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Review

Roles and Mechanisms of Human Cathelicidin LL-37 in Cancer

Xi Chen[a,b] Xianqiong Zou[a] Guangying Qi[b,c] Ying Tang[a] Yong Guo[a] Jia Si[a,b] Lihua Liang[d]

[a]College of Biotechnology, Guilin Medical University, Guilin, Guangxi, [b]College of Basic Medicine, Guilin Medical University, Guilin, Guangxi, [c]Laboratory of Tumor Immunology and Microenvironmental Regulation, Guilin Medical University, Guilin, Guangxi, [d]Department of Stomatology, Affiliated Hospital of Guilin Medical University, Guilin, Guangxi, P. R. China

Key Words
Cathelicidin • hCAP-18 • LL-37 • Tumorigenic effect • Anti-cancer

Abstract
LL-37, the C-terminal peptide of human cathelicidin antimicrobial peptide (CAMP, hCAP18), reportedly increases resistance to microbial invasion and exerts important physiological functions in chemotaxis, promotion of wound closure, and angiogenesis. Accumulating evidence indicates that LL-37 also plays a significant role in human cancer. LL-37 induces tumorigenic effects in cancers of the ovary, lung, breast, prostate, pancreas, as well as in malignant melanoma and skin squamous cell carcinoma. In contrast, LL-37 displays an anti-cancer effect in colon cancer, gastric cancer, hematologic malignancy and oral squamous cell carcinoma. Mechanistically, LL-37-induced activation of membrane receptors and subsequent signaling pathways lead to alteration of cellular functions. Different membrane receptors on various cancer cells appear to be responsible for the tissue-specific effects of LL-37. Meanwhile, the findings that vitamin D-dependent induction of cathelicidin in human macrophages activates the anti-cancer activity of tumor-associated macrophages (TAMs) and enhances antibody-dependent cellular cytotoxicity (ADCC) support critical roles of vitamin D-dependent induction of cathelicidin in cancer progression. This review describes novel advances involving the roles and mechanisms of human cathelicidin LL-37 in cancer.

Introduction

Cathelicidins are antimicrobial peptides produced by mammals in response to various pathogenic microbes [1-5]. Human cathelicidin antimicrobial peptide (CAMP, hCAP-18) is the only member of the cathelicidin protein family in humans [1-5]. hCAP-18 (18kDa) is processed by proteolytic cleavage to bioactive cathelicidin LL-37 (37 amino acid residues with diLeucine at the N-terminus) by exposure to specific serine proteases like proteinase 3, kallikrein 5 and kallikrein 7 [1]. hCAP-18 is widely expressed in various epithelial cells

Dr. Xianqiong Zou
College of Biotechnology, Guilin Medical University
Guilin 541100, Guangxi, (P. R. China)
E-Mail xianqiongzou2009@yahoo.com

and innate immune cells (neutrophils, monocytes, macrophages, dendritic cells, natural killer (NK) cells, lymphocytes and mast cells) [4]. The expression of hCAP-18 is constitutive in most epithelia although its expression in keratinocytes is induced by infection, vitamin D, butyrate, short-chain fatty acids and endoplasmic reticulum stress signaling [3-5]. hCAP-18 can be downregulated by pathogens such as *Shigella* and *Neisseria*, and some bacterial exotoxins [3-5].

