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Breast Cancer, Non-Selective Transient Receptor Potential (TRP) Cation channels, and Antimicrobial Peptides: A Search for Potential Cancer Targets

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Abstract

Breast Cancer (BC) is one of the most common types of cancer in women throughout the world. However, it is now recognized that there exists new and improved therapeutic treatments and modalities for this devastating disease in women. Although early detection and treatment of BC can avert about one-third of the cases, women over 70 years of age and female patients diagnosed with triple negative tumor markers display the worst outcomes. Even though women administered HER2 drugs have been effective in many BC patients, there still exists a constant need to search for new drugs and novel treatment approaches to identify more effective targets intended for BC therapy. Recent research advances have been made regarding cell-membrane intrinsic cation (Ca++) channels that are essential for cell division, growth, and proliferation of BC cells. These ion channels have been localized both in various cells and tissues associated with BC and throughout normal and malignant cells of the body. Specific ion channels have now been localized and identified as Transient Receptor Potential (TRP) channels which are non-selective cation channels for the influx of Ca++, Mg++, Mn++, and Na+ ions into cells. The present treatise reviews TRP channels in light of their structure, function, and biological activities in cancer and presents potential novel therapies intended for BC cells.

Keywords: Alpha-fetoprotein; Cation channels; Transient receptor potential; Instability; Breast cancer; Triple negative.

Introduction

One of the most common cancers in women worldwide is Breast Cancer (BC), thus making it a global health concern [1,2]. There presently exists an ongoing need for novel diagnostic and therapeutic tools to both detect and treat BC, especially in older women populations. In women greater than 70 yrs, 1 in 8 women will get or have had breast cancer in their lifetime. If detected early and aggressively treated, about one-third of these deaths can be averted [2]. Drugs for BC which target the HER2 protein (Epidermal Growth Factor Receptor-2) have been very effective in treating several different types of breast cancers [3]. However, the most difficult cancers to treat are the triple negative biomarker diagnosed breast cancers. The triple negative BCs express low or near absent levels of specific tumor biomarkers which encompass the following: 1) the estrogen receptor alpha (ER-α); 2) the Progesterone Receptor (PR); and 3) the HER2 receptor [4]. Their absence makes the triple negative diagnosed breast cancers highly limited in their therapeutic response to biomarker treatment options, and such cancers experience frequent recurrences. Unlike triple negative breast cancers, additional and varied treatment modalities exist for other BCs such as BRCA-mutated, basal cell, and luminal cell cancers [5].

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The HER2 cell surface receptor protein: The HER2 protein is a member of the epidermal growth factor receptor family also known as the receptor tyrosine-protein kinase ERB B-2, identified as CD340, a type of cluster of differentiation (CD) protein. HER2 is also known as a proto-oncogene product encoded by the ERBB2 (Neu) gene [6]. Over-expression of such oncogenes plays a vital role in the growth, development, and progression of aggressive-type BCs with the ERBB2 oncogene, an important biomarker for about 30% of total breast cancers [3]. As a final notation, Herceptin is a monoclonal antibody (also called Trastuzumab) which is produced by the immune system and is directed against the antigen, the HER2 protein [7].

Transient Receptor Potential (TRP) cation channel properties and their functions: Cell surface membrane ion channels are essential for overall bodily maintenance, cell growth, and proliferation and are present as insertions into the cell surface membrane bilayer. The TRP channels play a major role in cell division via involvement in the cell growth cycle [8]. In such an involvement, the TRP channels are capable of regulating the cyclin-E/Cdc2 induced transition of the G1 to the S-phase of the cell's growth cycle [9]. Cells undergoing growth and cell division in the G1-phase of the cycle display a depolarized membrane electrical potential corresponding to a large engagement of a TRP-induced current [10]. It is this hyper-depolarization that leads to arrest and stoppage of the various cell cycle growth phases. Calcium (Ca^{++}) dependent channels, like TRPs, function to control multiple cellular events with the following items: 1) cell membrane voltage, 2) intracellular Ca^{++} concentrations, and 3) intracellular signal transduction in cells undergoing growth and proliferation [11]. Thus, TRPs are now known to act as transmembrane non-selective channels for cations which include Ca^{++}, Mg^{++}, and Mn^{++}. However, unlike potassium selective channels, TRP channels are constitutively open and are gated by a variety of sensory stimuli (i.e., spices) as displayed and listed in (Table 1).

TRP channel functions and locations: TRP channels have been localized in cells such as smooth and cardiac muscles, fibroblasts, and endothelial cells [8]. Such cation channels are capable of coupling to kinases and other enzymes such as phospholipase-C, and protein-kinase-C (PKC); this coupling is in addition to binding to various scaffold proteins (signal plex) that participate and interact with a cluster of proteins comprising a cell membrane structure called a signal plex [12,13]. Thus, the TRP channel is associated with a complex of multiple proteins that can respond to restoring intracellular calcium stores (by resupplying Ca^{++} to these stores); such channels also react to stimuli such as increased alterations in hypertension and hypertrophic growth activities. TRPs are further involved in other activities such as dendritic cell cytotoxicity, neural-stage cell maturation, differentiation, and sensor activations that are associated with cardiovascular disorders and various states of fibroblast differentiations [13].

