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The Interaction Between Transient Receptor Potential Channels and Antimicrobial Peptides: Relevance to Cancer Therapies

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Abstract

Transient Potential Receptor (TRP) channels function to mediate multiple sensory functions such as vision, nociception, taste transduction, temperature sensation and pheromone signaling. Such channels in mammals serve as nonselective cation influx channels expressed in many tissues on mammalian cell surface membranes and these act to regulate the flow of Ca^{++}, Mg^{++}, and Mn^{++} into cells. TRP channels also serve as interactive responses for sensory phytochemical compounds (such as spices) to activate and open TRP channels for cation influx. Serving as interactive partners for TRPs, antimicrobial-like (AMPL) peptides constitute a unique class of naturally occurring agents that serve as the first line of defense of the mammalian innate (immediate) immune response system. The AMPLs provide protection and defense against microorganisms that gain entrance into the body; such microbes can include bacteria, parasites, and fungi. The present report reviews the interactive activities between the TRPs and the AMPLs that both aid and benefit physiological interactions in the course of cancer treatments, therapies, and chemotherapeutic procedures. Such therapeutic interactions between TRPs and AMPLs lead to propose the concept that tumor growth suppressive activities, exemplified by the interaction between TRPs and AMPs, can and do occur and could be efficacious in treating various types of cancers such as gastrointestinal, sexual/reproductive, and urogenital malignancies.

Keywords: Alpha-fetoprotein, peptides, cation channels, cell cycle, spices, instability, cancers, malignance, antimicrobials

I. Introduction Purpose and Objectives

The purpose of the present report is to review the interactive biologic activities between the TRP cation channels and the antimicrobial (AMP) peptides. Thus, the overall goal of this treatise is to present and propose new and novel cancer therapeutics and treatments utilizing this potential dual combination of TRPs and AMPs. Secondarily, the scope of this paper will encompass a discussion of the dual molecular interactions of TRPs and AMPs in light of their cell surface membrane phenomenon and subsequent cytoplasmic signal transductions and protein-to-protein interactions in cancer cells.

A) Historical: TRP Cation Channels

The Transient Receptor Potential channels (TRPs) function as chemical biosensors of natural, toxic, and physical stimuli in addition to serving multiple roles in cell and tissue growth regulation [1]. In the present treatise, the structures and functions of TRPs are first introduced and discussed regarding their participating roles in various physiological and pathological conditions. Secondarily, the introduction and added functions of the AMPs are likewise described in the course of addressing disease states and their employing therapeutic interventions in combination with TRPs. Thus, an understanding of the growth regulatory roles of TRP channel interactions together with AMPLs in cancers could possibly lead to improved preventions and treatment regimens for malignant diseases and associated benign growth disorders.

The existence, presence, and discovery of TRP channels were first proposed in 1969, the source having been identified as a mutant gene in fruit flies displaying a transient rather than a continuous response to increase bright light rays [2]. In 1975, Minke et al. named this receptor-like protein after an electrophysiologic light responsive phenotype [3]. The TRP gene was later cloned in 1989 by Montell & Li, at which time the protein-gene product was identified and localized as a transmembrane associated protein [4,5]. It was later discovered that TRPs are cell membrane bright light activated components that regulate the influx of Ca^{++} and other cations into cells by serving as voltage-gated channels.