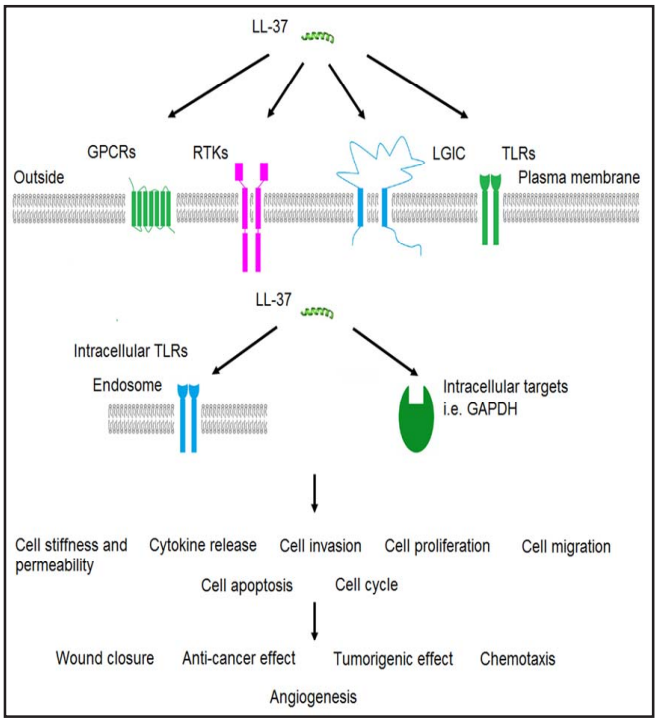

Fig. 1. Human cathelicidin LL-37 associated receptors and their cancer-related roles. GPCRs, G protein-coupled receptors. RTKs, receptor tyrosine kinases. LGIC, ligand-gated ion channel. TLRs, toll-like receptors. GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

It is well known that hCAP-18/LL-37 has antimicrobial activities against bacteria, fungi, viruses, and parasites [5-9]. Low concentrations of LL-37 can prevent biofilm formation, and higher concentrations of LL-37 can destroy pre-existing biofilms [2, 10, 11]. Additional effects of human cathelicidin LL-37 on cellular functions include activation of cell migration [2, 12], cell proliferation and invasion [2, 12-14], regulation of cell apoptosis (including inhibition and enhancement on different cells) [2, 15, 16], cell cycle arrest [2, 15, 16], modulation of cytokine release [17, 18], enhancement of stiffness and reduction of the transepithelial permeability of epithelial cells (Fig. 1) [19]. These LL-37 induced alterations stimulate chemotaxis that directly attracts cells of innate immune system (e.g. monocytes, neutrophils, dendritic cells, mesenchymal stromal cells (MSCs)) [5, 20-22], while also promoting wound closure [2, 12] and angiogenesis (Fig. 1) [2, 23].

Emerging evidence supports cathelicidin LL-37 involvement in various types of human cancer [1-5, 24, 25]. Surprisingly, however, current data indicate that LL-37 can exert either pro-tumorigenic or anti-cancer effects [1-5, 24, 25]. To explain this conundrum, it has been proposed that the cell and tissue effects induced by LL-37 are mainly mediated via activation of specific cell surface receptors, membrane channels or intracellular targets that are differentially expressed in different cell types [26]. These LL-37-targeted receptors include at least four G protein-coupled receptors (GPCRs), three receptor tyrosine kinases (RTKs), a ligand-gated ion channel (LGIC) and toll-like receptors (TLRs) (Fig.1) [4, 26]. In particular, LL-37 targets include GPCRs such as N-formyl peptide receptor 2 (FPR2; formerly known as formyl peptide receptor like-1, FPRL1), CXC chemokine receptor type 2 (CXCR2), mas-related gene X2 (MrgX2) and purinergic receptor P2Y11 (P2Y11) [26]. Epidermal growth factor receptor (EGFR/ErbB1), insulin-like growth factor 1 receptor (IGF1R) and erb-b2 receptor tyrosine kinase 2 (ErbB2) are targeted RTKs by LL-37 [26], whereas LGIC is a targeted transmembrane channel purinergic receptor 7 ($P2X_7$) [26]. TLR-targets of LL-37 are type I transmembrane glycoproteins that are functionally important in the activation of innate immune cells [27]. Cell surface TLRs include TLR1, TLR2, TLR4, TLR5, TLR6 and TLR10, whereas endosomal TLRs include TLR3, TLR7, TLR8, and TLR9 [26-28]. LL-37 can also access other intracellular targets such as cytosolic protein glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and consequently affects various intracellular biological processes [26, 29].