The cell membrane-intrinsic protein cluster known as a signal plex can be defined as a group of proteins surrounding and incorporating within itself a TRP channel protein all of which is inserted into the bilayer cell membrane itself [12]. Thereby, the total signal plex protein constituents are comprised of the following proteins: 1) phospholipase-C beta; 2) protein kinase-C; 3) calmodulin; 4) myosin; 5) beta-2-adrenergic receptor; 6) Na^{+}/H^{+} co-transporter; 7) the Ezrin-Radixin-Moe sin complex, and a TRP channel itself.

A descriptive comparison of TRP channels interacting with antimicrobial-like peptides: The Antimicrobial-Like (AMPL) peptides consist of broad-spectrum antibiotic agents that are comprised of peptide members of the innate host defense networks of mammalian immune systems [14,15]. In recent years, these AMPL-molecules (i.e., defensins) have also been determined to function as adjunct therapeutic compounds for cancer therapies and treatments [16]. The biologic cancer therapeutic properties of AMPLs can be attributed to their ability to home onto and attach to the cancer cell surface bilayer membranes. This cell surface membrane attachment (binding) is followed by the AMPL's ability to penetrate into the cancer cell interior (cytoplasm) without requiring a receptor-mediated endocytosis step [17]. This attachment and pore-forming phase has been attributed to a net negative electrical charge on the cell membrane surface; this electrical charge property bestows upon a peptide the capability of AMPLs to attach, destabilize, and disrupt the bilayer cell surface membrane.

Even though the AMPs are not generally associated with pregnancy, an AMP-like pregnancy associated peptide has been reported by the author (GJM) in the literature and has gained attention regarding cell penetration into the cell's cytoplasmic interior [18]. This AMPL-peptide has been termed the "Growth Inhibitory Peptide" (GIP) and has recently been described in multiple published reports [19-21]. Such GIP-associated publications have demonstrated a significant suppression of cancer growth in both in vivo animal models and in vitro human BC cell cultures (Table 2).

In the last decade, the AMPL-GIP has been demonstrated to interfere, block, and inhibit the growth of cancer cells in the course of interacting with calcium-associated channel influxes into malignant cells [21]. As described above, these calcium-associated influx channels have been identified as members of a Transient Receptor Potential (TRP) channel family [22]. The TRP channels function to maintain and regulate cell membrane voltage currents, intercellular calcium concentrations, and receptor crosstalk and signaling during a cancer cell's growth cycle [23]. Although the TRP channels normally contribute to the regulatory function of cation influxes into the cell cytoplasm, TRP channels can also participate in other cell cytoplasmic activities that involve cell growth, migration, proliferation, and protein-to-protein interactions [24]. Biological activity studies of the AMPL associated GIPs have been further studied in various cell functional assays such as a global RNA microarray analysis which utilizes human MCF-7 BC cell lines. Results of the RNA microarray studies revealed that GIP, after 8 days uptake and exposure within cultured MCF-7 cells, affected numerous cellular RNA transcripts via the regulation of 717 RNA transcripts. These included the up-regulation of 431 RNA transcripts and downregulation of 286 RNA transcripts in cultured MCF-7 BC cells (Table 3). In addition, the utilization of a computer "in silica" program model has further identified multiple allosteric GIP peptide molecular docking and interaction sites. In such computer models, GIP was shown to interact with both cell growth cycle and calcium associated protein allosteric binding and/or localization sites (Table 4). In an added study, it was found that excessive, uncontrolled, and unrestricted Ca^{++} influx into cancer cells can be detrimental to cancer cells.

If unchecked, excessive intracellular calcium levels can result in dysfunctional receptor signaling, faulty gene transcription and DNA repair, and ultimately in programmed cell death, i.e., apoptosis of cancer cells [25,26].

