Anticancer potential of bioactive peptides from animal sources (Review)

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Abstract. Cancer is the most common cause of human death worldwide. Conventional anticancer therapies, including chemotherapy and radiation, are associated with severe side effects and toxicities as well as low specificity. Peptides are rapidly being developed as potential anticancer agents that specifically target cancer cells and are less toxic to normal tissues, thus making them a better alternative for the prevention and management of cancer. Recent research has focused on anticancer peptides from natural animal sources, such as terrestrial mammals, marine animals, amphibians, and animal venoms. However, the mode of action by which bioactive peptides inhibit the proliferation of cancer cells remains unclear. In this review, we present the animal sources from which bioactive peptides with anticancer activity are derived and discuss multiple proposed mechanisms by which these peptides exert cytotoxic effects against cancer cells.

Contents

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Abbreviations: ACE, angiotensin-converting enzyme; ACPB-3, anticancer bioactive peptide-3; SALF, shrimp anti-lipopolysaccharide factor; KLH, keyhole limpet hemocyanin; CTX, chlorotoxin; LAAOs, L-amino acid oxidases; Bl-LAAO, *Bothrops leucurus*; Ltc2a, latarcins 2a; Pen-2, penaeidin-2; mPTP, mitochondrial permeability transition pore; MOMP, mitochondrial outer membrane permeabilization; OPA1, optic atrophy1; PHB1, prohibitin 1; DAMPs, death-associated molecular patterns

Key words: bioactive peptides, anticancer activity, animal sources

1. Introduction

Although the rates of death due to cancer have been continuously declining for the past 2 decades in developed nations, cancer remains a major public health threat in many parts of the world (1). The incidence of cancer in the developing world is currently increasing. Specifically, 55% of new cases arise in developing nations, a figure that could reach 60% by 2020 and 70% by 2050. Worldwide, cancer also causes a substantial burden of economic cost and human suffering; the cost associated with cancer cases worldwide was approximately US$1.16 trillion in 2010, the equivalent of >2% of the total global gross domestic product. Nevertheless, this high figure is a lower bound and does not include the substantial longer-term costs to families and caregivers (2).

The current gold standard of care for cancer is a combination of surgery, radiation therapy, and chemotherapy (3-5). However, traditional methods are associated with drawbacks, such as a lack of screening tests for early diagnosis and a lack of tumor-specific drug delivery systems. Moreover, most classical anticancer drugs cannot differentiate between cancerous and normal cells, thus leading to systemic toxicity and adverse side effects. Selective and more efficient new drugs are urgently needed to address this problem. In this context, bioactive peptides are increasingly being considered as good drug candidates for cancer therapeutic applications. A growing body of peptides from natural animal sources has been demonstrated to possess physiological functions, such as immunomodulatory (6), antimicrobial (7), antihypertensive (8), antithrombotic (9), anticancer (10), antioxidative (11), and cholesterol-lowering activities (12). However, this review focuses on bioactive peptides from animal sources that may specifically target cancer cells and could consequently serve as anticancer agents that are less toxic to normal tissues. In addition, as shown in Fig. 1, bioactive peptides usually consist of 2-50 amino acid residues (~10^2-10^3 Da). Thus, they easily traverse or disrupt the cell membrane and result in apoptosis or necrosis. Therefore, the study and modification of bioactive peptides with anticancer activity will offer new opportunities for cancer prevention and treatment.

The objectives of this study are to 1) review the current understanding of anticancer bioactive peptides derived from different animal sources and 2) summarize the mechanisms of action by which bioactive peptides affect cancer cells. In addition, this review highlights the potential applications of natural animal source-derived peptides as pharmaceutical candidates in the auxiliary therapy of cancer.

2. Animal sources of bioactive peptides with anticancer activity

Terrestrial mammals and by-products. Although bioactive peptides with anticancer activity from terrestrial mammals are not well documented, one report has described four bovine meat-derived peptides that inhibit angiotensin-converting enzyme (ACE) and also exhibit anti-proliferative activity (13). Specifically, this study has demonstrated the cytotoxic effect of four peptides: GFHI, DFHING, FHG, and GLSDGEWQ. GFHI has been found to exhibit the most potent cytotoxic effect on the human breast cancer cell line (MCF-7) and to decrease the viability of a stomach adenocarcinoma cell line (AGS) in a dose-dependent manner, whereas GLSDGEWQ significantly inhibits the proliferation of AGS cells.

The group of Su identified the novel anticancer bioactive peptide-3 (ACPB-3) (14,15), which was isolated from goat spleens or livers. This peptide has been found to exhibit anticancer activity against a human gastric cancer cell line (BGC-823) and gastric cancer stem cells (GCSCs) *in vitro* and *in vivo*. Moreover, it significantly inhibits the growth of BGC-823 and $CD44^+$ cells in a dose-dependent manner, suppressing the proliferation of spheroid cell colonies and inhibiting their clone-forming capacity. *In vivo*, ACBP-3 alone or in combination with cisplatin suppresses xenograft tumor growth, and this peptide enhances the chemotherapy tolerance of mice by reducing the toxicity of the treatment during long-term experiments (15,16). The Su group also investigated the anticancer activity of ACBPs in a human colorectal tumor cell line (HCT116) *in vitro* and *in vivo* (17). Specifically, treatment with ACBPs significantly inhibits HCT116 cell growth, enhances UV-induced apoptosis, increases the expression levels of PARP and p53, and decreases the expression of Mcl-1. Moreover, ACBPs markedly inhibit human colorectal tumor growth in a xenograft nude mouse model and induce changes in the expression levels of PARP, P53, and Mcl-1, consistently with the changes observed *in vitro*, without producing apparent changes in body weight. These studies indicate that ACBPs inhibit human colorectal tumor cell growth and induce apoptosis by modulating the PARP-p53-Mcl-1 signaling pathway.

Milk and dairy products contain numerous components that exhibit a wide variety of physiological and functional activities. Moreover, bioactive peptides have been considered to be the important bioactive components of milk and dairy products, and they have been identified within the amino acid sequences of milk proteins. The intrinsic bioactivities of peptides encrypted in major milk proteins are latent until they are released and activated in three ways: 1) digestive enzyme-mediated hydrolysis, 2) hydrolysis by proteins from proteolytic microorganisms, and 3) digestion by proteolytic enzymes derived from microorganisms or plants (18).

A number of studies have reported the anticancer effects of milk protein-derived peptides on various cancer cells. Roy *et al* (19) found that bovine skim milk digested with cell-free extract from the yeast *Saccharomyces cerevisiae* inhibits the proliferation of a human leukemia cell line (HL-60). Meisel and FitzGerald reported the anticancer activity of casein fraction-derived caseinophosphopeptides (CPPs) (20), which inhibit cancer cell growth and stimulate the activity of immunocompetent cells and neonatal intestinal cells. Moreover, the bacterial hydrolysis of casein by commercial yogurt starter cultures yields bioactive peptides that influence colon cell kinetics *in vitro* (21), and a yogurt fraction obtained by membrane dialysis has been found to have an anti-proliferative effect on Coca-2 and IEC-6 mammalian intestinal cells (22).