B) The TRP Cation Channel Family and Its Functions

The mammalian TRP channel family members have presently been classified into six TRP subfamilies based on both their amino acid sequences and their topological membranous structure traits. The TRP channel family includes the following subtype members: 1) Canonical (TRPC); 2) melastatin (TRPM); 3) vanilloid (TRPV); 4) ankyrin (TRPA); 5) polycystic (TRPP); and 6) mucolipin (TRPL) channels [5]. All TRP subfamily channel members play essential roles in cation flow transduction in the influx and transfer of monovalent and divalent ions such as Na^{+}, Mg^{++}, Mn^{++}, and Ca^{++} into cells. These TRP channels regulate transduction flux pathways for a variety of sensory perceptions encompassing taste, pungent compounds, thermo-mechanical, pain, temperature, osmoregulation, and hormone/pheromone influx [20-23]. In addition to the TRP's role in sensory perception, TRP channels can further mediate certain physiological, pathological, and functional roles in both cancer and immune system activities [6-9]. Thus, TRP channels can contribute to cancer pathologies and modulate growth activities via intracellular cation (especially Ca^{++}) elevations and oscillations; such activities can affect cell growth cycle functions, cell spreading and migrations, receptor crosstalk and signaling, and the initiation of programmed cell death (apoptosis) activities.

C) TRP Subfamilies Structural Topology

All mammalian TRP channels share common topological transmembrane (TM) peptide stretches that transverse the cell membrane six times comprising the formation of intramembranous segment loops. All TRP channels also display a spiral pore-forming loop between transmembrane segments 5 and 6 in which the amino acid sequence contents are highly conserved among family members which function to coordinate cation influx activities [14]. Overall, the TM diverse domains and motifs have been found to include and consist of coiled coils, calmodulin binding sites, lipid interaction domains, EF hands, and phosphorylation sites. Nonetheless, the individual and precise structural motifs and domains can slightly vary within the individual class members of the TRP subfamilies [13]. Furthermore, there appears to be few cancer-induced gene mutations in the TRP families. Moreover, these changes can include various increases in the genetic expression of the TRP channels, especially in the TRPC, TRPM, and TRPV subfamilies [15].

D) The TRP Channels in Signal Transduction Pathways

The TRP channel have been localized to the cell surface mem-

brane within the lipid bilayer in juxtaposition to a cluster of eight signal activating protein members collectively called the "Signalplex" unit. This signaling protein cluster unit is located at the point of membrane insertion where the TRP channels enter into the cell membrane and cluster together within the signalplex unit into the surface cell bilayer membrane [18]. This signalplex cluster composing eight signal proteins consist of an array of scaffolding and targeting proteins clumped in conjunction to form the signal complex together with the TRP channel; hence, the total signal proteins (8 +1) make up the molecular cluster nine proteins in the signalplex structure [19]. Thus, the nine signaling proteins of the signalplex are comprised of the following members: 1) the TRP channel itself; 2) Beta phospholipase-C; 3) Rhodopsin; 4) Protein kinase-C; 5) calmodulin; 6) myosin; 7) Beta-2-adrenergic receptor; 8) $Na^{+}H^{+}$ transporter; and 9) the Ezrin-Radin--moesin tricomplex unit [20].

II. Comparison of Characteristics and Traits of the Antimicrobial Peptides that Interact with the TRP Channels

The antimicrobial peptides (AMPs) are a class of broad-spectrum antibiotic agents that comprise various protein/peptide members of the innate host defense immune system present in many vertebrate animal species [21]. Different AMPs are widely found and distributed among fish, amphibians, reptiles, birds, and mammals including man [22]. In recent years, the AMPs have been found to function as additional adjunct compounds that aid in anti-cancer therapeutics. These therapeutic actions are accomplished via the AMPs homing in and onto cancer cell surface membranes followed by their penetration into the cancer cell interior cytoplasm [23]. The AMPs owe their capability to penetrate into cancer cells to their ability to attach, lyse, destabilize, and disrupt bilayer membranes and forms pores. These AMP interactions with cancer cell biomembranes can be traced to their binding to the cell surface net negative charge on the cell membrane which is also found present on microorganisms (bacteria), cancer, and stem cells [24]. The AMPs, which can be produced from both synthetic and natural sources, demonstrate high targeting specificity toward and onto cancer cells but not onto normal, non-malignant body cells.