Tumorigenic effects

Compared to normal tissues, hCAP-18/LL-37 expression levels are upregulated in ovarian cancer, lung cancer, breast cancer, prostate cancer, pancreatic cancer, malignant melanoma (MM) and skin squamous cell carcinoma (SCC) [1, 2, 24, 30-33]. These observations suggest that LL-37 exerts a tumorigenic effect in these cancers [1, 2, 24, 30-34].

Ovarian cancer

LL-37 expression levels significantly increase in ovarian cancer tissues compared to the normal ovary tissues suggesting it might be a potential biomarker of ovarian cancer [2, 35]. In ovarian cancer cells, recombinant LL-37 induces cell proliferation, cell invasion, chemotaxis, and matrix metalloproteinase (MMP) expression [35]. The release and activation of MMPs mediate extracellular matrix (ECM) degradation that promotes cell invasion and metastasis of tumor cells [36, 37]. Mechanistically, LL-37 interaction with FPR2, a GPCR member, recruits MSCs into the tumor stroma, which enhances tumor progression [36, 38]. MSCs contribute to the carcinogenesis of ovarian cancer by enhancing the secretion of cytokine IL-1β, IL-6, IL-8, IL-10 and TNF-α, while diminishing IL-12 secretion (Fig. 2A) [36, 39]. MSCs are also responsible for the immunomodulation of various immune cell populations [36]. When MSCs are cultured with lung cancer cells, sphere formation and pluripotency markers including Nanog, Oct4A, and Sox2 are upregulated in lung cancer cells, suggesting a direct effect on the cancer stem cells (CSCs) population [40]. More recent findings confirm a direct link for hCAP18/LL-37 acting on pancreatic CSCs to negatively affect tumor growth [30].

Meanwhile, contrary effects of LL-37 on ovarian cancer cells have also been reported [41]. A combination of LL-37 with CpG-oligodeoxynucleotides (CpG-ODN), a TLR9 ligand, increases the CpG-ODN delivery into endosomes, which upregulates the expression of interferon γ (INFγ), and then induces proliferation and activation of NK cells that can inhibit the cancer cells (Fig. 2A) [41].

A recent interesting report indicates that enhanced hCAP18/LL-37 expression in macrophages promotes ovarian cancer progression and that ovarian cancer cell-produced versican V1 enhances expression of hCAP-18/LL-37 in cultured macrophages [42]. The findings suggest that immune stromal cells (mainly monocytes and macropahges) are also an important source of LL-37 [42-45], and that cancer cells may manipulate the immune stromal cells into producing the LL-37 that they need.

Lung cancer

hCAP-18/LL-37 is expressed at elevated levels in human lung cancer cells at both the mRNA and protein levels [2, 42, 46, 47]. Lung cancer cell lines that stably overexpress the hCAP-18 peptide also grow faster [46]. When these stably transfected cells were subcutaneously injected into nude mice, increased tumorigenicity and significantly larger tumor mass were observed [46]. Mechanistically, LL-37 induces EGFR phosphorylation and