The TRP channel's insertion into the cell membrane: Both the potassium voltage-gated channels and the TRP channels display six helical transmembrane stretches of amino acid sequence stretches that assemble into homo- and/or hetero-tetramers. These amino acid stretches are assembled as groupings of tetramers that function in the non-selective cation activities of TRP channels [27]. The six TRP transmembrane domain structures form a pre-channel segment between the four transmembrane segments while transmembrane segments 5 and 6 are assembled to form the ion channel regulating the cation influx segment itself. Interestingly, all six TRP family members show 20-60% overall sequence homologies among the various TRP channel sub members [22]. All six TRP subfamily members are ubiquitously expressed in many normal and cancer cells, and in various tumors throughout the mammalian body. The pore of the TRP channel lies between helical Transmembrane Segment-5 (TM5) and the Transmembrane Segment-6 (TM6) amino acid stretches and contribute to the overall structural pore of the tetramer [21]. The helical protein loops weave in and out the cell membrane six times leading with the amino-terminal segment of the loop. The NH2 amino acid segment is known to be comprised of ankyrin repeats, a coiled region, and a caveolin binding segment. Ankyrins are known to mediate protein-to-protein interactions, and Caveolin interacts and stimulates cell signaling activities with scaffold proteins. The Carboxy-Terminal (COOH) cytoplasmic region consists of a short TRP signature amino acid motif sequence (i.e., EWKFAR), a Proline-rich motif and, a CRIB region (Calmodulin receptor binding region employed for cell signaling), all of which finally ends in a coiled-coil region.

Ankyrin repeat segments are utilized for TRP cell membrane cytoplasmic targeting and for ion channel insertions into cell surface membranes; these channel insertions function to regulate various other intracellular physiologic activities [28]. Coiled coils are protein motif segments that are utilized to regulate oligomerizations, while heptad repeats wind in and about each other in a membrane and link proteins to coiled-coil domain segments of peptides. CRIB motifs (Cdc 42/RAC) are interactive binding sites which bind to Calmodulin for intracellular signaling via calcium ions [22]. PDZ domains, found mainly in signaling proteins, play multiple roles in anchoring cell membrane receptor proteins to the cell's cytoskeletal proteins [27,28]. Finally, PDZ binding motifs are short C-terminal 3-to-5 amino acid components that serve as protein interaction modules.

TRP channel sensor activation factors: Various sub-member family TRP channels are gated and sensor-activated by the following activation factors: 1) cell membrane voltage; 2) intracellular Ca^{++} ions; 3) pH levels; 4) REDOX agents; 5) pain activated sensors; 6) heat and/or cold; 7) menthol and camphor; and 8) phytochemical plant derived sensor agents. The photochemical substances can include spices such as mustard, wasabi, ginger, peppermint, and capsaicin (chili powder). Other such variable activating sensors can include touch, pressure, vibration, and mechanical motions [29] (Table 1).

TRP channel subfamily members: In order to encompass responsiveness and carry out the above multiple sensory stimuli, the TRP family of cation channels have been determined to consist of six major family members which are described below with their subfamily constituent numbers [8,22]:

1. The Canonical (C) type, (TRPC), 7 submembers;
2. The Vallonoid (V) type, (TRPV), 7 submembers;
3. The Metastatin (M) type (TRPM), 8 submembers;
4. The Mucolipin (TRPML channel family, 3 submembers;
5. The ankyrin (TRPA1) channel family, 1 submember;
6. The Polycystin (TRPP3) channel family, 3 submembers;

The TRP Polycystin ion channels are mechanosensory transduction channels and not metabolic sensory channels; hence only first five TRP channels will be described below.

1. The TRPC (Canonical) family members: The TRP channel-C is a calcium influx channel mainly associated with phospholipase-C signaling. TRP-C channels release calcium ions from cytoplasmic organelle intracellular storage areas and such channels can also function as second messenger-operated cation channels [30]. The TRP-C subfamily also binds to microtubules which act to destabilize phosphoproteins and activate diacyl glycol-induced linear currents. These linear current events produce both inward and outward rectification current changes [31]. Thus, most of the family members of TRP-C subfamily are mainly calcium ion selective channels and comprise one of the larger TRP channel subfamilies associated with heart disease and other related disorders.

2. TRPV (Vallonoid) family member: The TRP valloniid sub members play a major role in calcium ion transport and a lesser but still important role in Mg^{++} and Na^{+} channel influx [32]. TRPV channels also function as taste sensors and such channels can respond to spices such as garlic (allicin), hot chili peppers (capsaicin), alkyl isothiocyanate, mustard, wasabi, and various other spicy compounds [33] (Table 1). Additionally, TRP-Vs play a vital role as sensors in the detection and regulation of body temperature and further serve to function as thermoreceptors (excessive heat), mechanoreceptors, chemical sensors, chronic pain sensors, and nociception (toxic pain) sensations. Furthermore, TRPV channels can be activated by linoleic and arachidonic fatty acids in the course of inflammatory immune responses [34]. Certain TRPVs have also been found in the brain, neurons of the peripheral and central nervous systems, and in organs such as the pancreas and breast. Endogenous sensory activations of TRPV channels also encompass cold temperatures, low pH, and conjugated dopamine regulation. TRPVs can further be activated by inflammatory phospholipid mediator-release as a result of tissue damage which stimulates TRPVs which involve both phospholipase-C and PKC pathways [35]. Furthermore, TRPV can interact with cell cycle CdK5s proteins which serve to mediate phosphorylation as a result of ligand induced channel influx events. During cell cycle growth, an over-stimulation of TRPV channels can lead to cell cycle arrest via increased expression of p21 and p27 CDK cell growth cycle inhibitors [36,37]. TRPV channels are known to activate calcium cation influx which leads to membrane depolarization and increased action potential. Studies performed using Sharp's electrodes and patch-clamp Electrophysiologic (EP) methods have been utilized to demonstrate these latter EP activities [21].