Lactoferrin is an 80-kDa iron-binding glycoprotein that belongs to the transferrin family and has a variety of biological functions, including antibacterial, antiviral, anticancer, anti-inflammatory, and immunomodulatory activities (23). Moreover, lactoferricin is a cationic peptide generated by the acid-pepsin hydrolysis of lactoferrin and exhibits a range of biological activities, including cytotoxic activity against various microorganisms (24,25) and cancer cells (26-28). The major anticancer mechanisms of lactoferrin and lactoferricin include cell cycle arrest, apoptosis, anti-angiogenesis effects, anti-metastasis effects, immune modulation and necrosis (28). Thus, the aforementioned studies suggest that milk proteins are not only a nutritious part of a normal daily diet but also have potential for the prevention and/or management of cancer.

Marine animals. Bioactive peptide compounds from marine animals have been reported to have a broad range of bioactive properties (29-31). An increasing number of recent studies have focused on bioactive peptides with potential anticancer activity isolated from various marine animals, such as sponges, tunicates, ascidians, mollusks, fish, and other marine organisms (32-35).

Fish. Fish is a popular seafood item worldwide and have been identified as a source of bioactive peptides with potential anticancer activities. Selected fish-derived bioactive peptides with potential anticancer activity are listed in Table I.

The potential anti-proliferative activity of hydrolysate of a by-product from dark tuna muscle has been examined in MCF-7 cells (36). Specifically, peptide fractions with molecular weights ranging from 400-1400 Da exhibit the strongest anti-proliferative activity. Two anti-proliferative peptides, LPHVLTPEAGAT from papain hydrolysate and PTAEGVYMVT from Protease XXIII, have been identified in those fractions. Guha and others (33) have reported a 100-kDa Thomsen-Friedenreich disaccharide (TFD)-containing glycopeptide, named TFD-100, purified from the Pacific cod. TFD-100 binds to galactin-3 (β-galactoside-binding lectin) and inhibits the adhesion of androgen-independent prostate cancer cells (PC3) to endothelial cells, angiogenesis, and gal3-induced T-cell apoptosis.

Lee and colleagues (37,38) have reported that peptides isolated from anchovy sauce induce apoptosis in a human lymphoma cell line (U937) by increasing the activities of caspase-3 and caspase-8 activity, and the authors have purified

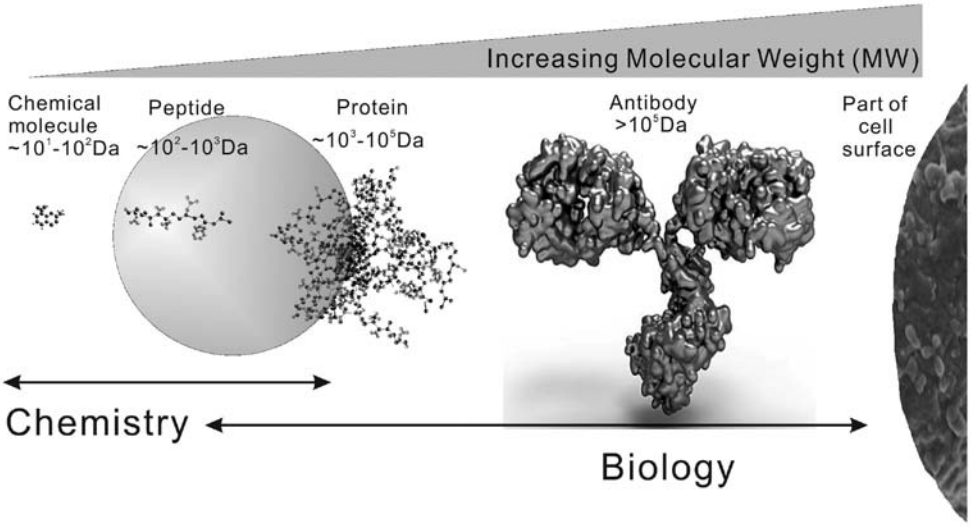

Figure 1. Left to right shows the sizes and molecular weight (MW) increasing from chemical molecular to biology cell. The anticancer peptides mentioned in this review mainly focus on circle area.

Table I. Fish sources of selected bioactive peptides with potential anticancer activity.

Fish	Peptide name	Anticancer activity	References
Anchovy		Induce apoptosis in a U937 cells	(37,38)
Blue whiting		Antiproliferative activity on MCF-7/6 and MDA-MB-231	(39)
Cod	TFD100	Inhibited adhesion of PC3 to endothelial cells, angiogenesis, and gal3-induced T-cell apoptosis	(33)
Cod		Antiproliferative activity on MCF-7/6 and MDA-MB-231	(39)
Grouper	Epinecidin-1	Inhibited the proliferation of U937 cells	(42)
Plaice		Antiproliferative activity on MCF-7/6 and MDA-MB-231	(39)
Red sea bream	Chrysophsin-1	Antitumor activities and modulates the inflammatory response in RAW264.7 cells	(43)
Red sea flatfish	Pardaxin	Antitumor activity toward MN-11 cells *in vitro* and *in vivo*	(44)
Salmon		Antiproliferative activity on MCF-7/6 and MDA-MB-231	(39)
Tilapia	TH1-5, TH2-2, and TH2-3	TH1-5 and TH2-3 exhibited anticancer activity against HeLa cells and HT-1080 cells, respectively	(40,41)
Tuna		Antiproliferative on MCF-7 cells	(36)

a 440.9-Da hydrophobic peptide. Moreover, the anti-proliferative activities of protein hydrolysates from different fish species, including blue whiting, cod, plaice and salmon, have been investigated *in vitro* in two human breast cancer cell lines (MCF-7/6 and MDA-MB-231) (39). Hepcidin consists of three hepcidin-like antimicrobial peptides (named TH1-5, TH2-2, and TH2-3) and has been isolated from tilapia. Of these peptides, TH1-5 and TH2-3 exhibit anticancer activity against epithelial carcinoma cells (HeLa) and human fibrosarcoma cells (HT-1080), respectively (40,41).

In addition, several studies have shown that peptides from different fish sources exert clear anticancer activity against various carcinoma cell lines, such as human hepatocellular liver carcinoma cells (HepG2), U937 cells, HeLa cells and murine fibrosarcoma cells (MN-11) (42-44). These data suggest the potential of fish as a valuable source of anticancer peptides for incorporation into functional foods.

Shrimp. Wilson-Sanchez *et al* (45) have demonstrated the anti-mutagenic and anti-proliferative activities of lipidic extracts from white shrimp. Specifically, the lipid fraction of white shrimp contains compounds that have been found to reduce the mutagenicity of aflatoxin B1 and the proliferation of a B-cell lymphoma cell line. Moreover, shrimp anti-lipopolysaccharide factor (SALF), an antimicrobial peptide from black tiger shrimp (46,47), enhances the anticancer activity of cisplatin *in vitro* and inhibits HeLa cell growth in nude mice. These peptides also exhibit significant anticancer activity in human colon and liver cancer cell lines, even when they are isolated from shrimp waste (48).