Mammals exhibit two major classes of AMPs, namely: 1) the cathelicidins, and 2) the defensins [25]. Both classes of AMPs demonstrate antibacterial and anti-tumor properties. However, it is only the defensins class of AMPs that have been found to occur in human beings. Both human alpha and beta defensins are produced and have been localized on body cells such as neutrophils, leucocytes, macrophages, and certain epithelial cells. Such cells can be found and localized in respiratory, digestive, and excretory systems [26,27]. In addition, AMPs have also been found on certain circulating vascular blood cells.

Even though the AMPs are commonly not associated with pregnancy, an AMP-like pregnancy peptide was discovered by the author (GJM) and published in 1996. This peptide is a pregnancy associated AMP-like (AMPL) peptide that has been named the Growth Inhibitory Peptide (GIP-34) [28]. The fetal GIP comprises a peptide derived as an intrinsic amino acid segment found buried and concealed within the Alpha-fetoprotein molecular folds and is present in mammalian pregnancies [29]. Interestingly, the AFP pregnancy-derived GIP peptide was found to have many properties in common and has been classified with the cationic β sheet AMPL-peptides being most similar to the human defensin family of peptides [30]. Both the GIP and the defensin class of peptides contain 2 to 8 cysteine residues forming at least one or more sets of disulfide bridges crucial for many biological functions. The defensin peptides, like GIP, also contain beta-hairpin loops, beta sheet formations, excess hydrophobic amino acids, and a short segment stretch of alpha-helical secondary structures [38]. Overall, the GIP peptide was found to share many of the above secondary structures in common with the AMPL-defensin peptides [31].

III. Interactions Already Known Between TRPs and AMP-Like Peptides

The calcium dependent TRP channels play multifunctional roles in cell growth, tumorigenesis, and cell growth cycle-associated functions. These calcium-associated cation channels function in determining cell membrane voltage, cytoplasmic Ca^{++} concentrations, and receptor signaling mainly in proliferating cells [32]. As described above, the TRP channels are transmembrane cation channels similar in function with other voltage-gated Ca^{++} channels (Table-2). The TRPs and similar ion channels are constitutively open and gated by voltage, ATP, pH, redox agents, and multiple sensory activation factors such as spices and phytochemicals (Table-1) [33]. As described above, the TRP channels act in concert with a cluster of eight other protein members that make-up the signal-

plex cluster for receptor signaling purposes. These proteins can be summarily described as phosphatases, kinases, co-transporters, receptors, and cytoskeletal-like proteins [18-20]. The TRP channels normally function in the regulatory activities of the Ca^{++} and other cation influx into the cytoplasmic interior and further participate in activities regarding cancer growth and proliferation (Table-2). However, excessive and non-regulated Ca^{++} influx into the cell can result in dysfunctional receptor signaling and gene transcription, faulty DNA repair, and ultimately in apoptotic- induced cell death [35] (see below).

Table 1: Listed below are the phytochemical chemosensitizing agents (spice) and sensors that activate and stimulate the cation non-selective channels of vertebrate cells. Such cation channels belong to a family of proteins referred to as Transient Receptor Potential (TRP)* channels (See legend).