3. The TRPM (Meta statins) channel family: The TRPM metastatic channels contain sub-family members named on behalf of the tumor suppressor, “meta statin” found in melanoma cancers [38]. These channels are expressed in the brain and are associated with bipolar disorders, manic depressions, autism, and Alzheimer’s disease. The TRPM channels are also expressed in breast and pancreas; these latter organs are involved with insulin secretion, gout, obesity, and diabetes. TRPM is further activated by ADP-ribose in the glucose metabolism pathway and with pregnenolone activities in the pancreas; these activities regulate calcium ion influx, insulin release, and immune system derived lymphocyte cell migration. Finally, the TRPM channels serve as key components for the taste sensations of bitter, sweet, and umami flavors.

4. The TRPML mucolipin channel family member: The TRPML (Transient Receptor Potential Mucolipin) subfamily consists of three members: TRPML1 (MCOLN1), TRPML2 (MCOLN2), and TRPML3 (MCOLN3). These TRP ion channels have been localized to intracellular vesicular membranes, such as lysosomes and endosomes [11]. These vesicles play significant roles in regulating membrane trafficking, endocytosis, and exocytosis. TRPML1 (MCOLN1) is the most studied subfamily member and is ubiquitously expressed and functions as the primary calcium ion channel for lysosomes. TRPML2 (MCOLN2) channels are largely expressed in immune associated cells of lymphoid and myeloid (bone marrow) tissues and are involved in enabling the release of viruses from endosomes [39]. The TRPML3 (MCOLN3) channels are also expressed in tissues such as skin, inner ear, and kidneys. Mutations in these latter cation channels are known to result in hearing loss, vestibular dysfunction, pain, and pigmentation problems [40]. The TRPML3 channel has further been localized to a variety of other intracellular vesicular membranes. In other activities, the TRP mucolipin channels can bind to and activate phosphatidylinositol-3, 5-biphosphate molecules. TRPML1 channel is also known as a therapeutic target for neurodegeneration and for involvement in viral infections. Finally, the TRP mucolipin channels exhibit short cytosolic tail extensions and these parts of such channels share high amino acid homologies (75% similarities) with other TRPML subfamily members [41].

5. The TRP ankyrin channel family member: TRPA1, the Transient Receptor Potential Ankyrin channel is the sole member of the mammalian TRPA family, which acts as a non-selective calcium cation influx channel [42]. TRPA1 is known for its extensive N-terminal ankyrin repeat domains (typically consisting of 14-18 such repeats per channel). This ankyrin associated channel serves as a sensor for pain, cold, and noxious chemical irritants (e.g., mustard oil, reactive oxygen species) in sensory neurons [41]. Since calcium ions are an essential signaling molecule in many different bodily cells of mammals, this trait makes such a channel (i.e., TRPA1) a significant factor in cell signaling. Finally, TRPA1 has been implicated in multiple disorder states involving chronic pain, skin disorders, gastrointestinal diseases, and urinary bladder maladies [26]. Symptoms caused by this TRPA-associated channel disorder can include anorexia, fever, abdominal pain, and various abdomen disorders.

TRP and breast cancer research results: Research studies have been performed to identify TRP expression patterns of the many different human TRP channels in clinical patients in samples derived from breast cancer biopsies and breast cancer cell cultures. A selected commercial transcriptome was analyzed for 11 different breast cancer tissues using a RNA-Seq program (illumine, San Diego, CA). This transcriptome was designed to be composed of sets of all RNA molecules in a cell or a certain population of cells. Only 2 TRP subfamily channels were found to be expressed in every cell and tissue sample obtained regardless of origin; namely, these channels included the TRPV1 and TRPM7 subfamily members. Due to the fact that TRPM7 is known to be expressed in a large number of different cell types throughout the body, this TRP channel was used with cautious discrimination.

1. TRP channel expression patterns in the breast cancers: Breast cancer expression profiles revealed a high cell membrane presence of TRPV and TRPM channels in samples of 1) BRCA-induced breast cancer cells; 2) basal cell breast cancer cells; 3) luminal breast cancer cells; and 4) in triple negative breast cancer cell samples. As described above, triple negative breast cancers are the most difficult to treat and are known to be present in 20% of all known breast cancer cases and thus served as an ideal test target for cancer types [4].