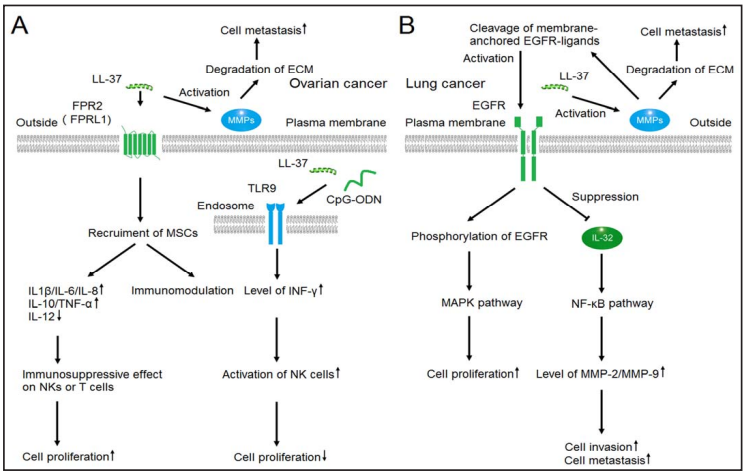

Fig. 2. Proposed tumorigenic mechanism of human cathelicidin LL-37 involvement in ovarian and lung cancer cells. (A) Ovarian cancer. (B) Lung cancer. FPR2, N-Formyl peptide receptor 2. FPRL-1, formly peptide receptor like-1. MSCs, mesenchymal stem cells. ECM, extracellular matrix. MMPs, matrix metalloproteinases. NK, natural killer. EGFR, epidermal growth factor receptor. MAPK, mitogen-activated protein kinases. IL, interleukin. INF, interferon. CpG-ODN, CpG oligodeoxynucleotides.

activation of downstream mitogen-activated protein kinase (MAPK) signaling pathways, which increases cell proliferation and growth of anchorage-independent colonies in lung cancer cells (Fig. 2B) [46, 47]. LL-37 activates the EGFR through MMP-mediated cleavage of membrane-anchored EGFR-ligands (Fig. 2B) [2, 48]. On the other hand, IL-32 expression is distinctly altered in lung cancer cells and closely associated with increased lung cancer invasiveness, metastasis and poor prognosis [48, 49]. Recent reports show that IL-32 also is involved in the invasion and metastasis of primary lung adenocarcinoma via NF-κB induced MMP-2 and MMP-9 expression [2, 49, 50]. Because LL-37 can significantly suppress IL-32-induced production of pro-inflammatory cytokines and IL-32-mediated phosphorylation of Fyn (Y420) Src kinase [48], it was proposed that LL-37 can affect the carcinogenesis of lung cancer by suppressing the biological activity of IL-32 (Fig. 2B) [2, 51].

Breast cancer

The expression levels of hCAP-18/LL-37 in breast cancer tissues are higher than those of normal breast tissues [52]. In breast cancer cells the LL-37-targeted receptor, ErbB2, is amplified which helps induce cell migration, invasion and poor prognosis [53-55]. ErbB2 upregulation by LL-37 activates Heregulin (an ErbB3/ErbB4 ligand)-mediated MAPK signaling pathway in breast cancer cells, resulting not only in enhanced cell migration but also anchorage-independent growth (Fig. 3A) [56]. Overexpression of hCAP-18 in breast cancer cell line MJ1105 reportedly promotes the development of metastases in mice with severe combined immunodeficiency (SCID). The findings also revealed enhanced activation of MAPK signaling in hCAP-18 transgenic tumors [56]. It has been shown that LL-37 induces migration of breast cancer cell lines (MCF7, MDA-MB-435s and MDA-MB-231) by activating the transient receptor potential cation (TRPV2) and recruiting it to pseudopodia through activation of the PI3K/Akt pathway [54]. During this activation process, Ca^{2+} entry via the TRPV2 occurred in concert with K^+ efflux through the Ca^{2+}-activated K^+-channels (BK_{Ca}) [57]. However, no specific receptor binding was found and a modification of the membrane lipid physical properties was proposed as being responsible for the activation (Fig. 3A) [57]. Indeed, Ca^{2+} signaling is generally considered to be a significant intracellular regulatory driver of the dynamic and complex metastatic cascade [58, 59].