Ascidians. Bioactive peptides with anticancer activity have also been identified in tunicates and ascidians. Didemnins are a family of cytotoxic peptides isolated from tunicates (49), and acyclic depsipeptide, Didemnin B, has been widely studied because of its high anticancer potential (50,51). Didemnin B inhibits proliferation by inhibiting the synthesis of RNA, DNA and protein (51,52). Aplidine, a cyclic depsipeptide isolated from the Mediterranean tunicate *Aplidium albicans*, has anti-angiogenic activity both *in vitro* and *in vivo* (53), and aplidine was first identified on the basis of its enhanced cytotoxicity against different tumor cell lines, such as breast, melanoma, lung and ovarian cancer cell lines, and its lower myelotoxicity relative to Didemnin B (53-57). Tamandarins A and B are also cytotoxic depsipeptides from a marine ascidian of the family Didemnidae, and the effects of these peptides have been evaluated in various human cancer cell lines (58,59). Mollamide and Trunkamide A obtained from ascidians both are cytotoxic to different human tumor cell lines (58).

A novel polypeptide (CS5931) with anticancer activity has been identified by the group of Lin (60,61), who have demonstrated that CS5931 extracted from *Ciona savignyi* induces apoptosis via a mitochondria-mediated pathway in human colorectal carcinoma cells (HCT-8) in a dose- and time-dependent manner. CS5931 is strongly anti-angiogenic *in vitro* and *in vivo*, and this effect may be mediated by vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs). These studies indicate that CS5931 has the potential to be developed as a novel angiogenesis inhibitor for the treatment of cancer.

Sponges. Marine sponges are an abundant source of bioactive peptides with anticancer potential. In recent years, most researchers have focused on bioactive cyclic peptides and depsipeptides with highly unique structures that contain a wide variety of unusual amino acids and other building blocks (62-64).

Seven cytotoxic cyclic peptides (Callyaerins A-F and H) isolated from the Indonesian sponge *(Callyspongia aerizusa)* are cytotoxic to murine lymphoma cells (L5178Y), HeLa cells, and pheochromocytoma tumor cells (PC12) (63). Furthermore, reniochalistatins A-E, five cyclic peptides (including four heptapeptides and one octapeptide) from the marine sponge *Reniochalina stalagmitis*, and the cyclic octapeptide reniochalistatin E are cytotoxic to different tumor cell lines (65). Rolloamides A and B are cytotoxic cyclic heptapeptides isolated from the Caribbean sponge *(Eurypon laughlini)*, androlloamide A has been found to significantly suppress the growth of a panel of histologically diverse cancer cells (66). A new peptide, gombamide A, isolated from the Korean sponge *Clathria gombawuiensis* is weakly cytotoxic to human lung carcinoma (A549) and myelogenous leukemia (K562) cell lines and moderately inhibits Na^+/K^+-ATPase.

Jaspamide is a cyclic depsipeptide isolated from sponges of the genus *Jaspis* and *Hemiastrella* (32) and induces apoptosis in HL-60 (67,68) and Jurkat T cells (69). Two jaspamide derivatives, jaspamide 2 and 3, have been isolated from an Indonesian sponge *(Jaspis splendens)*, and low concentrations of these peptides inhibit the growth of L5178Y cells *in vitro* (70). Nine cyclodepsipeptides from the sponge *Homophymia* sp., homophymines B-E and A1-E1, have exhibited very potent cytotoxic activity with IC_{50} values in the nM range against a panel of human cancer cell lines (71). Recently, two cyclic depsipeptides isolated from a Madagascan sponge *(Homophymia lamellosa)*, pipecolidepsins A and B (64), have been found to exhibit cytotoxic activity against human lung, colon, and breast cancer cells (64,72).

Geodiamolide H, a depsipeptide isolated from a Brazilian sponge *(Geodia corticostylifera)*, inhibits the migration and invasion of breast cancer cells by modifying the actin cytoskeleton (73).

Three lipodepsipeptides (Lipodiscamides A-C) isolated from the marine sponge *Discodermia kiiensis* are moderately cytotoxic to murine leukemia cells (P-388) and HeLa cells (74). Moreover, taumycin A, another lipodepsipeptide from a Madagascan sponge (*Fascaplysinopsis* sp.), has been found to inhibit the growth of a human leukemic cell line (75).

Callyptide A, a newly identified cytotoxic peptide from the Red Sea marine sponge *(Callyspongia)*, has been found to inhibit the growth of different cancer cell lines, including MDA-MB-231 cells, A549 cells and human colorectal adenocarcinoma cells (HT-29), with GI_{50} values of 29, 18.5 and 30 μM, respectively (31). Smenamides A and B are two isomerichybrid peptide/polyketide compounds isolated from a Caribbean sponge *(Smenospongia aurea)* that contain a dolapyrrolidinone unit and show potent cytotoxic activity at nanomolar levels against lung cancer Calu-1 cells (76).

Mollusks. Several studies have reported that mollusks, such as shellfish, sea slugs, and sea hares, are rich sources of bioactive peptides that exhibit anticancer activity. Wang *et al* have isolated oligopeptide-enriched hydrolysates from oysters by using protease (77) and have shown that these hydrolysates markedly and dose-dependently inhibits sarcoma-S180 tumor cell growth in BALB/c mice. Furthermore, Cheong *et al* (78) and Kim *et al* (79) have reported two novel anticancer peptides isolated from oysters and mussels, respectively. The sequences of these two anticancer peptides differ, but both exhibit clearly superior cytotoxic activity and effectively induce cell death in prostate, breast and lung cancer cells.

Keyhole limpet hemocyanin (KLH) is a high-molecular-weight copper-containing protein found in the hemolymph of the marine mollusk Megathura crenulata (80). This extracellular respiratory protein has many bioactive properties (81-83), including immunostimulatory, antitumor, and antimicrobial activity. Riggs *et al* and McFadden *et al* (84,85) have shown that KLH from the giant keyhole limpet significantly inhibits the growth of different cancer cells *in vitro*, including estrogen-dependent breast cancer cells (MCF-7), estrogen-independent breast cancer cells (ZR75-1), pancreatic cancer cells (PANC-1), prostate cancer cells (DU145), and Barrett's esophageal adenocarcinoma cells (SEG-1 and BIC-1). Moreover, a cytokine analysis has revealed that KLH directly affects the production of cellular inflammatory and pro-apoptotic mediators. Furthermore, KLH increases early and late apoptotic activity in MCF-7 cells, whereas it reduces late apoptotic activity in the ZR75-1 cells. In contrast, KLH does not affect the early or late apoptotic activity of PANC-1 cells. These results suggest that KLH directly inhibits the growth of human breast and pancreatic cancer *in vitro* by modulating apoptotic and non-apoptotic mechanisms (86).

Dolastatins are a family of cytotoxic peptides isolated from the mollusk *Dolabella auricularia*. In this family, the linear pentapeptide Dolastatin 10 and the depsipeptide Dolastatin 15 have been reported to exhibit promising anti-proliferative activity (87,88). In recent years, synthetic dolastatin 10 analogs have been widely used in anticarcinogen drug development (89-91). These studies have provided strong evidence showing that Dolastatin 10 analogs effectively inhibit cell growth by dampening microtubule dynamics, inducing apoptotic cell death, and inhibiting tumor growth.

Aurilide is a small cyclodepsipeptide isolated from *Dolabella auricularia* that induces apoptosis in human cancer cells at low concentrations (92). Specifically, aurilide selectively binds to prohibitin 1 (PHB1) in the mitochondria, activating the proteolytic processing of dynamin-like GTPase optic atrophy 1 (OPA1) and resulting in mitochondria-induced apoptosis. The mechanism of aurilide cytotoxicity suggests that PHB1 is an apoptosis-regulating protein amenable to modulation by small molecules. Thus, aurilide may serve as a small-molecule tool for studies of mitochondria-induced apoptosis (93,94).