2. TRPs and breast cancer interaction results: TRPV1 channels were highly expressed in all four breast cancer cell types (see above), especially triple negative ones; these were present in either low amounts or absent from normal (non-cancer) breast cell biopsies and cell culture samples. Since TRPV1 channels are strongly activated by sensory stimulators such as capsaicin (10uM to 500 uM) [33,35], the hot pepper spice activator was used as a common ligand agonist to hyper stimulate TRPV1 and other related such channels. Capsaicin is an 8-methyl-N-vanillyl-8-nonenamide (a thermal irritant) which causes a seemingly burning taste sensation in the patient.

3. Review and summary of TRP and breast cancer: TRPV1 channels are expressed in many bodily cells over a broad range in mammals and are known to be associated and involved with breast cancer growth and proliferation [32]. Hence, when using a known database [41], TRPV1 was shown to be overexpressed in breast cancer tissues compared to non-malignant, normal breast tissue samples. Some TRP channels (i.e., TRPC5, TRPC7) were not at all expressed in both normal (non-malignant) and cancer breast samples. Moreover, TRPA1 was not expressed in normal breast cells but was specifically localized in luminal breast cancer cells [42]. In comparison, TRPM8 was not expressed in normal breast cells but occurred in many different breast cancer cell type samples. Although the high channel expression of TRPV2 occurred in normal breast cells, this particular TRP channel subfamily member was not detected in any of the breast cancer samples tested. Luminal cancer cell breast samples showed the least expression among the many sample BC cell types, while some cells showed no expression at all. High activation patterns of the TRPV1 channels by capsaicin ligands notably observed to decrease and interfere with intracellular signaling in all breast cancer cells tested. Interference also occurred in intracellular Ca^{++} cation signaling which resulted in: 1) inhibition of cancer cell growth; 2) cell cycle arrest (G1 to S phase); 3) cellular necrosis,

Table 1: Listed below are the chemo-sensitizing agents, spice and environmental sensors or irritants that activate and/or stimulate the cation selective and non-selective channels of vertebrate cells. Such channels interact with a family of proteins referred to as Transient Receptor Potential (TRP)* channels.

Name of channel stimulation/sensor activation chemo-sensitizing agent	Type of cation TRP calcium channel activated	Functions of activated TRP channels	Type of cancer affected, suppressed
1. Mustard seed or oil spice	TRP A1 TRP M2 TRP M8 TRP V1 TRP V4	Cell cycle arrest, apoptosis, blocks cell migration and invasion	Lung, liver, digestive tract, pancreas, colorectal, and ovarian cancer
2. Ginger spice	TRP V4 TRP V1	Induction of programmed cell death i.e., apoptosis	Embryonic kidney cells, colorectal, bone, testis, ovarian cancers
3. Wasabi (Japanese Horseradish)	TRP A1 (Ankyrin)	Triggers cell signals to suppress programmed cell death, lipid peroxidation	Colon, pancreatic, central nervous system, lung, and breast cancers
4. Cayenne Pepper, Hot chili powder, Capsaicin, Camphor	TRP V1 TRP C6 TRP M2 TRP M7 TRP V6	Upregulates liver apoptosis or programmed cell death, growth factor	Breast carcinoma, renal, cervix, non-small cell lung carcinoma, hepatoblastoma, kidney, colorectal, thyroid, stomach, bone, ovary, testicular cancer
5. Menthol (peppermint oil) mint leaves (powder)	TRP M1 TRP M2 TRP M7 TRP M8 BK channels	Increases cell migration, spreading, motility, limits metastasis, tumor growth	Prostate, brain, glioblastoma, skin, melanoma, bone, and lymphoma cancers
6. Garlic	TRP A1 TRP M1	Activation of dendritic endothelial cells	Mast cell cancer, head and neck, squamous cell cancers, t-cell lymphomas, prostate, melanomas
7. Cinnamon (Cinnamaldehyde)	TRP A1 TRP M8	Gut mobility, inflammation, pain, O_2 stress	T-cell lymphoma, prostate, skin, bone cancers
8. Turmeric, Curcumin	TRP A1 TRP M2 TRP V4	Migration, cell proliferation cell cycle	Lung, ovary, testis, bone cancers

Legend: * The Transient Receptor Potential (TRP) superfamily can be subdivided into 6 subfamilies: these subfamilies included: TRP A (Ankyrin), TRP V (Vanilloid), TRP M (mela statin), and TRPC.