Prostate cancer

Silencing of $P2X_7$ can inhibit migration and invasiveness of prostate cancer cells both *in vitro* and *in vivo* [31]. $P2X_7$ stimulation of cell invasion and metastasis in prostate cancer cells involves certain epithelial/mesenchymal transition (EMT)/invasion-related gene products such as Snail, E-cadherin, MMP-3, ERK1/2 and PI3K/Akt signaling pathways (Fig. 3B) [60, 61]. In prostate tumors, overexpressed mouse orthologue cathelicidin-related AMP (CRAMP) initially chemo-attracts immature myeloid progenitors (IMPs) to the tumor microenvironment (TME) and mediates differentiation and polarization of early myeloid progenitors into protumorigenic type 2 (M2) macrophages to help drive prostate cancer progression [62]. The stimulation of $P2X_7$ can promote migration of PC9 lung cells and T47D breast cancer cells [30], suggesting involvement of a similar $P2X_7$-based mechanism in other solid tumors [63]. $P2X_7$ can trigger massive release of vascular endothelial growth factor (VEGF) from immune cells as well as tumor cells [31].

Pancreatic cancer

The expression level of hCAP-18/LL-37 is high in the tumor stroma of advanced primary and secondary pancreatic ductal adenocarcinomas (PDACs) [30]. The $K\text{-}Ras^{+/LSL\text{-}G12D}$; $Trp53^{LSL\text{-}R172H}$; PDX1-Cre mouse model (KPC) has been found to develop PDACs and metastases over 30 weeks [30, 64]. Tumorigenesis can be dramatically inhibited by either reconstituting the KPC mice with bone marrow from cathelicidin-related antimicrobial peptide knockout mice or by pharmacologically inhibiting FPR2 and $P2X_7$ using the genetically engineered mouse model of pancreatic tumorigenesis [30].

Tumor-associated macrophages secrete hCAP-18/LL-37 in direct response to CSC-secreted Nodal/Activin-A/tumor growth factor-β1 [30]. Recombinant LL−37 increases

sphere-derived CSC-mediated tumor formation and fitness, leading to enhanced growth and proliferation [30]. The established direct link between hCAP-18/LL-37 and pancreatic CSC-mediated tumorigenesis is critically important because CSCs are believed to be root of the tumors [30, 65-67]. It was also proposed that targeting pancreatic CSCs using inhibitors of the LL-37 receptors could provide a possible therapeutic approach to block the tumor promoting cross-talk that exists within the tumor microenvironment [30]. Indeed, inhibitors against some LL-37 receptors, such as RTK or FPR2 inhibitor, have been used for therapeutic purposes and show promising effects [1, 42, 68-70].