Kahalalides are a family of peptides isolated from *Elysia rufescens*. Among them, Kahalalide F is regarded as an important anticancer candidate for tumor therapeutics, owing to its high cytotoxicity (95-97). However, the mechanism of action of Kahalalide F is not well understood, and Kahalalide F has been observed to disturb lysosomal function and to potentially result in intracellular acidification and cell death. Thus, this peptide may effectively combat cancer cells exhibiting high lysosomal activity, such as prostate and cervical cancer cells (98). Moreover, Janmaat and others have demonstrated that ErbB3 and the downstream phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway are important determinants of the cytotoxic activity of Kahalalide F *in vitro* (99).

Finally, Keenamide A is a cytotoxic cyclic hexapeptide isolated from the notaspidean mollusk *Pleurobranchus forskalii* that significantly inhibits the proliferation of P-388, A-549, and HT-29 cells (100).

Amphibians

Frog and toad skin secretions. Skin secretions from amphibians (e.g., frogs and toads) contain a wide range of compounds with biological activity and have garnered attention because of their potential for drug development (101). In addition, the Chinese have traditionally administered secretions from frog skin and toad parotid glands for medicinal purposes since ancient times (102). Hundreds of such peptides have been identified since the discovery of the first antimicrobial peptide from this source (103), and some naturally occurring amphibian skin peptides and analogs are selectively cytotoxic to tumor cells and are promising anticancer agents (101). The primary structures of selected bioactive peptides with anticancer properties isolated from frog skin secretions are listed in Table II.

Alyteserin-2a, obtained from the midwife toad *(Alytes obstetricans)*, exhibits relatively weak antimicrobial and cytotoxic activities (104). However, analogs of alyteserin-2a are potently cytotoxic to A549 cells, human hepatocarcinoma cells (HepG2), MDA-MB-231 cells, and HT-29 cells (105).

Conlon *et al* (106) have reported two bioactive peptides, ascaphin-8 and peptide XT-7, isolated from the skin secretions of *Ascaphus truei* and *Silurana tropicali*s. These peptides are highly cytotoxic to HepG2 cells. Moreover, the analogs of these peptides are more cytotoxic to HepG2 cells than the natural bioactive peptides.

Several aurein peptides exhibiting anticancer activity have been reported by Rozek *et al* (107), who extracted Aureins 1, 2 and 3.1 from the green and golden bell frog *(Litoria aureus)* and the southern bell frog *(Litoria raniformis)*.

van Zoggel *et al* (108) have reported that two bioactive peptides of the dermaseptin family (dermaseptin B2 and B3) isolated from skin secretions of the South American tree frog *(Phyllomedusa bicolor)* exhibit antitumor and angiostatic properties. Specifically, the authors demonstrated that these two peptides inhibit both the proliferation of a human prostatic adenocarcinoma cell line (PC-3) by >90% *in vitro* and the differentiation of bovine aortic endothelial cells. Most recently, Shi *et al* (109) have identified two novel members of the dermaseptin antimicrobial peptide family, dermaseptin-PD-1 and dermaseptin-PD-2, in the skins/skin secretions of the phyllomedusine leaf frog *(Pachymedusa dacnicolor)*. These two peptides have been found to modulate the growth of PC-3 cells, a human non-small cell lung cancer cell line (H157), and a human neuronal glioblastoma cell line (U251MG) with low hemolytic activity. Moreover, both dermaseptins are less cytotoxic to normal human cell lines (109). Dermaseptin L1 and phylloseptin L1, isolated from the skin secretions of the lemur leaf frog *(Agalychnis lemur)*, are both cytotoxic to HepG2 cells (110). Dermaseptin L1 is cytolytic to HepG2 cells but not human erythrocytes, whereas phylloseptin L1 is approximately equipotent against both HepG2 cells and erythrocytes. In addition, the novel phylloseptin-PBa, isolated from the skin secretion of the purple-sided leaf frog *(Phyllomedusa baltea)*, has been found to inhibit the proliferation of several human cancer cell lines: lung cancer cells (H460), PC-3 cells and a neurospongioma cell line (U251MG). However, it is less active in a normal human micro-vessel endothelial cell line (HMEC-1) (111).

Magainin-2, isolated from *Xenopus laevis*, and its analog magainin G, exhibits tumoricidal activity against human small cell lung cancer cell lines (112) and bladder cancer cell lines (113). Another modified magainin-2 peptide, MSI-238, is markedly more potent than the parent peptide, displaying a significant cytotoxic effect on A549 cells *in vitro* and P-388 cells, ascites (S180), and a spontaneous ovarian tumor *in vivo* (114). In addition, several studies have reported other magainin-2 analogs that are cytotoxic to U937 (115) and HeLa cells (116). Li *et al* (117) have isolated a small antibacterial peptide, *Xenopus laevis* antibacterial peptide-P1 (XLAsp-P1), from the skin of *Xenopus laevis* by using reverse-phase high-performance liquid chromatography, and this peptide strongly and dose-dependently inhibits breast cancer cells.

Moreover, pentadactylin from *Leptodactylus labyrinthicus* reduces the viability of murine melanoma (B16F10) cells in a dose-dependent manner without significantly affecting normal human fibroblast cells (118). Specifically, pentadactylin alters cell morphology, disrupts the membrane, fragments DNA, arrests cells in the S phase of the cell cycle, and alters mitochondrial membrane potential, thus suggesting that this peptide affects B16F10 cells via an apoptosis pathway.

Attoub and colleagues have extracted the frog-derived peptide Hymenochirin-1B, which is highly cytotoxic to

Table II. Primary structures of selected bioactive peptides with anticancer properties from frog skin secretions.