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 GIP peptide for six days, fixed, and stained with sulforhodamine-β. 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 HCC-299 HCT-116	AC AC AC	75 80 75	Suppression Suppression Suppression
Ovary	OVCAR-3 SK-OV-3 IGROV1 OVCAR-4	AC AC AC AC	80 60 75 85	Suppression Suppression Suppression Suppression
Breast	MCF-7 MDA-MB-231 MDA-MB-435	AC AC AC	80 80 70	Suppression Suppression Suppression
Prostate	PC-3 DU-145	AC AC	80 90	Suppression Suppression
Non-small cell lung	HOP-62 NCI-H460	CA CA	75 80	Suppression Suppression
Melanoma	UACC-62 SK-MeL-2 UACC-257	Epithelial Squamous Squamous	80 50-75 75-80	Suppression Moderate Suppression Suppression
Central nervous system	SF-295 U-251 SNB-75	CA CA CA	80 45 50	Suppression Moderate Suppression Moderate Suppression

Kidney	TK-10 A498 ACHN CAK-1	Renal CA Renal CA Renal CA Renal CA	85 75 80 50-75	Suppression Suppression Suppression Moderate Suppression
White blood cell	K-562 Molt-4 SR	Leukemia Leukemia Leukemia	45 10-15 25	Moderate Suppression Slight Suppression Slight Suppression

AC: Adenocarcinoma; CA: Carcinoma
*National Cancer Institute Therapeutics Screening Program, Bethesda, MD, used with permission.
Data were derived and extracted from Ref. 19, 20, 21.

Table 3: Growth Inhibitory Peptide (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 are presented.

Gene title	Fold decrease (-)	Cell function
I. Apoptosis associated proteins		
1. p53-regulated apoptosis-inducing protein 1 (P53AIP1)	-9.8	Mediates apoptosis
2.Epithelial Membrane Protein 1 (EMP1)	-5.6	Promote carcinogenesis
II. Calcium involved factors		
1.Phospholipase C, epsilon 1 (PLCE1)	-8.0	CDC25-associated
2.Solute carrier family 22 (SLC22A16)	-6.1	Cation transporter
3. Dystrophin (DMD)	-6.1	Muscle/ECM connection
4. Cadherin 13 (CDH13)	-4.9	Cellular adhesion
III. Channel directly associated proteins		
1. Potassium voltage-gated channel (KCNB2)	-8.0	Shab ion channel
2. Transmembrane Channel Like 5 (TMC5)	-5.2	Ion transporter
3. Potassium voltage-gated channel, KQT-like (KCNQ3)	-4.0	Cation signaling
4. Calcium Channel, Voltage dependent 2 (CACNA2D4)	-2.0	Calcium signaling
5. Calcium/Calmodulin-dependent Kinase (CAMK2B)	-1.9	Calcium regulation
6.Calcineurin A gamma (PPP3CC)	-1.8	Calcium phosphate 3 protein
7.Calcium Channel, Voltage Dependent (CACNC6)	-1.8	Calcium transport

**: real time PCR
*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 (430) were downregulated, while 286 were up regulated.
*Global RNA microarray was performed by Affymetrix Genomics Laboratory at Yale/Keck University facility, New Haven, CT, in collaboration with Dr. Kathleen F. Arcaro, University of Massachusetts, Amherst, MA.

Table 4: Molecular docking and peptide interaction binding sites on the Growth Inhibitory Peptide (GIP) were identified. Such sites were localized by means of proprietary computer software (Peptomer Discovery platform). See legend reference 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 445-480 as follows:
NH2- L S E D K L L A C G E G A A D I I T G H L C I R H E M T P V N P G V N P G V G Q- COOH (GIP amino acid sequence)

Accession # (Protein Bank)	Protein	Functions	Computer Hits
I. Cell growth cycle-associated proteins			
1.O14757	Ser/Thr protein kinase CHK2	Regulates S-phase, G2/M checkpoint	Helical region near kinase for ser 178
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.NP_009125	Protein kinase CHK2	S-phase checkpoint regulator of the cell cycle	FHA region, a fork head transcription factor phosphatase;
5.NP_005188	Checkpoint Suppressor (CHES1)	Suppresses checkpoint mutations of cell cycle proteins	QS kinase substrate sites, fork head region for transcription
6.CA140077	CNNM2	Cyclin-M2	Transporter associated region
II. Calcium cation and channel-associated proteins			
7.CAD12456	Titin	Ca^{++} dependent, myosin-binding ECM muscle protein	Ca^{++} binding domain
8.NP_004761	KCNNB2	Volt-gated K-channel outflow	Channel pore
9. NP_113669	SLC22A16	Carnitine, cation transporter	Cation binding region

10. BAA037730	Calpain	Cys protease, Ca binding; DNA-repair	Ca^{++} binding region
11. AAH58266	TRP-M1; Transient receptor potential (M-1 family)	A cation channel of the melastatin family; expressed in melanocytes associated with development of melanomas, permeable for Ca^{++} and Mg^{++} ions	TRP consensus site; EWKFAR (amino acid sequence)
12. NP060124	TRP-M6 Transient receptor potential (M-6 family)	A channel permeable to Ca^{++} and Mg^{++} ions. Regulates parathyroid hormone production, energy production and DNA maintenance	TRP consensus site: LPXPFXPSPK (amino acid sequence)

Legend Reference: Mizejewski GJ (2026). Is there a clinical potential for antimicrobial peptides to serve as a second option for cancer therapy? Intl J Res Oncol. 5: (1):1-7.

and 4) induction of apoptosis. Hence, many breast cancer cells appeared to display growth reduction by specific TRP channels, however, many BCs did not flourish in high spice-containing environments.