Name of Channel Stimulation/Sensor Activation Chemo sensitizing Agent	Type of Cation TRP Calcium Channel Being Activated	Function of Activated TRP Channel	Type of Cancer/cells Affected, Suppressed
1) Mustard seed or oil spice (Allythiocyanate)	TRP A1, TRP M8, TRP V1, TRP V4	Cell cycle arrest, apoptosis, blocks cell migration and invasion	Lung, Liver, digestive tract, pancreas, colorectal, and myeloma cancers
2) Ginger spice, Allicin, Shagaol spice	TRP V4, TRP V1	Induction of programed cell death. i.e., apoptosis	Embryonic kidney cells, colorectal cancer cells
3) Wasabi (Japanese Horseradish)	TRP A1, TRP M2, TRP M8, TRP C3, TRP C7	Triggers cell signals to promote programmed cell death, lipid peroxidation	Colon cancer, pancreatic, central nervous system, lung and breast cancers
4) Cayenne Pepper, Hot Chili Powder, Capsaicin, Camphor	TRP V1 TRP M2 TRP V6 TRP V8 TRP C6 TRP M7 TRP V4	Upregulates apoptosis, or programmed cell death	Breast carcinoma, renal cell cancer, cervix cancer, non-cell lung cancer, kidney colorectal, thyroid cancer, liver, and stomach cancer
5) Menthol (peppermint oil) (Mint leaves)	TRP M1, TRP M2, TRP M7, TRP M8, TRP A1, TRP V8	Increases cell liver migration, spreading, motility, limits (reduces) metastasis, tumor growth	Prostate cancer, Brain glioblastoma, skin, cancer, melanoma, lymphoma cancers
6) Garlic	TRP A1, TRP M1	Activation of dendritic and endothelial cells.	Mast cells, T-cell lymphoma, prostate, and skin melanoma cancer
7) Cinnamon (cinnamaldehyde)	TRP A1, TRP M8	Gut mobility induction, pain, O2 stress	Head & neck squamous cell cancers
8) Phorbol esters, a plant extract (ester derivatives, biomedical tool)	TRP A1, TRP V1, TRP V4, TRP V3, TRP V2	Activates cell membrane channel opening, for calcium and potassium flow	Human embryo kidney cancer cells

Legend: *The transient receptor potential (TRP) superfamily can be subdivided into 6 subfamilies: these subfamilies include: 1) TRPC (canonical); 2) TRPV (vanilloid); 3) TRPM (melastatin); 4) TRPA (ankyrin); 5) TRPP (polycystin); 6) TRPML (mucilipin)

Table 2: Amino acid sequencing Matching of Alpha-fetoprotein derived Growth Inhibitory Peptide*(GIP) with various cation channel-associated and calcium interacting proteins. **

		% Identity/Similarity	% Total
Hum GIP #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 V G	100/100	100
Fragments GIP*	* 1.GIPa | 2.GIPb | 3.GIPc		
Xen Na/K ATPase (#252)	L S C T R L I A C C Y G N C T G A I X H L C X X T N L S S I	36/23	59
Na Channel Protein (#55)	Y V Q D Q L Q A C G E G	58/25	83
Hum Calmodulin (#27)	L S E I E L L	71/0	71
Piso ATP-syn A (31165)	A A N L T A G H L L	45/45	90
Hum Calcitonin R (#210)	N S M I I I I H L C	50/30	80
Pig Calcitonin R (#195)	N S I I I I I H L V	50/30	80
Rat Caclitonin R (#195)	N S I I I I I H L V	50/30	70
Hum calreticulin (#3692)	I Q S I I V G H L G	50/20	70
Hum Calcitonin (#1550)	L C I R H S F T P A	60/30	90
Mus K-Chanel P (#18)	L C I R G T L T P R	60/20	80
Bov ATP-Channel (P) (#385)	C I Q F E L P P V N	50/30	80
Rat Ca/ATPase	C I H N Q M Q P V H	60/40	100

*GIP can be divided into three smaller peptide fragments, termed GIPa 12 amino acids; GIPb 14 amino acids; GIPc 8-9 amino acids [Refs. 45, 50,51, 52]. Hum = human; Xen = Xenopus amphibians; Mus= mouse; Bov = bovine (cow).

**Amino acid matching can lead to the binding of the amino acid matched protein to the GIP peptide by the method of Root-Bernstein [53].

The expression patterns of TRPs in cancer cells (i.e., breast cancer) revealed that certain TRP channels (namely TRPV1 and TRPM8) were heavily over-expressed in various breast cancer cell types including glandular, ductal, basal, and interstitial (fibrous) cells [36]. Hence, it is of further interest that the use of an in-silica computer allosteric docking/binding program used for GIP (see technical endnotes below) revealed that GIP was capable of binding (docking) with TRP channels and cell growth cycle proteins (Table-3). Two activating sensory factors (spices) involved in allowing high Ca^{++} influx into the breast cancer cells were identified first as capsaicin and secondly as peppermint oil (menthol), among other spices [36-39] (Table-1). It is of interest that recent reports indicated that the aforementioned GIP was capable of interacting with the TRPM and TRPV subfamilies of TRP channels among others [40-45]. These latter data have been verified by electrophysiological (EP) procedures employing sharps electrode and patch clamp methodologies using micro-manipulated electrode probes inserted into cultured breast cancer cells [37,38]. Since those reports emerged, additional activation factors (spices) for TRPs have been described in such cancers as lungs, colon, prostate, pancreas, brain, and urinary bladder tumors (Table-1) [39, 40-45].

