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Emerging Insights into the Biological Activities of an Alpha-Fetoprotein Derived Peptide and its Sub-fragments: Relevance of the Peptide Fragments to Cancer Therapies: A Review and Commentary

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Abstract

The antimicrobial peptides (AMPs) constitute a unique gene/protein family comprised of peptides involved in the first line innate immune defense in the body of mammals and lower animals. The first line of the immune defense function is to protect against a group of microorganisms which encompass bacteria, fungi, and parasites. The main subject of this review focuses on a particular AMP-like 34-mer peptide segment derived from a pregnancy protein termed alpha-fetoprotein (AFP). The AFP-derived peptide is a 34 amino acid fragment derived from full-length AFP that displays growth inhibitory properties in the malignant progressive growths of human and animal tumors. However, in recent years, it was discovered that AMP-like peptides could be utilized as anti-cancer agents with the ability to home onto malignant tumors and penetrate into their cell surface bilayer membranes. Further research into this fetal AFP-derived peptide segment revealed that the 34-mer segment could be further parsed into three sub-fragments, in which each of the three fragments was found to possess biological activities of their own. Moreover, the three individual sub-fragments were found to contribute to the overall biological activity of the entire 34-mer peptide fragment. Hence, the present treatise reviews the roperties, traits, and activities of the overall 34-mer peptide and each of its three individual peptide sub-fragments.

Keywords

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

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Introduction

A) Historical Aspects

Alpha-fetoprotein (AFP) is a predominant blood transport protein throughout the entire pregnancy gestational period in mammals and in their postnatal (puerperium) stages. Within the last two decades, multiple studies have documented that the full-length AFP polypeptide is a regulator of cell growth during both ontogenic and oncogenic stages which encompasses both pregnancy and tumor growth [1]. Evidence presently supports the observation that AFP polypeptide is largely a growth promoting protein which is accomplished via an AMP-protein kinase-A growth activation system [2,3]. Although sustained fetal growth is necessary during pregnancy, growth is a process that requires continual fine-tuning during the pregnancy period, including both

elevated and down-regulated periods. Such pauses in fetal cell growth are necessary to efficiently function over discontinuous time periods, such as would occur in pregnancy and malignant tumor growth [4]. Especially during each gestational trimester, there may exist periods of temporary or transient pauses in normal fetal growth that might seemingly be required at various stages during differentiation, tissue repair, and stress/shock events; such episodes could take place in both extracellular and intracellular fetal milieux. Thus, fetal growth in cells, tissues, and in the extracellular matrix compartments may often require a temporary halt in areas of growth until fetal homeostasis can be compartmentally re-established [5]. Such transient growth cessations may further be necessary until compensated signal transduction pathways and receptor crosstalk signals could be reset, repaired, renewed, and regenerated in periods of distressed fetal growth [6,7]. Therefore, what is needed during pregnancy is a biochemical backup to temporarily halt growth for short time periods in fetal cells and tissues. Thus, it would be necessary, convenient, and logical that a fetal growth peptide inhibitor be readily available and positioned as a temporary back-up during times that unexpected fetal stress/shock events occur. At least one such inhibitory peptide has been discovered and named the Growth Inhibitory Peptide (GIP) which is derived from the full-length AFP polypeptide as shown below.

B) AFP Exposure of a Concealed Peptide Fragment

As previously described, the full-length AFP polypeptide is known largely as a growth promoting and/or enhancing agent [7]. Surprisingly, in contrast to this growth enhancement trait, a fetal AFP-derived peptide fragment named the Growth Inhibitory Peptide (GIP) can manifest from a concealed occult growth-sensitive site. This intrinsic segment is concealed within the intermolecular folds of the AFP molecule [8,9]. Hence, when the AFP molecule is present in extreme stress/shock microenvironmental conditions, the full-length AFP polypeptide (69kD) can unfold to expose an encrypted 34 amino acid intrinsic GIP fragment (3,756 Daltons). The peptide segment can be exposed from within the AFP molecular folds following a molecular conformational charge in the entire full-length AFP polypeptide [10]. Such shock events in the afflicted fetal compartment area could be due to altered conditions of osmolarity, pH, O_2 tension, ischemia, osmotic pressure, anemia, anorexia, and excessively high ligand concentration (estrogens, fatty acids) [11,12].

