* and *in vivo* models. Studies of GIP were assayed at the National Cancer Institute (NCI) in *in vitro* cell cultured cell panels consisting of 60 different tumor cell lines utilizing five GIP concentrations at 10-fold intervals [23]. The *in vitro* cancer panels were assayed in the NCI's Investigational Antitumor Screening Program using both a 2-day and a 6-day continuous peptide exposure protocol. At the time of cell harvest, a sulforhodamine B (SRB) protein methodology was

used to estimate cell viability and percent cell growth [24]. GIP suppressed the *in vitro* growth of 38 of 60 different NCI cancer cell lines representing 9 different organ/cell types. Cytostatic results ranged from 50-90% of the growth inhibition at GIP doses of 10^{-7} M or greater [25] (Tables 1 & 2).

Table 1: GIP-34 treatment on multiple cultured human cancers were performed by the National Cancer Institute (NCI) cancer drug screening program.

Human Tissue Origin	Number of Cell Lines	Concentration (Molar)	Inhibition (%)
Breast	3	10^{-7}	70-80
Prostate	2	10^{-7}	80-90
Colon	3	10^{-7}	75-80
Lung (NSC)	2	10^{-7}	75-80
Ovary	3	10^{-7}	75-85
Kidney	3	10^{-7}	75-85
Leukemia	6	10^{-5}	5-45

- 6-day Proliferation Assay.
- GIP was labeled as “Cytostatic” by the NCI.
- 38 of 60 cell lines (9 cancer types).

Studies using *in vivo* Implanted Breast Cancer in Nude Mice

GIP was further employed to study an *in vivo* nude mice assay using subcutaneously implanted GI-101 human breast cancer cells [26]. In this *in vivo* assay, human breast tumor studies were performed after implanting eight weeks old female athymic nude mice with 4 mm³ fragments of GI-101 breast cancer cells into the host animal right flank. On day 10 the post-implant tumor volume was measured, and the mice were divided into groups of 12 animals

for uniform volume and shape measurement [27]. Time release GIP pellets (Innovative Research of America, Sarasota Springs, FL) were injected into mice employing GIP release pellets with rates of 500ng/day. Tumor volume metrics were monitored by linear measurements throughout the experimental period. Animals were scarified on day 60 to determine body weight and tumor volume. The *in vivo* xenograft studies employing the GI-101 human breast cancer implants in nude mice revealed that the GIP-released pellet suppressed tumor growth by 72-84% over a 60-day period [28,29] (Table 3).

In Vivo Studies Employing Mouse Mammary Tumors Producing Ascites Fluids

GIP was further assayed *in vivo* in a mouse mammary tumor (6WI-1) model which produced tumor ascites fluid accumulation in the body cavity and host death at 14 days post-implantation [30]. These *In vivo* mouse mammary studies were performed using NYLAR/Nya mice inoculated with 3×10^6 mouse mammary adenocarcinoma tumor cells. An inoculated control group received daily saline injections while the treatment group received GIP in addition to an albumin peptide control group with each receiving 10µg/day for 14 days (Table 4). Tumor growth was reflected as an increased body weight due to the accumulation of ascites fluid in the mouse peritoneal cavity [31]. These *in vivo* mouse isograft studies utilizing a murine mammary tumor model in adult mice demonstrated a total body weight reduction caused by the inhibition of tumor produced ascites fluid production in the GIP treated mice over a 14-day transplant period. Hence, ascites tumor volume and the tumor cell number in GIP treated mice was shown to decrease by more than 55% [32] (Table 4). Furthermore, most of the GIP-treated animals survived for 90 days compared to normal control mice dying at 14 days post implantation. Tumor

Table 2: Multiple tumor types treated with GIP-34 are depicted for various breast cancers using xenograft procedures and time release peptide pellets*.

Tumor Designation	Model Type	Cancer Type	Concentration of GIP used	Treatment Duration	Inhibition (%)
MCF-7	<i>In vitro</i>	Glandular	10^{-7}	6 days	80
MCF-7 (xenograft)	<i>In vivo</i>	Glandular	0.25 µg/day*	60 days*	85+
MDA-MB-231	<i>In vitro</i>	Glandular	10^{-7}	6 days	80
MDA-MB-435	<i>In vitro</i>	Glandular	10^{-7}	6 days	70
GI-101 (tamoxifen resistant) *	<i>In vivo</i>	Ductal	0.50 µg/day*	60 days	75
GI-101 (tamoxifen resistant)	<i>In vitro</i>	ductal	10^{-6}	6 days	80

*Time Release GIP Pellets (60 day release)

GIP = Growth Inhibitory Peptide; 34= amount of amino acid in the peptide fragment.

Table 3: GI-101 Human breast tumors were implanted into nude mice and treated with GIP-34 and controls for 60 days.