The electrophysiologic (EP) based methodologies revealed that the previously mentioned phytochemical (spice) activated channels treated with 10mmol GIP peptide functioned to increase the influx of Ca^{++} ions into the cancer cells while increasing the membrane potential of the cultured breast cancer cells [8,38]. This increase, in turn, immobilized the current membrane potential which extended across a range of -30--to-45 mVolts persisting for a 90-minute time duration [45]. Additional studies using the EP methods against LNCAP prostate cancer cultured cells confirmed that the GIP peptide results reported in the breast cancer cell studies were further confirmed in prostate cells [7,36]. Upon measurements of the slope conductance, the GIP peptide treatments demonstrated a substantial membrane current increase (with decreased resistance) in both cancer cell studies. Thus, the data in two dif-

ferent cancer cell types demonstrated and confirmed that the membrane potential and resistance effects exemplified by the highly enhanced (increased) Ca^{++} influx had affected the cytoplasmic Ca^{++} stores. Such organelle storage compartments occur in the mitochondria and secondarily in the Ca^{++} stores of the endoplasmic reticulum. This 2-stage storage activity, reflecting the overload of Ca^{++} ions in two organelles, initiated the process of apoptotic cell death observed in both the cultured breast and in the prostate, cancer cells [36,45].

As described above, it has also been reported that the AFP-derived GIP can act as a sensor agonist to TRP channels in the course of enhancing phase interactions that can inhibit the cell growth cycle of cancer cells [37,38]. Thus, the TRP channel activation and subsequent interactions with AMPLs can directly affect various stage phases of the cell growth cycle [8]. Cells in the cell cycle G1 phase have been reported to display depolarized membrane potentials corresponding to a large contact engagement with the TRP channel current. The use of cultured breast cancer cells involved a millivolt range known to represent the cation channel that corresponds to and regulates the G1 phase of the cell cycle [38]. Thus, an increased hyper-polarization current occurs that corresponds to an increased intensity of a cation induced TRP membrane current that occurred in the phases in the cell growth cycle [8].

Table 3: Molecular docking and protein interaction sires on alpha-fetoprotein and Growth Inhibitory Peptide (GIP) were identified. Such sites were localized by means of proprietary computer software (peptimer discovery platform). See legend below. The amino acid segment of human alpha-fetoprotein and Growth Inhibitory Peptide (GIP) that were probed for computer interaction sites employing allosteric modulation designs. The single letter protein amino acid code was used for the Human Alpha-fetoprotein amino acid sequence of GIP 445-478 as follows.

NH2-L S E D K L L A C G E G A A D I I T I H L C I R H E M T P V N P G V N P G V –COOH

Acc #	Protein	Function	Computer Hit
1. O14757	Ser/Thr protein kinase CHK2	Regulates S-phase, G2/M checkpoint	Helical region near kinase for ser178
2. AAC37594	BRCA1	Cell cycle checkpoint for DNA damage response	Tumor suppressor region near carboxy terminus
3. NP_005188	CHES1	Cell cycle checkpoint regulator	Glu/Ser kinase substrate site
4. BAA037730	Calpain	Cys protease; Ca^{++} binding; DNA-repair	Ca^{++} binding region
5. NP_009125	Protein kinase CHK2	S-phase checkpoint regulator of the cell cycle	FHA region, a fork head transcription factors phosphatase; *NLS zip code site
6. NP_005188	Checkpoint Suppressor (CHES1)	Suppresses checkpoint mutations of cell cycle proteins	QS kinase substate sites, fork head region for transcription
7. CA140077	CNNM2	Cyclin-M2	Transporter associated region
8. AAH58266	TRP-M1; transient receptor potential (M-1 sub-family)	A cation channel of the melastatin family; expressed in metanocytes associated with development of melanomas, permeable influx for Ca^{++} and Mg^{++} cations	TRP consensus site; EWKFAR
9. NP060124	TRP-M6 Transient receptor potential (M-6 sub-family)	A channel permeable to Ca^{++} and Mg^{++} ions. Regulates parathyroid hormone, production, energy production, and DNA maintenance	TRP consensus site: LPXPFXPSPK