C) The AFP-derived GIP as an AMP-like Peptide

In subsequent years following its discovery, the hidden 34-mer GIP segment has been chemically isolated, purified, synthesized, and biologically characterized as an isolated 34-mer peptide [13]. The GIP peptide has since been described as belonging to a particular class of peptides known as "Antimicrobial Peptides" (AMPs) (Table 1). Such peptides (AMPs) are known to exist in mammals and throughout the animal kingdom as shown in Table 1. The AMPs serve as a first line of defense in the innate immune system of mammals and lower animals to protect against infections of microorganisms. It has subsequently been discovered that the AMPs had the unique property of homing onto and penetrating into the cell membrane bilayers of cancer cells. This penetration into the bilayer surface membrane of cancer cells is accomplished by the presence of a cell surface electro-negative zeta potential charge (also seen in micro-organisms) and this trait has been utilized in targeting tumors in combination with cell membrane pore forming and cell-penetrating membrane processes.

D) The Use of GIP-Sub Fragment Peptides in Biological Activities

The 34 amino acid GIP segment was subsequently fractionated into three peptide sub-fragments and their individual properties studied. After its discovery and isolation, the purified 34-mer GIP and sub-fragments were subjected to growth bioassays which determined its anti-growth activity [14]. This bioassay has been employed to test anticancer (anti-growth) agents in both cultured human cells and in animal model implants. Subsequent studies after this were initiated to study and research each of the three individual fragments of the 34-mer GIP (see below). These peptide fragments were found to possess individual biological

Table 1: Antimicrobial Peptide (AMP) Amino Acid Sequences in a Variety of Vertebrates (defensins), Invertebrates, and Plants Matched to Human Alpha-Fetoprotein (GIP) Sequences from Amino Acids #465-503.

AFP 465-503 (GIP)	L	C		I	R	H		E	M	T	P	V		N	P	G	V	G	Q	C	C	T	S	S	Y	A	N	R	R	P	C	F	S	S	L	V	V	D	T	Y	V
Insect Defensin	A	K	A	H	A	H	F	K	L	E	R	K	N	S	G				H			N	G	K	C	C	R	R	G	V		W	R	Y	F	G	V	K		K	V
Insect CSαβ	T		G	A	R	V	K	N	J	W	P	A	A	C	S				A			S	P	S	V			Q	L	R		F	A	L	R	Y	P	C				
Plant CSαβ	H			G	K	Q	R	L	D	I	C	L	G	N	H				Y			H	K	R	D				W	A		T	I	H	E	Q						
Crustacean	Q			R	S	S	A	W	S	S	N	V	L	K	G				V			V	C	W					R	R		Y		S	K	V						
L-Protegrin	I				F	K		S	H	K	G		C	Y	R				W			R	S	F					A	Y		K		I	C	R						
A-Defensin-L (HNP-3)	C					R			G	F			M		Q				I			Y	A	T					S	N		R		G	P							
Gaeguin									C	W									F			K	R						K	E		L			D							
Tachyplesin-1									A										R			T																				
Polyphemusin																			K																								

Antimicrobial Peptide Families*: α-defnesin = HNP-3 (Human); β-defensin = M (murine); insect defensin = phormicin (protophomia); Insect CS-αβ = Drosophila; Plant CSαβ = Ah-AMP-1 (aesculus); Crustacean = Big Defensin (tachylpleus); Gaeguin = Gaeguin-1 (Rano); Tachyplesin-1 (Tachypleus); Polypemusin = polyphemusin (limulus. *GIP = Growth Inhibitory Peptide derived from AFP sequence amino acids #445-503. AMP data was derived from Proc Natl Acad 101:7363-7368, 2004.