Species	Family	Peptide name	Primary structure	Activity	References
Midwife toad *(Alytes obstetricans)*	Alytidae	Alyteserin-2	ILGKLLSTAAGLLSNL	Cytotoxicity on A549 cells	(105)
Tailed frog *(Ascaphus truei)*	Ascaphidae	Ascaphin-8	GFKDLLKGAAKALV KTVLF	Cytotoxicity on HepG2 cells	(106)
Green and golden bell frog *(Litoria aureus)*	Hylidae	Aurein 1.2	GLFDIIKKIAESF	Anticancer activity	(107)
Green and golden bell frog *(Litoria aureus)*	Hylidae	Aurein 3.1	GLFDIVKKIAGHIAGSI	Anticancer activity	(107)
Giant monkey frog *(Phyllomedusa bicolor)*	Hylidae	Dermaseptin B2	GLWSKIKEVGKEAAKAA AKAAGKAALGAVSEAV	Inhibited the proliferation of PC-3 cells	(108)
Giant monkey frog *(Phyllomedusa bicolor)*	Hylidae	Dermaseptin B3	ALWKNMLKGIGKLAG QAALGAVKTLVGAE	Inhibited the proliferation of PC-3 cells	(108)
Phyllomedusine leaf frog (*Pachymedusa dacnicolor*)	Hylidae	Dermaseptin-PD-1	GMWSKIKETAMAAAK EAAKAAGKTISDMIKQ	Inhibited growth of PC-3 cells, H157 cells, U251MG cells	(109)
Phyllomedusine leaf frog (*Pachymedusa dacnicolor*)	Hylidae	Dermaseptin-PD-2	GMWSKIKNAGKAAAKA AAKAAGKAALDAVSEAI	Inhibited growth of PC-3 cells, H157 cells, U251MG cells	(109)
Lemur leaf frog *(Agalychnis lemur)*	Hylidae	Dermaseptin L1	GLWSKIKEAAKAAGKAA LNAVTGLVNQGDQPS	Cytotoxic activity against HepG2 cells	(110)
Lemur leaf frog *(Agalychnis lemur)*	Hylidae	Phylloseptin L1	LLGMIPLAISAISALSKL	Cytotoxic activity against HepG2 cells	(110)
Peruvian purple-sided leaf frog *(Phyllomedusa baltea)*	Hylidae	Phylloseptin-PBa	MAFLKKSLFLVLF(F/L)GL VSLSIC	Anti-proliferative activity against H460 cells, PC3 cells and tU251MG cells	(111)
Pepper frog *(Leptodactylus labyrinthicus)*	Leptodactylidae	Pentadactylin	GLLDTLKGAAKNVVGSL ASKVMEKL	Cytotoxic activity on B16F10 cells without high specificity	(118)
Congo dwarf clawed frog *(Hymenochirus boettgeri)*	Pipidae	Hymenochirin-1B	KLSPETKDNLKKVLK GAIKGAIVAKMV	Cytotoxic activity against A549 cells, MDA-MB-231 cells, HT-29 cells, and HepG2 cells	(119)
South African clawed frog *(Xenopus laevis)*	Pipidae	Magainin-2	GIGKFLHSAKKFGKAFV GEIMNS	Tumoricidal activity against human small cell lung cancer cell lines and bladder cancer cell lines	(112,113)
South African clawed frog *(Xenopus laevis*)	Pipidae	XLAsp-P1	DEDDD	Inhibition activity against breast cancer cell	(117)
Tropical clawed frog *(Silurana tropicalis)*	Pipidae	Peptide XT-7	GLLGPLLKIAAKVGSNLL	Cytotoxicity on HepG2 cells	(106)
Chiricahua leopard frog *(Lithobates chiricahuensis)*	Ranidae	Esculentin-2CHa	GFSSIFRGVAKFASKGLGK DLAKLGVDLVACKISKQC	Cytotoxic activity against A549 cells	(120)

A549 cells, MDA-MB-231 cells, HT-29 cells, and HepG2 cells (119). Moreover, the (D9K) analog is most potent against all four cell lines (up to 6-fold increase in cytotoxicity), but its hemolytic activity is also increased. In contrast, the (D9k) and (E6k, D9k) analogs retain relatively high cytotoxicity against tumor cells but are less hemolytic than the parent peptide (119). Moreover, the same group has identified another frog-derived peptide, Esculentin-2Cha, which is highly cytotoxic to A549 cells (120). In this study, the authors found that two analogs both remain cytotoxic to A549 cells but have completely contrary effects on hemolytic activity.

Crocodile and turtle. Crocodilians are minimally affected by infections or death from microorganisms, and cancer has not been observed in crocodiles to date, thus suggesting that these animals have a strong innate immune system that protects against undesirable cells. These characteristics make crocodilians a good choice for the study of anticancer

agents. Previous studies have indicated that alligator serum, including leukocyte extract, has a broad spectrum of activity against bacteria, viruses and amoeba via the complement system (121-124). Pata *et al* have reported four novel antibacterial peptides isolated from the white blood cell extract of the Siamese crocodile, Leucrocin I-IV, which exhibit strong antibacterial activity against *Staphylococcus epidermidis*, *Salmonella typhi* and *Vibrio cholera* (125). On the basis of this work, Yaraksa *et al* designed and synthesized the novel antibacterial peptides L-and D-NY15 by using the peptide Leucrocin I as a sequence template, and these peptides exhibit potent antibacterial activity without any toxicity to mammalian cells at their bacteriolytic concentrations (126).

Additionally, Patathananone and colleagues (127) have investigated the anticancer activity of crocodile leukocyte extracts. Specifically, they have shown that the percentage of viable HeLa cells significantly decreases in a dose- and time-dependent manner after treatment with white blood cell extracts. They have further demonstrated that the anticancer compounds from crocodile leukocyte extracts induces apoptosis in HeLa cells via both caspase-dependent and caspase-independent pathways (127).

Recently, Theansungnoen *et al* (128) have indicated that the cationic antimicrobial peptides KT2, RT2 and RP9 from *Crocodylus siamensis* leukocyte extract exhibit anticancer activities against human cervical cancer cells but do not affect non-cancer cells.

He *et al* (129) have reported antitumor peptides derived from the enzymatic hydrolysates of the Chinese three-striped box turtle *(Cuora trifasciata)*. Two fractions, T1 and T2, inhibit HepG2 and MCF-7 cancer cells, and three peptides have been identified in these fractions: RGVKGPR (T1-1), KLGPKGPR (T1-2), and SSPGPPVH (T2-1). T2-1 was found to be a novel peptide that had not been listed in any database and exhibits the most potent inhibition toward MCF-7 cancer cells.

Animal venoms. Animal venoms and toxins consist of a complex cocktail of proteins and peptides and are enriched in approximately 100-1,000 biologically active peptides. Thus, they have been used as a therapeutic resource in folk and traditional medicine for centuries, and they remain largely unexplored resource for the discovery of novel bioactive peptides.

Scorpion venom. Among venomous animals, scorpions, the oldest arthropods on Earth, possess a venom apparatus connected to the telson, which is used to inject the venom. Scorpions can be phylogenetically divided into 18 distinct families consisting of >1,500 species (130), and scorpion venom has been used in traditional medicine for many centuries (131). However, possibly <1% of all venoms from known scorpion species have been studied in detail (132).

Scorpion venom is a source of peptidyl neurotoxins, which are used as tools to study different ion channels, such as the Na^+, K^+, Ca^+, and Cl^- ion channels. Chlorotoxin (CTX) is a small neurotoxin of 36 amino acids that was isolated in 1993 from the venom of the Israeli scorpion *Leiurus quinquestriatus* (133). Initially, CTX was used as a pharmacological tool to characterize chloride channels. However, CTX cannot kill cancer cells on its own, despite its ability to inhibit tumor invasion. CTX can target cancer cells, including glioma, melanoma, small cell lung carcinoma, neuroblastoma and medulloblastoma cells. These properties make CTX a very attractive peptide for targeted cancer therapy or imaging (134). Moreover, CTX has been demonstrated to deeply diffuse into tumors, unlike other targeting agents, such as antibodies (135,136). Therefore, CTX should limit changes in cell shape in the setting of glioma, thereby hampering the ability of the tumor to invade tissue. This mechanism corroborates the reported anti-invasive effects of CTX on glioma cells and the inhibition of metastasis (137-140). Recently, Guo *et al* identified two linear α-helical peptides in the venom of the Brazilian yellow scorpion, TsAP-1 and TsAP-2 (*Tityus serrulatus* antimicrobial peptide) and demonstrated their anti-proliferative effects on human cancer cells, namely a human squamous carcinoma cell line (NCI-H157) and a human lung adenocarcinoma cell line (NCI-H838). Moreover, TsAP-2 is three times more active than TsAP-1 against an androgen-independent prostate adenocarcinoma cell line (PC-3), MCF-7 cells, and a human glioblastoma cell line (U251) (141). Ali *et al* have isolated a new chlorotoxin-like peptide (Bs-Tx7) from the venom of the common yellow scorpion *(Buthus sindicus)*. This peptide inhibits thechlorotoxin (ClTx) and CFTR channels (GaTx1) by 66% and 82%, respectively, and an amino acid sequence analysis of Bs-Tx7 has identified a scissile peptide bond (i.e., Gly-Ile) for human MMP2, whose activity is increased in malignant tumors. This finding suggests that Bs-Tx7 inhibits tumor proliferation by decreasing MMP2 activity (142).