Tumor Post-Implantation in Days	Control Sham Tumor Volume (mm ³)	GIP-treated Tumor Volume (mm ³)	GIP-Treated Tumor Percent (%) Reduction
15	20	20	0%
25	10	10	0%
35	50	45	20%
40	80	55	32%
45	110	52	50%
55	180	51	72%
65	300	50	84%

Legend: GIP-34 = Growth Inhibitory Peptide-34.

cell numbers in the GIP-treated animals were non-measurable at time of mouse biopsies.

Table 4: Effects of GIP on 6WI-1 tumor induced ascites* fluid accumulation in NYLR/Nya mice.

Treatment	Sample Size N = Number	Body Weight in grams (with ascites fluid)	Body Weight Decrease
Saline-treated mice	N= 21	22 ± 1.0	0%
Albumin peptide control	N = 5	20 ± 3.0	9%
GIP peptide treated	N =12	11 ± 5.0	55%

Legend: GIP= Growth Inhibitory Peptide.

*Tumor induced ascites fluid accumulation in mouse body cavities.

N = sample number of mice employed in the study.

Tumor Cell Death (Apoptosis) Induced by Calcium Ion Excess in GIP Treated Tumor Cells

As demonstrated above, GIP-34 was found capable of growth suppression (cytostatic type) in a multitude of human tumor cells both *in vitro* and *in vivo*. The use of AMPL-GIP was further shown capable of inducing apoptotic cell death in breast cancer cells; cell death was induced by means of a calcium cation channel overload within a transient receptor potential (TRP) cation channel undergoing cation influx [33,34]. Initial targeted tumor cell homing attachment by GIP was demonstrated by microscopical methods utilizing MCF human breast cancer cells; for such studies, GIP was labeled with a fluorcein dye and administered to the cultured cells in a pulse chase fashion. These histochemical studies demonstrated that GIP cell surface attachment occurred within 5 minutes without requiring a receptor [30,31,35]. GIP-34 is capable of homing onto and attaching to the cancer cell membrane surface and subsequently forming pores in order to penetrate into the cytoplasmic interior [35,36]. One hour following GIP penetration into the cancer cell cytoplasm, immunohistochemical evidence demonstrated that the GIP had become distributed throughout the cytoplasmic interior in a diffuse distribution manner within 1 hour [37]. Later, GIP migrated and was found to be concentrated and formed into a distinct peripherally localized ring pattern surrounding the entire outer nuclear membrane [35]. This concentrated peripheral rim of GIP surrounding the nuclear membrane, is known to be an area which is an extension storage area for the endoplasmic reticulum. However, the localization and condensation of GIP into a perinuclear rimmed localization area may have a further proposed implication suggestive of a nuclear membrane gating function for GIP [35,37]. In the process of nuclear pore gating, it is tempting to speculate that the GIP perinuclear rim localization might possibly impede the intake trafficking of various nuclear receptors' and their ability to enter into the interior of the nucleus mass compartment [35,38]. In such a blocking manner, GIP-nuclear gating could ultimately interfere with the interaction of transmitted nuclear receptors (i.e., estrogen and other steroid receptors) combining with the DNA machinery of the cell to prevent DNA-initiated transcription [39,40].

Discussion
Potential Medical Applications of GIP-34

These above-described discoveries of the GIP-34 properties and traits opens up a myriad of potential applications, particularly in oncology therapies and the treatment of other benign growth disorders. Below are listed some of the key areas where GIP-34 could possibly produce a significant medical impact: GIPs ability to inhibit the cancer cell growth cycle presents a novel means for developing targeted cancer chemotherapeutic modalities. By integrating GIP as an adjunct cancer treatment regimen, it may be possible to enhance the efficacy of existing cancer therapeutic treatments in addition to reducing harmful side effects of chemotherapy. GIP-34 might further serve as a biomarker for multiple cancer types and pregnancy disorders and diseases; this function might serve to provide a tool for early detection and monitoring of disorder/disease progressions. This event might be capable of improving patient outcomes by enabling more timely and precise interventions [11].

In summation, GIP-34 peptide is a regulator of dysfunctional and unrestricted growth in which GIP attaches to growth distressed cells that have a demonstrable a net negative cell surface membrane charge (See Postscript notes below). Such negatively charged growth distressed cells become notably viable as targets for circulating and monitoring white blood cells (WBC) seeking destruction of distressed cell. As examples of distressed cells, abnormal cell growths could include: a) dysfunctional growth; b) non-regulated growths; c) stress-induced growth; d) benign growths; e) disorganized growth; and f) non-malignant (benign) growth. In overall descriptive terms, cancer cells become a rogue, outlaw type of cell demonstrating unregulated and unrestricted cell growth. It has been proposed that cancer could be depicted as originating from a mutated gene/chromosome instability state of the distressed cell [30,31,36,37].