activities of their own, while each subfraction contributed to the overall GIP-34 antigrowth function. However, other biological activities of each of the sub-fragments were discovered which encompassed 1) heavy metal binding to zinc (Zn^2) and cobalt (Co^2); 2) hydrophobic dye binding to Congo Red, 3) fluorescent binding to anilinonaphthalene-sulfonic acid (ANS); and 4) binding to cytoskeletal associated regulatory factors [15,16]. Thereafter, the 34-amino acid GIP has been further studied both in its intact 34 amino acid peptide form and individually with each of the three separate smaller peptide fragments. In summary, the three separate fragments of GIP-34 consisted of the following constituents: a) GIP-A as an amino terminal segment consisting of 12 amino acids; b) a GIP-B midpiece segment containing 14 amino acids; and c) a GIP-C peptide comprising a carboxy terminal segment 8-9 amino acid fraction [15-17].

Properties and Traits of the Three Individual Peptide Sub-Fragments of GIP-34

The GIP Peptide Sub-fragments

The amino acid segments of the three GIP-derived peptides (GIP-A, GIP-B, and GIP-C) have been compared and matched to other protein/peptide AA sequences found in the protein bank of the National Institute of Health (NIH). The AA-matched comparisons were detected, derived, and displayed from the Genbank Swiss Protein and PIR sequence software databases using the GCD-Wisconsin software program for FASTA sequence analysis (Table-1). Short amino acid sequence matches were found and matched with protein/peptide AA sequences from various other biological entities associated with growth, adhesion, and cytoskeletal activities [17].

A) The Amino-Terminal GIP-A Twelve AA Peptide Sequence of "LSEDKLLACGEG" Have Been Matched to Peptide Segments from Various Proteins

The AA protein bank matches detected with GIP-A matches included multiple proteins such as the human estrogen receptor (HER), and with several estrogen receptor co-activating factors, namely, SRC-I, SRC-II, and SRC-III [18] (Table 2). These data exhibited matched AA associations with GIP-34 demonstrating possible interactions sites with the HER and its steroid co-activator agents [17]. Segments from other protein AA segments were further compared to the amino-terminal segment of GIP-34 that matched to cytoskeleton, nuclear membrane, and microtubular proteins as described [17,18]. It was of interest that these AA matched segments were associated with cytoskeletal protein segments such as nestin, myosin, cofilin, annexin, ezrin, and actinin. AA matches also occurred with cytoskeletal motor proteins such as entactin, myosin, and dynein. These motor proteins are known to participate in cytoplasmic fibrous-like transport rails in which protein complexes and organelles travel throughout the cell's internal cytoskeletal transport system [17,19]. One such report indicated that GIP was capable of inducing a physical change in the overall cytoskeletal-determined cell shape [20]. Further AA matches were found with the human estrogen receptor (HER) in the region of the estrogen receptor's major binding site which has been named the estrogen receptor Domain-D [17]. These latter observations

Table 2: Selected examples of amino acid sequence matching of growth inhibitory peptide (GIP) with various estrogen receptor, cytoskeletal, and nuclear membrane proteins.