Spider venom. Spider venom contains versatile proteins and peptides including enzymes (such as proteases, hyaluronidases, and phospholipases), neurotoxins (most have disulfide-rich peptides affecting ion channels), and cytolytic peptides (143). Latarcin 2a (Ltc2a), a short cationic linear α-helical peptide isolated from the venom of a spider *(Lachesana tarabaevi)*, is cytotoxic against human erythroleukemia K562 cells. This cytotoxicity is primarily related to plasma membrane destabilization; Ltc2a induces the formation of small (approximately 2.0 nm) membrane pores on the plasma membrane of K562 cells and subsequent blebbing, swelling and eventual cell death (144). Spider venom-derived peptide lycosin-1 strongly inhibits cancer cell growth *in vitro* and effectively suppresses tumor growth *in vivo* by interfering with cell signaling pathways via the attenuation of the activities of key proteins (145).

Bee and wasp venom. Venom from bees and wasps is now being studied to design and develop new therapeutic drugs from the proteins and peptides in venom (146). Melittin (MEL), an amphiphilic peptide (26 amino acid residues) isolated from the honey bee *Apis mellifera*, is the most studied and well-known bee venom-derived peptide (147). MEL inhibits different cancer cells *in vitro*, including astrocytoma, leukemic, lung tumor, ovarian carcinoma, squamous carcinoma, glioma, hepatocellular carcinoma, osteosarcoma, prostate cancer and renal cancer cells (148-152). Although it is cytotoxic to a broad spectrum of tumor cells, this peptide is also toxic to normal cells. Thus, MEL must be accurately delivered to a targeted area to optimize results (153,154).

Similarly to MEL, mastoparan is a well-studied 14-amino acid amphipathic and cationic peptide obtained from Vespula

lewisii venom that has shown antitumor activity *in vitro* (146). It also needs to be precisely delivered to avoid side effects, as described by Yamada and colleagues (155). Moreover, several structural modifications may improve the pharmacodynamic parameters of chimeric mitoparan *in vivo* (146,156).

Snake venom. The therapeutic use of snake venoms is frequently studied by scientists. Most venoms are a complex mixture of several proteins, peptides, enzymes, toxins and non-protein components. Bioactive peptides from snake venoms have significantly contributed to the treatment of many medical conditions, and some peptides and enzymes from snake venom may specifically target cancer cell membranes, affecting the migration and proliferation of these cells (157,158).

Crotamine, a polypeptide of 42 amino acids first isolated from South American rattle snake venom, was the first venom-derived peptide classified as a natural cell-penetrating and antimicrobial peptide with pronounced antifungal activity (158). Pereira *et al* have investigated the toxicity of this peptide toward cancer cells *in vitro* and *in vivo* in a mouse model of melanoma; they have tested the viability of B16-F10 (murine melanoma cells), SK-Mel-28 (human melanoma cells), and Mia PaCa-2 (human pancreatic carcinoma cells) at crotamine concentrations of 1-5 μg/ml. Noteworthy, a final crotamine concentration of 5 μg/ml is lethal to B16-F10, MiaPaCa-2, and SK-Mel-28 cells but not to normal cells (159,160).

Cathelicidin-BF (BF-30) is a cathelicidin-like polypeptide consisting of 30 amino acids and a natural antibacterial peptide extracted from the venom of the snake *Bungarus fasciatus*. BF-30 inhibits B16F10 cell proliferation *in vitro* in a dose- and time-dependent manner. Moreover, BF-30 significantly suppresses melanoma growth in B16F10 tumor-bearing mice without inducing losses in body weight (161). Naumann *et al* have isolated and purified L-amino acid oxidases (LAAOs) from *Bothrops leucurus* (Bl-LAAO) and have reported the biochemical features of Bl-LAAO associated with its effect on platelet function and cytotoxicity. Bl-LAAO is cytotoxic to the stomach cancer cell line MKN-45, the adenocarcinoma cell line HUTU, the colorectal cancer cell line RKO and the human fibroblast cell line LL-24. Specifically, this enzyme releases sufficient amounts of H_2O_2 into the culture medium to induce apoptosis in cells in a dose- and time-dependent manner (162).

3. Mechanisms of action of bioactive peptides underlying their anticancer effects

Since anticancer peptides non-specifically destroy the plasma membrane, they show therapeutic potential for tumors that are not responsive to conventional pharmaceutical therapy. Although some major mechanisms of action have already been outlined, the exact mechanism by which bioactive peptides kill cancerous cells remains controversial. In general, the anticancer effect of bioactive peptides may be mediated either by membranolytic or by non-membranolytic mechanisms (163)

Membrane-related mechanisms. The plasma membrane of cells is a very effective selectively permeable barrier. Although this phospholipid bilayer is essential for cell survival and function, many studies have indicated that natural antimicrobial peptides kill cancer cells by disrupting the cellular membrane (128,164,165). Specifically, peptides target negatively charged membrane components in the membrane, such as phosphatidylserine (PS), sialic acid or heparan sulfate. In fact, the exposure of the negatively charged lipid PS on the outer leaflet of the cancer cell membrane is a key difference between cancerous and non-cancerous cells, which are overall neutrally charged, owing to zwitterionic phosphatidylcholine and sphingomyelin (166,167).

Papo *et al* have found that a short host defense-like peptide selectively targets cancer cells, primarily by binding to PS exposed on the surfaces of cells, thus resulting in cytoplasmic membrane depolarization and cell death. Consequently, peptide-lipid interaction is a critical step for the effective disruption of the cell membrane (168). Latarcins 2a (Ltc2a), a peptide extracted from the venom of the spider *Lachesana tarabaevi*, is cytotoxic to human erythroleukemia K562 cells. Specifically, the peptide affects the plasma membrane of cells and induces membrane blebbing, swelling and eventual cell death, as observed with fluorescently labeled Ltc2a. Moreover, the peptide binds to the outer membrane leaflet of K562 cells, consequently triggering PS externalization. Cytotoxicity is due to the formation of membrane pores (approximately 3.7 nm), which are more permeable to anionic than cationic molecules, and the redistribution of PS toward the outer leaflet of the membrane has been detected in the cells. Of note, the peptide does not activate apoptosis (144). Pore formation is accompanied by self-assisted Ltc2a internalization and accumulation in mitochondria, mitochondrial inactivation and apoptosis-independent phosphatidylserine externalization (169).