*Note that GIP displayed direct computer hits on the melastatin family of the TRP calcium channels. # 8,9 blocks. FHA= Forkhead kinase active.

Table 4: Global RNA Microarray: Expression of mRNA 716 transcripts** were significantly altered in MCF-7 cultured breast cancer cells after 8 days of treatment with GIP as compared to treatment with the scrambled control peptide.

Microarray Data: Transcripts displaying 1.0 or larger log fold (log base 2.0) decrease for genes associated with cell division and proliferation processes.	
Gene Title	**Fold Decrease (-) of Transcript**
I. Cell Cycle Regulation:	
1. F-Box, WD40, Domain 10 (FBXW10)	-14.9
2. Checkpoint Suppressor-1 (CHES1)	-9.2
3. Cyclin-E**	-4.6
4. SKP2**	-4.3
5. Calpain	-32.5
6. CDC20 Cell Division	-4.3
7. Transcription Dp-1 (TFDP1)	-4.3
8. CDC20 Cell Division Homolog	-4.3
9. Histone-1, A4g (HIST1H4G)	-3.2
10. Fanconi Amennia-D2 (FRANCD2)	-2.0
11. Establishment of Cohesion-1, Homolog (ESC02)	-9.2
II. Ubiquitin-Associated Proteins:	
1. Tripartite Motif-containing-62 (TRIM62)	-3.0
2. SH3 Domain Protein (EVE1)	-2.3
3. SUMO/Sentrin/SMT3 Specific Protease (SENP3)	-2.1
4. Ubiquitin Specific Protease-49 (MGC20741)	-2.1
5. Ubiquitin Ligase Protein Complex (KIAA0804)	-2.1
III. Apoptosis Associated Proteins:	
1. p53-regulated apoptosis-inducing protein 1 (P53AIP1)	-9.8
2. p53-regulated apoptosis-inducing protein-1 (mitochondria)	-3.3
3. Epithelial membrane protein-1, cell death	-2.5
4. Bcl2 β cell CCL/Lymphoma, anti-apoptosis, release of Cytochrome-C from mitochondria	-2.2
5. NACHT, leucine-rich repeat and PYD (pyrin domain, induction of apoptosis, regulation caspase)	-1.2
5. β cell, CLL Lymphoma, member-B, zinc finger protein	-1.1

**= real time PCR

In order to more fully understand the functional effects of the GIP-34 interaction with TRPs in the cell growth suppression of breast cancer cells, a global RNA microarray assay was subsequently performed (Table-4). It was subsequently demonstrated that GIP affected the RNA outcome analysis by altering the RNA expression transcripts of 716 proteins after 8 days of GIP peptide treatment in the breast cancer cell cultures. A total of 431 RNA transcripts were down-regulated, while 286 transcripts were up-regulated. Some of the RNA transcript for proteins involved cell growth examples in which eleven

transcripts were down-regulated in cell growth cycle associated proteins that included Cyclic-E, SKP2, and checkpoint suppressor-1 (CHES1) proteins (Table-4). Other RNA transcripts in table-4 included cell cycle-associated proteins such as the ubiquitin protein degradation system which included the SUMO/Sentrin/SMT3, protease-49, and the ubiquitin ligase system. The third group of RNA transcripts that were down-regulated included the apoptosis associated (cell death) proteins (Table-4) [51,52].