																																		% Identity/ Similarity	& Total
HAFP 445	L	S	E	D	K	L	L	A	C	G	E	G	A	A	D	I	I	I	G	H	L	C	I	R	H	E	M	T	P	V	N	P	G		100/0	100
Fragments GIP	GIP-A												GIP-B														GIP-C									
Hum (ER) E-receptor	X	S	M	D	K	L	L		C	V	E	G	M	V	E	I				F	V	C	L	K						L	N	S	G	V	54/21	75
SRC-1	L	T	E	D	H	I	L																												57/43	100
SRC (I-III)	E	S	Q	Q	K	L	L																												58/42	99
SRC-2	L	S	E	Q	T	L	L																												42/42	100
SRC (I-III)	D	K	K	N	K	L	L																												71/14	85
SRC-3	L	S	N	N	K	L	L																												43/14	57
SRC (I-III)	E	Q	G	H	K	L	L																													
Annexin	L	S	D	E	K	L	L	A	C	I																									75/16	91
Activin	L	S	E	Q	R	L	L	P	R	G	E	G																							58/42	100
Actin 475													S	L	D	I	I	V	S	H	L														75/16	91
Ankyrin													I	D	D	I	T	V	S	H	L	P	L												50/40	90
Lamin													A	A	S	V	D	V	G	H	D	A	V	R											44/22	66
Nuc. Envel.													A	A	G	R	V	R	G	R	L	C	P	A											47/17	64
Ankyrin																										X	M	T	P	L	K	P	G		44/22	66
Gephyrin																										E	M	T	P	V	L	X	G		52/38	100
Kinesin																										G	M	T	P	L	S	P	G		50/40	90
A-Tubulin																																P	G		50/40	90

Legend: HER: Human estrogen receptor; Human SRC: Steroid receptor co-activator; AA: Amino acid; Activin: Growth Factor signalling protein; Annexin: Ca^{++} dependent membrane protein; Actin: Micro-filament cell shape factor; Ankyrin: Links cytoskeleton to cell membrane; lamin: Intermediate filament forming nuclear laminin; NucEvl: Nuclear envelope protein links the nuclear pore to the cytoskeleton; Ankyrin: Microtubular scaffold protein; Kinesin: Motor protein that transports intracellular cargo. GIP: Growth Inhibitory Peptide.

were detected in addition to AA segments that matched to the nuclear membrane envelope, the protein nuclear pore complex, and the inner nuclear membrane protein. Finally, GIP-A was found effective as an inhibitor of unregulated uterine growth as observed in cases of human endometriosis [17,21].

B) The Midpiece GIP-B Fourteen AA Sequence "AADIIIGHLCIRHE" Peptide Matches Detected in Other Proteins

The peptide AA segment from the mid-piece region of GIP, named GIP-B, included AA matches to peptide segments from caveolin, and various cytoskeletal proteins that were associated with actin, dynein, kinesin, dystrophin, and caveolae [17]. The cell caveolae consists of flask-shaped invagination pockets found within the bilayer cell surface membrane. These linked pockets could be viewed as vesicular mini organelles within cells. Caveolae are present in the cell surface bilayer membrane in most cells and have been functionally implicated in cell membrane activities such as transcytosis, cholesterol membrane trafficking, lipid signaling, and signal transduction. Even though caveolae are mostly present in cell surface membranes, they also occur as vesicles within the Golgi, cell bilayer membrane, cell membrane lipid rafts, and the endoplasmic reticulum membrane [4].

The GIP-B fragment also has the ability to bind the estrogen steroid molecule itself (i.e., estradiol); this binding activity is proposed as being responsible for initiating the conformational changes involved in exposing GIP-34 at the molecular surface of full-length AFP [14]. Interestingly, the middle segment of GIP (called GIP-B) is also noted as the most highly hydrophobic region of the entire 34-mer GIP peptide fragment. The GIP midpiece segment further displayed Congo Red dye binding capabilities in addition to binding a fluorescent dye compound referred to as Anilinonaphthalene sulfuric (ANS) acid. It is important to note that only the GIP-B segment was found capable of hydrophobic binding to both the hydrophobic Congo Red dye and the fluorescent ANS acid compound, and in complexing as binding to both zinc and cobalt metals [17]. The binding of GIP-34 Segment-B to cobalt further demonstrated the formation of a metal complex demonstrating the molecular form of a tetrahedryl symmetry confirmation [9]. Finally, the GIP-B peptide segment also showed sequence matches to microtubule-associated proteins such as dystrophin, ankyrin, and stratifin. In contrast to GIP-A, GIP-B produced only weak anti-growth suppressor activity (20%) as revealed by the uterine bioassay (see above) [14,17].