The AMP-like Growth Inhibitory Peptide can be Integrated into Cancer Treatments. Previous GIP studies have demonstrated an ability of such a peptide to inhibit growth of a variety of cancer cells making it a promising potential candidate for numerous cancer therapeutic modalities [36,37]. The discovery of the GIP-34 peptide has allowed opening of a myriad of potential applications, particularly concerning malignant and benign dysregulated and unwanted growths. Indeed, the ability of GIP to inhibit cancer cell growth could present novel approaches for further development of targeted cancer therapies. By integrating GIP into adjunct treatment regimens, it may be possible to enhance the efficacy of existing chemotherapeutic treatments by improving cell targeting, minimizing side effects, and reducing toxic drug effects in many cancer patients. Additional GIP biological activities have been reported and published; these could utilize GIP in a variety of cancer therapies. Such biological activities of GIP have been described in previous publications [45-49].

GIP can block cancer migration and metastasis of cancer cells from spreading and invasion; 2) GIP can be used to disperse blood clot

formations in the blood and in lymphatic vessels of the body; 3) GIP peptide can suppress the initiation of small start-up cancer cell foci in various areas and tissues of the body; 4) GIP could block cancer metastasis from transpassaging across the blood brain barrier; 5) GIP can serve as a drug transport system to deliver chemo-drug cargoes into the cytoplasm of cancer cells; 6) GIP could prevent cancer cells from establishing signaling communications with surrounding extracellular matrix cells; 7) GIP could prevent the formation of blood vessel networks from attaching to cancer cells seeking a source of nutrition (cutting off the blood supply to tumors); 8) GIP could also be used as a radioactive (labeled) tracer scanning agent to localize cancer clusters dispersed throughout the body; and 9) GIP could further be used as a radio-and chemo-sensitizing agent to enhance chemotherapy and radiation treatments.

GIP has been Found to be Effective against Cancer Growth in Three Possible Modes

GIP can initially serve as a cancer preventative agent to block initial start-ups of cancer cell growth foci by means of inhibiting cell cycle mitotic division in clusters of cancer cell clusters in various cells and tissues. GIP is capable of attaching to negatively charged cancer and stem cells, thus preventing future tumor stem cell-to-cancer cell transitions following the initial removal of tumor cells after treatment with chemotherapy, radiation, and surgical excision [50]. GIP also has the capability to override a cell's function of strictly regulating the amount of calcium influx into cells via TRP channel passage into the interior of cancer cells. Although calcium ions are essential for all body cells to exist, dysregulated and unrestricted amounts of excess calcium passage influx and accumulation into cells can induce cell death via apoptosis [33,34]. This occurs if excessive amounts of Ca^{++} cations are allowed to enter into cancer cells.

Conclusion

In summary, GIP-34 is present as a concealed fetal AMPL-peptide derived from an unfolded molecular form of the alpha-fetoprotein molecule. The exposure of the intrinsically hidden peptide is capable of inhibiting abnormal and cancer cell growth which can block subsequent cell proliferation and metastasis. Application of novel studies with GIP could potentially open new therapeutic pathways and modalities to treat afferent growth disorders found in cancer, benign tumors, and other dysregulated cell growths. In the future, such studies with GIP might be capable of enhancing our understanding of malignant cell growth mechanisms; this understanding could pave the pathways for innovative therapies by introducing adjunct GIP peptide treatments to accompany and bolster standard chemotherapy regimens in patients.

Future Directions Involving Indications of Strengths/Weaknesses

The strength of GIP usage for future usage including the following statements

GIP is a naturally occurring fetal peptide and is non-toxic at all levels of peptide concentrations tested. GIP is tumor specific and

guided to and only attaches to cancer cells and not normal non-malignant cells. The GIP peptide is anti-metastatic and can impede and block the spreading and migration of tumor cells to distal sites. GIP is anti-angiogenic and inhibits the formation of new blood supply networks that form around the mass of tumor cells. GIP is also cytostatic by suppressing both cancer cell proliferation and growth via the cell growth cycle. GIP can further induce apoptosis by producing an excess amount of calcium influx into cells causing the accumulation of cytoplasmic Ca^{++} cations which can cause cell death via programmed cell death. Lastly, GIP can serve as a targeted transport carrier agent capable of delivering drug cargoes into cancer cells for therapeutics purposes.

The Weaknesses of GIP usage including future pitfalls

The cost of the GIP peptide synthesis in addition to excipient reagents are considerably higher than synthesizing heterocyclic hydrocarbon chemo-therapeutic drugs from benzene. The costs of manufacturing and quality control measures of peptides can exceed organic heterocyclic chemo-drug productions. Drug delivery procedures via blood and/or lymphatics might be less rapid than other chemo-drug entities. The bio-availability of GIP peptide has a 6–8-hour half-life in human blood and may require 2 tablets/day for effectiveness. However, rapid protease degradation of blood-circulating peptides, like GIP, appears to be true for most peptides.

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