IV. Concluding Remarks

The present treatise has demonstrated that certain members of the TRP family of cation channels are over-expressed in various breast and other cancer cell types [7,8]. Over-expression can serve both as an aid, a benefit and an advantage in cancer therapy studies. This is due to the fact that many more TRP channels are involved in breast cancer cells compared to normal cells. Thus, the over-expressed TRP channels in cancer cells compared to those of non-malignant cells indicate that overly excessive amounts of Ca^{++} ions undergo unrestricted influx passage of Ca^{++} into the cancer cell cytoplasm. An unregulated highly excessive influx of Ca^{++} ions into the TRP channel can ultimately result in destroying the cancer cell by allowing excess Ca^{++} cation overflow into 1) the mitochondria Ca^{++}reserve and 2) the endoplasmic reticulum Ca^{++} reserve compartments. These two successive compartmental overflow events can result in cell death via a programmed cell death process (i.e., apoptosis) initiated by the cancer cell. Thus, it can easily be ascertained that cell death by apoptosis is not due to the direct GIP action of opened TRP channels, but rather to the excessive influx of Ca^{++} into the two cancer cytoplasmic reserve organelles. This is because GIP only functions to keep the Ca^{++} channel opened for a protracted time period. Instead, cell death can be solely attributed to the uncontrolled, unrestrictive and dysregulated excessive flow of Ca^{++} cations into the cell cytoplasm. This overflow enters into the MT and ER reserve chambers/compartments. These two overflow action of Ca^{++} ions into the mitochondria and endoplasmic reticulum, then triggers a program of cell death induction process of apoptosis within the cancer cells [46-49].

Postscript Notes

It should be noted and clarified that the molecular pathways and electrophysiologic mechanisms of action in the present report have not yet been fully elucidated at the present time. These molecular pathways and mechanisms are presently under study and have not yet been adequately explained and understood. Such events which are under further research study include: 1) the cell surface membrane electrical charge phenomenon on the cancer cell membrane. This event is in regard to the nature of the ionic medium in which the cells are found, and the valence of the ions found therein; 2) the measure of the Zeta potential of the electrical charge on the cell surface membrane in a liquid phase; 3) the linear current events regarding the inward and outward rectification current changes under defined test conditions; and 4) cell membrane measurements of the electrical currents, voltage, amperage, and resistance simultaneously taking place. These electrical physiological measurements in the above situations presently need further research study and have yet to be resolved or published to date [54,55].

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Conflicts of Interest

The author declares there are no known conflicts of interest used in the preparation of this manuscript.

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Technical Notes Addendum

Computer Supporting Data: An “in silica” search for pairing of peptide-to-protein Interactions:

“The Peptimer Discovery Program.” AFP and its derived pep-

tides are bristling with matching short amino acid segment sites matched to cytokines, chemokines, and immune system amino acid sequence identities which are located throughout the AFP polypeptide molecule. The protein-to-peptide amino acid pairing computer software program (peptimer) from Serometrix Biotech Company (Syracuse, NY) revealed that the GIP peptide contained multiple matched allosteric amino acid pairing interaction sites with cellular and cancer-associated proteins. Such protein sites (amino acid segments) can forecast potential targets for future therapeutic approaches for cancer therapies treatments (50). Such amino acid pairing interactions could affect signal transduction pathways by inhibiting (or enhancing) receptor binding by blocking protein--to-peptide interactions (53). As shown in Table-3, the matched interacting sites with GIP included: 1) growth factors; 2) cell cycle proteins; 3) ubiquitins; 4) apoptosis associated proteins; 5) calcium-linked proteins; and 6) TRP channel proteins. Matched detection of these pinpointed target interactions of cell growth cycle proteins might cause cancers to regress to less severe and reduce patient symptoms. Therefore, preventing such interactions in cancer patients could lead to new treatments and improved cancer and modalities in clinical patients.

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