The mechanism underlying the membranolytic activity of each peptide depends on the characteristics of the bioactive peptide and those of the target membrane, which in turn modulate peptide selectivity and toxicity. Bioactive peptide-induced membrane disruption can occur via different modes: pore formation in the lipid (barrel-stave and toroidal pore models), the thinning of the membrane bilayer, membrane dissolution (carpet model), or lipid-peptide domain formation (166,170).

The barrel-stave model describes the lateral insertion and diffusion of peptides through the lipid bilayer, where they arrange into helices and create barrel/stave-like channels that span the membrane (171). As shown in Fig. 2, cecropins (from moths) (172), pardaxin (from the Red Sea sole) (173), magainins (from frogs) (174) and melittin (from the European honey bee) (175,176) induce cell lysis via pore formation and follow this model.

According to the toroidal model, peptide molecules maintain a predominantly parallel orientation to the membrane, and a water core forms the center of the pore, with the bioactive peptides and lipid head groups forming the wall of the pore (177). As shown in Fig. 2, Magainins (from frogs) (174), melittin (from bee venom) (175,176), and protegrins (from porcine leukocytes) (178) all follow this mode of action.

Another classical mechanism of action is described by the carpet model. In this model, peptides do not form pores but bind parallel to the membrane surface, forming a 'carpet' in association with other peptide monomers. The bilayers are disrupted and form micelles, destroying the membrane

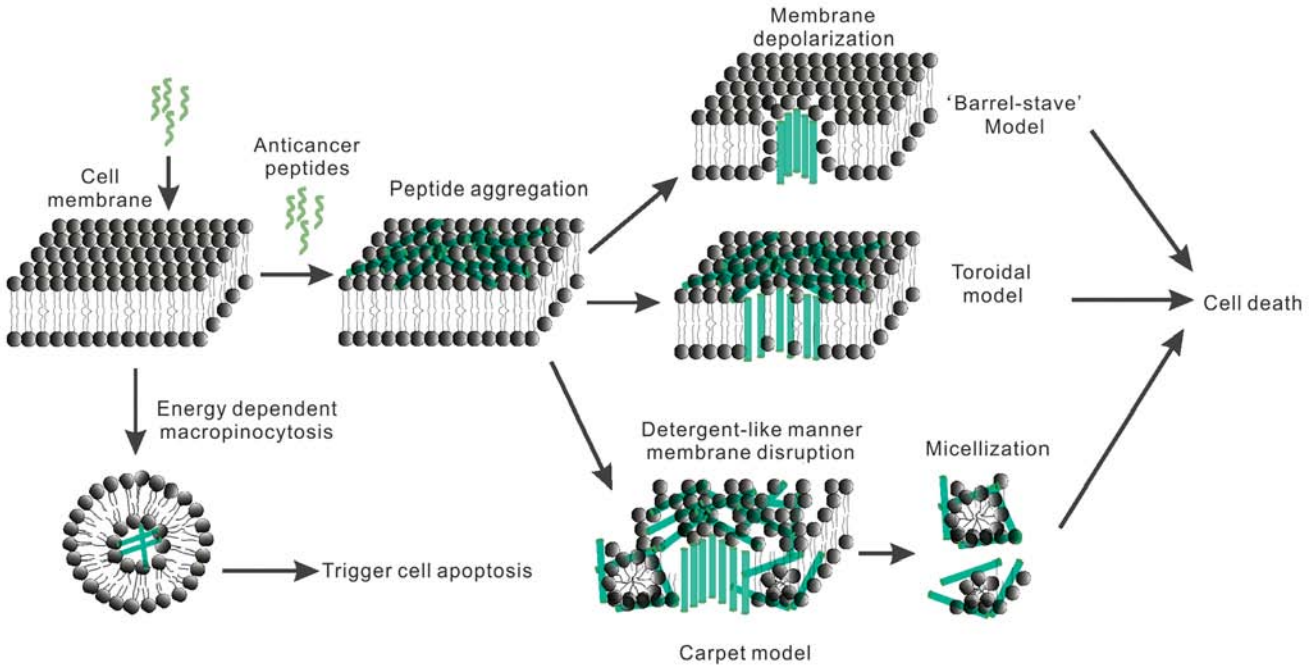

Figure 2. Schematic illustration of cell entry mechanisms of anticancer pepetides.

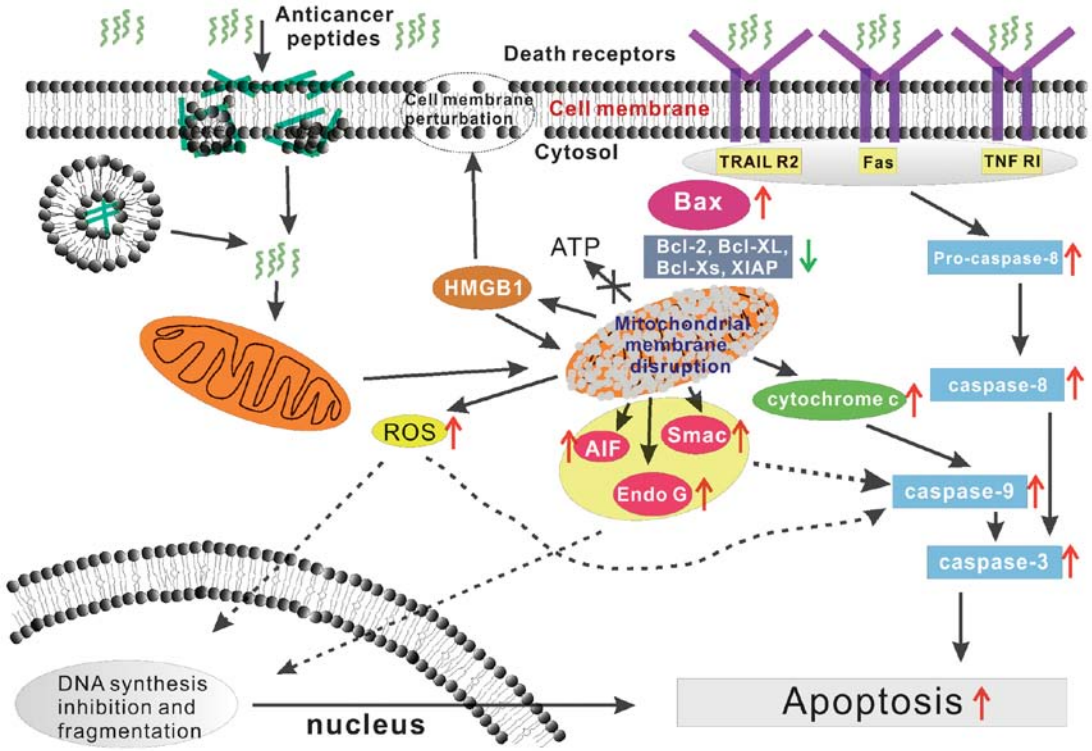

Figure 3. Mechanisms of action of anticancer peptides via mitochondrial-dependent pathways and death receptor-induced pathways.

structure in a detergent-like manner at a certain peptide concentration showed in Fig. 2 (179,180).