C) The GIP-C (AFPep) Peptide Eight AA Sequence "EMTPVNPG" was Matched to Several Other Protein-Peptide Segments

The Gene Bank protein AA matches made with the GIP-C fragment included several peptide segments associated with the microtubular cytoskeleton. The microtubules are known to produce the formation of structural scaffolding that defines and maintains the overall cell cytoskeletal shape. Such peptides also showed matched AA sequences to protein/peptides involving cytoskeletal fibers that serve as fibrous intracellular transportation tracks along which molecular complexes are transported throughout the cytoplasm (Table 2). Such fibrous-like proteins include tubulin, neurofilaments, stratifin, mechanosensory proteins, and gephyrin. The GIP-C fragment also displayed AA matches to amino acid segments of the estrogen receptor and to estrogen-associated steroid co-activators (see above), and with nuclear membrane cytoskeletal scaffold proteins. Such proteins include Lamin, nuclear membrane, and nuclear envelope proteins [17]. Unlike GIP-B, the GIP-C segment displayed significant anti-growth properties as in seen GIP-A. In contrast, the GIP segment-C was only affective against estrogen-dependent breast tumors (70-80%), but not against estrogen independent breast tumors (30%) [18]. It was notable that the GIP fragment-C did not bind the E2 receptor as did the GIP fragment-A. In further studies of anti-cancer E2-dependent growth, previous reports involving the GIP-C segment revealed that this carboxy terminal fragment inhibited the foci formation of E2-induced contact inhibitions in cell culture [8]. This contact inhibition activity resulted from the migration and subsequent accumulation of breast cancer cells that spread and clumped together due to a loss of contact inhibition [8].

Comparison of the Overall Anti-Cancer Cell Growth Properties of GIP-34 to Those of the GIP-C Sub-Fragment Peptide

A) The GIP 8-mer peptide (EMTPVNPG) was synthesized both as a linear and as a cyclic peptide by various other collaborative research groups which referred to GIP-8 as an octopeptide [22,23]. The 8-mer linear peptide (originally discovered by Mizejewski et al.) [8] was found to possess antiuterotrophic (AUT) activity as did the intact 34-mer GIP peptide. Both peptide versions were assayed and subjected to uterine bioassays and found to be growth inhibitory [24,25]. The GIP cyclized peptide was further named the AFPep segment by various investigators (GIP Fragment-C). Early experimental findings suggested that both the entire GIP-34 and the GIP-8 fragment displayed significant AUT and anticancer activity and suggested that the cyclized GIP-8 peptide might be further developed as a therapeutic agent to treat estrogen-dependent breast cancer [26,27].

B) A series of parsings and substitutions of amino acids within the GIP Fragment-C peptide sequence were employed to identify the shortest AA analog sequence that retained both AUT and anti-growth activity. The 8-mer peptide sequence retained full AUT and growth inhibitory activity, whereas all peptides shorter than eight amino acids in length were found inactive [22,23]. The cyclized version of GIP-8 was further found to prevent molecular aggregation and to retain full biological activity during prolonged periods of storage [22,23]. The cyclized structural modification was accomplished by substituting two proline amino acids with hydroxy-prolines and replacing the carboxyl terminal glutamic acid with glutamine. These substitutions and modifications resulted in cyclization of the amino terminal piece to the carboxy-terminal endpiece of the 8-mer peptide. These modifications produced a cyclized peptide that extended both the effective peptide dose

range and the peptide storage stability as compared to its linear counterpart [23,28].