Conclusion

In summation, TRP channels could potentially be employed as therapeutic targets even among the most aggressive breast cancer types, such as triple negative cancers [4]. It might be advantageous to further explore the spice ligand activation property known to be attributed to TRPs. Such a factor might provide a rationale for future therapies in breast cancer and other cancers that express the TRPV and TRPM channel sub-member types [33,35]. It can be further ascertained from the present treatise, that certain TRP cation channels are able to interact in some way or manner with breast cancer growth and progression following cell cycle growth activation. Breast cancer expression profiles were found to exhibit a high cell surface bilayer membrane content of TRPs, especially in regard to the TRPV and TRPM subfamily members. It is further significant that the two latter TRP subfamily channels were notably associated with BRCA-induced breast cancers, basal, and luminal breast cancers, together with triple negative breast cancers. Although breast cancer is known to be prevalent among both young and older BC patients, it is hopeful that triple negative BCs in women may someday be treatable with such TRP interference methods. Finally, it can be deemed feasible that the research findings of the present report might provide additional insight into the involvement of TRP channels in cancers; this is especially in combination with AMPL-peptides as future therapeutics in choosing targets to treat breast cancers.

Declarations

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References

1. Liobl S, Poortmans P, Morrow M, Denkert C. Breast cancer. Lancet. 2021; 397(10286): 1750-1769.
2. Wilkinson L, Gathani T. Understanding breast cance as a global health concern, BR J Radial. 2022; 95(1130): 2021-2023
3. Jeesun Y, Oh DY. HER2-targeted therapies beyond breast cancer- an update. Nav Rev Clin Oncol. 2024; 21(9): 675-700.
4. Yin L, Duan JJ, Bian XW, Yu SC. Triple negative breast cancer molecular subtyping and treatment. Breast Cancer Res. 2020; 22(1): 61.
5. Robson ME, Tung N, Conte P, Im SA, Senjus e, et al. Olympiad final overall survival and tolerability results: Olaparib chemotherapy treatment of physician's choice in patients with BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol. 2019; 30(4): 558-566.
6. Pan L, Li j, Xu Q, Yang M. HER2/PI3K? AKT pathway in Her2- positive breast cancer. Medicine (Baltimore). 2024; 103(24): 38508.
7. Sun L, Jia X, Wang K, Li M. Unveiling the future of breast cancer therapy: Cutting-edge conjugate strategies and clinical outcomes. Breast Journal. 2024; 78: 103830-10390.
8. Nishida M, Hata Y, Yoshida T, Inoue R, Mori Y. TRP channels: Molecular diversity and physiological function. Microcirculation. 2006; 13: 535-550.
9. Minke B, Cook B. TRP channels proteins and signal transduction. Physios Res. 2002; 10: 1152-1172.
10. Wonderlin WF, Woodfork KA, Strobl JS. Changes in membrane potential during the progression of MCF-7 human mammary tumor cells through the cell cycle. 1995; 165(1): 177-185.
11. Zhang M, Ma Y, Ye X, Zhang N, Pan Z, et al. TRP (transient receptor potential) ion channel family: Structures, biological functions and therapeutic interventions for diseases. Signal transduction and targeted therapy. 2023; 8: 261-273.
12. Zasshi NY. TRP channels: Formation of signal formation of signal complex and regulation of cellular functions. Nihon Yakurigaki. 2003; 121: 223-232.
13. Redondo P, Rosado J. Store-operated calcium entry: Unveiling the calcium handling signal plex. Intl Rev Cell Mol. 2015; 316:183-226.
14. Pasupaleti M, Schmidtchen A, Malmsten M. Antimicrobial peptides: Key components of the innate immune system. Crit Rev Biotechnology. 2012; 32: 143-171.
15. Lee HT, Lee CC, Yang JR, Lai JZC, Chang KY. Large scale structural classification of antimicrobial peptides. Biomed Res Int. 2015; 2015:1-6.
16. Arasre F, Abnous K, Hashemi M, Taghdisi SM, Ramezanni M. Peptide-based targeted therapeutics: Focus on cancer treatment. J. Control Release. 2018; 292: 141-162.

17. Wang CK, Shih LY, Chang KY. Large scale analysis of antimicrobial activities in relation to amphipath city and electrical charge reveals novel characterizations of antimicrobial peptides. Molecules. 2017; 22: 32-40.

18. Mizejewski GJ. Biological roles of alpha-fetoprotein during pregnancy and perinatal development. Exp Biol. Med (Maywood). 2024; 229: 439-463.

19. Mizejewski GJ, Dias JA, Hauer CR, Henrikson KP, Gierthy J. Alpha-fetoprotein derived synthetic peptides: Assay of an estrogen-modifying regulatory segment. Mol. Cell Endocrinal. 1996; 118:15-23.