Since peptides and lipids are highly dynamic, Bechinger (181) has proposed the 'Soft Membranes Adapt and Respond, also Transiently' (SMART) model, which describes the interaction between peptides and the membrane from a global dynamic viewpoint: peptides and lipids change and mutually adapt their conformations, and membrane penetration and morphology are described in detail on a local and a global level. As a result, peptides and lipids can form a wide variety of supramolecular assemblies. In contrast, charged amphipathic sequences tend to remain intercalated at the membrane interface, where they cause pronounced disruptions of phospholipid fatty acyl packing. With increasing local or global concentrations,

the peptides result in transient membrane opening, rupture and ultimately lysis. Therefore, the same peptide sequence can result in a variety of these responses, depending on the peptide-to-lipid ratio, lipid composition and environmental factors (temperature, buffer composition and ionic strength).

Mitochondrial membrane disruption and mitochondrial-dependent apoptosis. In addition to inducing cell death by disrupting the plasma membrane, some anticancer peptides induce apoptosis via the mitochondrial pathway (182), and mitochondrial membrane disruption-induced apoptosis plays a crucial role in both carcinogenesis and cancer therapy as showed in Fig. 3 (183). Hence, understanding this pathway is very important for bioactive peptide applications. The early opening of the mitochondrial permeability transition pore (mPTP) in the inner mitochondrial membrane (IMM) is a key event in primary necrosis. These events interrupt ATP synthesis and result in the influx of large amounts of water and small solutes to the matrix along their electrochemical gradients, which results in severe osmotic swelling of mitochondria and ultimately in necrotic cell death. Furthermore, mitochondrial outer membrane permeabilization (MOMP), allows the release of pro-apoptotic factors, including cytochrome c (Cyt c), which activate caspases, apoptosis-inducing factor (AIF), second mitochondria-derived activator of caspase (Smac) and endonucleases showed in Fig. 3 (184-186).

Penaeidin-2 (Pen-2) is an important antimicrobial peptide derived from the Pacific white shrimp, and recombinant pen-2 (rPen-2) has been found to strongly inhibit the growth of ACHN and A498 kidney cancer cells in a time- and dose-dependent manner. This effect is less pronounced in renal tubular epithelial HK-2 cells. Two different phenomena, apoptosis and lysis, have been observed, thus suggesting that rPen-2 caused membrane disruption and apoptosis of tumor cells (187). The antimicrobial peptides NRC-03 and NRC-07 from the Atlantic flounder target and damage mitochondria and consequently induce a loss of transmembrane potential in breast cancer cells. These peptides also induce the production of reactive oxygen species (ROS) and cell death via mitochondrial-dependent apoptosis or the inhibition of DNA synthesis showed in Fig. 3 (188,189).

Recently, Patathananone *et al* have reported that leukocyte extract from the crocodile *(C. siamensis)* is cytotoxic to human cervical cancer cells in a protein concentration-dependent manner. Specifically, the mitochondrial membrane potential (DWm) of HeLa cells rapidly decreases, indicating the formation of open mitochondrial pores, which increase the levels of the pro-apoptotic protein Bax and reduce the levels of the anti-apoptotic proteins Bcl-2, Bcl-XL, Bcl-Xs, and XIAP. Simultaneously, the open mitochondrial pore leads to the release of cytochrome c and the activation of caspase-9 and caspase-3. Mitochondrial membrane disruption also results in the release of the apoptosis-inducing factor endonuclease G (Endo G) via induction of the caspase-independent apoptotic pathway by mitochondria. Noteworthy, Endo G has not been found to translocate into the nuclei. Overall, these results suggest that anticancer agents in leukocyte extract induce apoptosis in HeLa cells via both caspase-dependent and caspase-independent pathways (127). Furthermore, Theansungnoen and colleagues have shown that the peptides KT2 and RT2, derived from crocodile leukocyte extract, act as death ligands and could upregulate death receptors including TRAIL R2, Fas and TNF RI. Fas-associated death domain is activated by peptide-receptor binding, and pro-caspase-8 is subsequently cleaved, thus generating caspase-8; high expression levels of pro-caspase-3 in HeLa cells and activation of the caspase-8 and caspase-3 apoptosis pathway have also been observed (Fig. 3) (128).

Aurilide, isolated from the Japanese sea hare, selectively binds to prohibitin 1 (PHB1) in mitochondria. PHB1 localizes in the inner membrane of mitochondria and may activate the proteolytic processing of optic atrophy1 (OPA1) and result in mitochondria-induced apoptosis. In detail, aurilide induces prolonged mitochondrial fragmentation by enhancing OPA1 processing, which results in a loss of membrane potential and induces apoptosis (93).

The nonamer peptide LTX-315, derived from bovine lactoferricin, exhibits oncolytic properties. Eike *et al* have further investigated the oncolytic activity of LTX-315 in human melanoma cells (A375) and have shown that LTX-315 treatment depolarizes the mitochondrial membrane and significantly alters mitochondrial morphology at the ultrastructural level. Simultaneously, death-associated molecular patterns (DAMPs), such as cytochrome-c, ATP, and HMGB1, are released and consequently damage cellular integrity in several ways. Specifically, the release of DAMPs perturb both the cell membrane and mitochondria as shown in Fig. 3 (190). Burns *et al* have reported a pH-selective peptide $(KL\ AKLAK)_2$ analog that inhibits breast cancer cell growth in a dose- and pH-dependent manner. In addition, they have identified pHLIP-KLAKLAK as a better modifier because of its low cytotoxicity at physiological pH levels, chemical stability, high anti-proliferation potency and specific induction of apoptosis at lower pH levels via mitochondrial membrane disruption (191).

The group of Su has reported that ACBP extracted from goat spleens induces apoptosis and blocks the cell cycle by decreasing the gene expression levels of cyclin D1, c-myc, and bcl-2 as well as the protein expression of PCNA. It also increases p16Ink4, p21Waf1, p27Kip1 and bax expression (14). Furthermore, *in vitro* and *in vivo* findings suggest that PARP, p53, and Mcl-1 mediate ACBP-induced apoptosis. These studies suggest that ACBPs inhibit human colorectal tumor cell growth and induce apoptosis by modulating the PARP-p53-Mcl-1 signaling pathway. Further studies are needed to elucidate the role of mitochondrial membrane disruption in this apoptosis cascade (17).

4. Summary and perspective

The use of anticancer peptides has become more prevalent for the clinical treatment of cancer. However, in addition to their many advantages these peptides also have drawbacks, such as their lack of oral bioavailability and low stability under physiological conditions; gastric acids and complex enzymes in the gastrointestinal environment make anticancer peptides vulnerable to degradation (192,193). Strategies to develop a selective delivery system have been described (194,195), and these strategies result in highly efficacious treatment. Some cancer-targeting peptides have been designed on the basis of the pH difference between tumor tissue and normal tissues (196); the peptide selectively

kills tumor cells at acidic pH levels but is nontoxic against normal cells. Furthermore, owing to their unique optical, electronic, magnetic, photoresponsive, and structural properties, nanotechnology and nanomaterials have provided tremendous potential for application of anticancer peptides in tumor-targeted therapy, bio-imaging, and diagnosis (197,198). Moreover, a new methodology based on dynamic multiple complex views is needed to study the mechanism of action of anticancer bioactive peptides (181). Anticancer peptide-related pharmaceutical research and development are likely to garner significant attention and investment over the next several decades, to integrate their characteristics and fully exploit their potential to benefit thousands of patients who are suffering from cancer.

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