C) The cyclized GIP peptide was then subjected to a series of bioassays to determine its effectiveness and clinical utility as an estrogen-dependent breast cancer therapeutic agent. In one such study, the cyclized GIP was compared head-to-head with tamoxifen (TAM) therapy to measure its growth inhibitory activity in breast cancer xenografts implanted into immuno-deficient mice [27]. It was further reported that both the cyclized GIP and tamoxifen (TAM) prevented growth of estrogen-receptor positive MCF-7 and T47D human breast cancer xenografts. Moreover, it was shown that TAM stimulated dysregulated growth in the inner lining of the uterus in immature mice *in vivo*, and that GIP-8 significantly inhibited such growth of the inner lining of the uterus [28,29]. Furthermore, GIP-8 did not interfere with the binding of estradiol to the estrogen-receptor in E-dependent tumors in addition to the TAM-resistant estrogen-receptor positive human breast cancer [28]. In another study, the Andersen & Bennett research group elucidated the basic amino acid composition that composed the pharmacophore of the cyclized GIP-8 (C-GIP-8) [29]. It was later determined by the same research group that C-GIP-8 was orally active in all animal models studied. In summary, it was found that C-GIP-8 was both safe and effective for the treatment and prevention of breast E2-dependent cancer growth and to prevent development of endometriosis in rodent models [30].

D) Continuing research on the biological activities of C-GIP-8 demonstrated an effective anti-growth activity on several other human cultured breast cancer cell lines and animal models using computational design and experimental discoveries [31]. Moreover, it was documented in later studies, that C-GIP-8 could also prevent the development of carcinogen-induced (methyl-nitrosourea) mammary cancer in rat studies [32]. Using confocal microcopy, C-GIP-8 was further observed and tracked during the cell entry of the cyclized peptide into T47D breast cancer cells and was found to be localized in the lysosomes and in early endosomal vesicles [34]. In subsequent studies, it was also demonstrated that C-GIP-8 markedly interfered with signaling in the regulation of MAP kinases. Working in concert of c-erbB2 proteins with C-GIP-8, it demonstrated that an inhibitory effect was on the release of matrix metalloprotease proteins in studies using canine mammary gland cancer cells [35]. A subsequent study by Tower et al. further demonstrated that while C-GIP-8 prevented and treated breast cancer in rodents, GIP did not disrupt the estrus cycle and/or hamper fertility in rats [36]. In comparison to such traits, tamoxifen disrupted the estrous cycle and showed marked inhibitory effects on animal fertility, mating behavior, birth of offspring, maternal body weights, and pregnancy outcomes. In comparison with these studies, C-GIP-8 showed no discernable animal toxicity and was effective as an inhibitory growth agent in the treatment of many different subtypes of breast cancers [37]. Finally, a study by Mansouri et al. demonstrated that C-GIP-8 was effective as an anticancer agent, showed no toxicity, and was well-tolerated in both lower and higher mammals intended for therapy of ER-positive breast cancers [38].

Concluding Statements

The present review and commentary represent a discourse on a peptide, named GIP-34, which was derived from the full-length alpha-fetoprotein pregnancy-associated polypeptide. This review and commentary are unique because, the AFP-derived GIP-34 peptide and its sub-fragments, have many diverse biological activities which were confirmed in a multitude of cancer reports [13,14]. In the pursuit of further research, it was discovered by the author (GJM) [14,17], that the 34 amino acid peptides could be parsed into three distinct and separate subfraction peptides. It was further found in an amino acid sequence matching computer program, that many of the detected biological activities provided functional clues from each of the three individual 34-mer peptide fragments. It was further shown that the activities of these individual subfractions contributed biological activities relevant to the overall 34-mer GIP peptide [17]. When each of the three peptide segments derived from GIP-34 were synthesized and assayed for biological activities, it became evident that the entire GIP-34 was not only a sum of its separate parts, but that each of the three separate sub-fragments had contributory activities of their own [38]. In summary, the present treatise has served to provide the "proof of concept" that 34-mer GIP is indeed an anti-growth AMP-like peptide with multiple functions related to estrogen binding and growth inhibition in addition to its cytoskeletal associated activities [39]. In summary, the GIP-34 and its sub-fragment peptides adequately demonstrated anti-cancer activities in both human and animal cancers.

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