20. Mizejewski GJ. An alpha fetoprotein derived peptide suppresses growth in breast cancer and other malignancies: A review and prospectus. Med. Res. Archives. 2023; 11(7): 1-13.

21. Mizejewski GJ. Unveiling the relationships of calcium ions, transient receptor potential channels, and fetal peptides with calcium induced cell death: A review and commentary. Ric. Trends. Can. Res. 2024; 1(1): 1-9.

22. Clapham DE, Runnels LW, Strubing C. The TRP ion channel family. Nat Rev Neurosis. 2001; 2: 387-396.

23. Marini M, Titiz M, Monterio de Araujo DS, Geppetti P. TRP channels in cancer: Signaling mechanisms and translational approaches. Biomolecules. 2022; 13: 1557-1567.

24. Mizejewski GJ. Breast cancer and Transient Receptor Potential (TRP) cation channels: Is there a role for non-selective TRP channels as therapeutic cancer targets? A commentary. Intl. J. Can. Res. and Develop. 2017; 2: 4-7.

25. Zhiotosky B orrenius. Calcium and cell death mechanisms: A perspective from the cell death community. Cell calcium. 2011; 50: 21-221.

26. Thompson CB. Apoptosis in the pathogenesis and treatment of disease. 1995.

27. Kalia J, Swartz KJ. Exploring structure-function relationships between TRP and Kev channels. Sci Reports. 2013; 3: 1523-1526.

28. Mizejewski GJ. The third domain fragment of Alpha-Fetoprotein (AFP): Mapping AFP interaction sites with selective and non-selective cation channels. Curr Top. Peptide & protein Res. 2016; 16: 6-82.

29. Ferrer-Monteil A, Fernandez-Carvajal A, Planells-Cases R et al. Advances in modulating chemosensory TRP channels. Expert Open Pat. 2012; 22: 999-1017.

30. Goel M, Sinkins W, Keightley A, Kinter M, Schilling W. Proteomic analysis of TRPC5 and TRPC8 binding partners reveals interaction with the plasmalemmal Na (+)/K (+) ATPase. Aflugers Arch. 2005; 451: 87-98.

31. Arangeli A, Crociani O, Lastraioli E, Masi A, Pillozzi S, et al. A novel frontier in antineoplastic therapy. Curr Medicin Chem. 2009; 16: 66-93.

32. Weber L, Al-Refae K, Wolk G, Bonatz G, Altmuller J, et al. Expression and functionality of TRPV1 in breast cancer cells. Breast Cancer Targets and Therapy. 2016; 8: 243-248.

33. Xu S, Zhang L, Cheng X, Yu, Bao J, Lu R. Capsaicin inhibits the metastasis of human papillary thyroid carcinoma BCPAP cells through the modulation of TRPV1 channel. Food Functor. 2018; 9: 344-354.

34. Beech DJ. Integration of transient receptor potential canonical and vallinoid channels with lipids. Acta physios (Oxf). 2012; 204: 227-237.

35. Giangaspero F, Santoni G. Capsaicin-induced apoptosis of glioma cells is mediated by TRPV1 vanilloid receptor and requires p38 MAPK activation. J Neurochem. 2007; 102: 977-990.

36. Mistretta F, Buffi NM, Lughezzani G, Lista G, Larcher A, et al. Bladder cancer and urothelial impairment: The role of TRPV1 as potential drug target. Biomed Res Int. 2014; 987149.

37. Vriens J, Jannssens A, Prenen J, Nilius B, Wondergen R. TRPV channels and modulation by hepatocyte growth factor/scatter factor in human hepatoblastoma (HepG2) cells. Cell calcium. 2004; 36: 19-28.

38. Guo H, Carlson JA, Slominski A. Roe of TRPM in melanocytes and melanoma. Expel Dermatol. 2012; 21: 650-654.

39. Samanta A, Hughes T, Moiseenkova_bell VY. Transient Receptor Potential (TRP) channels. Subcell Biochem. 2018; 87: 141-165.

40. Gonzalez-Ramirez R, Chen Y, Liedtke WB. TRP channels and pain. In: Neurobiology of TRP channels. Boca Raton (FL): CRC Press/ Taylor & Francis; 2017. Chapter 8 Frontiers in Neuroscience. 2017.

41. Pedersen SF, Owsianik G, Nilius B. TRP channels: An overview. Cell calcium. 2005; 38(3-4): 233-52.

42. Legrand C, Merlini JM, de Denarclens-Bezencom C. New natural agonists of the transient receptor potential Ankyrin 1 (TRPA1) channel. Sciatic. Reprots. 2020; 10: 11238-11241.

43. Galluzzi L, Vitale I, Aaronson SA et al. Molecular mechanisms of cell death: Recommendations of the Nomenclature Committee on cell death. Cell Death Differ. 2018; 25: 486-541.