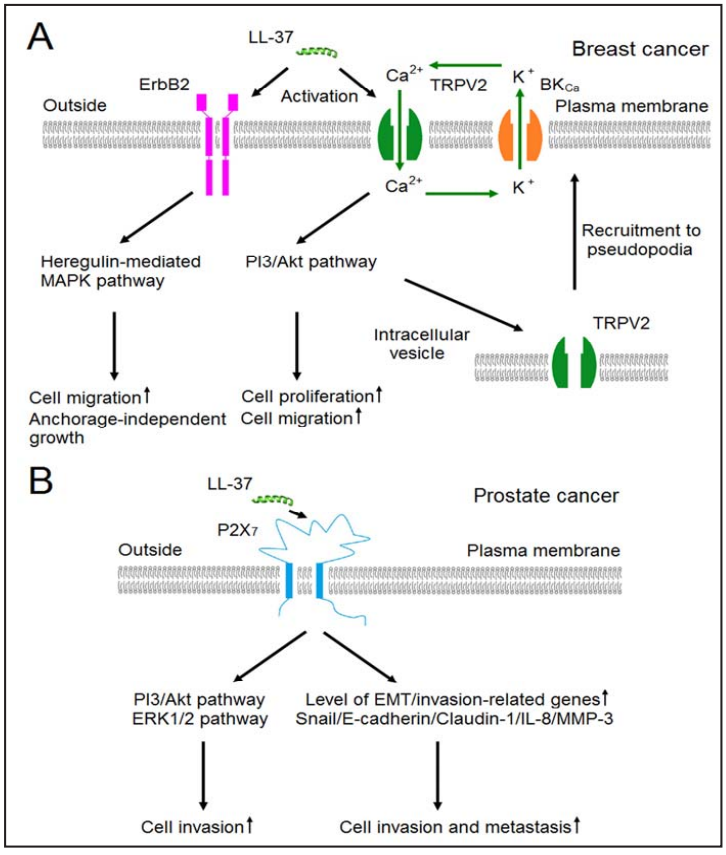

Fig. 3. Proposed tumorigenic mechanism of human cathelicidin LL-37 involvement in breast and prostate cancer cells. (A) Breast cancer. LL-37 activates TRPV2 and then PI3/Akt signaling and PI3/Akt signaling induce recruitment of TRPV2 from intracellular vesicles to the plasma membrane of pseudopodia. Ca^{2+} entry through TRPV2 occurs in concert with K^+ efflux through BK_{Ca}. (B) Prostate cancer. ErbB2, Erb-b2 receptor tyrosine kinase 2. TRPV2, transient receptor potential cation. BK_{Ca}, Ca^{2+}-activated K^+-channels. $P2X_7$, purinergic receptor 7. EMT, epithelial/mesenchymal transition.

Malignant melanoma

Immunohistochemical analyses showed that hCAP-18/LL-37 expression levels increased in malignant melanoma [71]. Recombinant LL-37 treatment could stimulate melanoma cell proliferation, migration and invasion *in vitro* [64]. TLR4 is vital to cell growth and migration in melanoma cells [72]. It was also suggested that LL-37, one of the agonists for TLR4, may promote melanoma progression through TLR4 signaling [73]. LL-37 may bind to gene promoter regions and modulate transcription in malignant melanoma [32]. Indeed, silencing hCAP-18/LL-37 gene in melanoma A375 cells alters expression of genes associated with cellular stress, histone, ubiquitination, metabolism, etc [32]. A recent report has indicated that LL-37 can upregulate Y-box binding protein-1 (YB-1) expression and activate the NF-κB signaling pathway to accelerate the malignant progression of the A375 and A875 MM cell lines, thus increasing tumor cell proliferation, migration and invasion [74].

Skin squamous cell carcinoma (SCC)

When serum-starved SCC A431 cells were treated with recombinant LL-37, the treatment promoted the proliferation and invasion of A431 cells by upregulating human DNA-binding protein A (dbpA) mRNA and protein expression [33, 34]. A431 cells treated by pyrollidine dithiocarbamate (PDTC), a transcription factor NF-κB inhibitor, were not susceptible to LL-37-driven induction of dbpA expression, showing that this process depends on the NF-κB signaling pathway [33, 34].

Anti-cancer effects

In colon cancer, gastric cancer, hematologic malignancy and oral squamous cell carcinoma (OSCC), the LL-37 expression levels are downregulated compared to the normal tissues [2, 14, 24, 75-77]. These findings show that LL-37 can exert anti-cancer effects in these cancers.

Colon cancer

LL-37 is strongly expressed in normal colon mucosa but is down-regulated in colon cancer tissues. The low LL-37 levels had been suggested to serve as a biomarker of colon cancer [14, 78]. LL-37 is known to increase the level of pro-apoptotic Bax/Bak and reduce the level of anti-apoptotic Bcl-2 [14]. LL-37 also increases the expression of PUMA and p53 [2, 14]. PUMA is a direct target of p53 and a modulator of apoptosis in colon cancer cells (Fig. 4A) [14]. In colon cancer cells, the nuclear levels of apoptosis-inducing-factor (AIF) and endonuclease G (EndoG) are prominently induced by LL-37, resulting in caspase-independent apoptosis [14]. A LL-37-based mechanism that activates a GPCR-p53-Bax/Bak/Bcl-2 signaling cascade to trigger AIF/EndoG–mediated apoptosis was proposed in colon cancer cells (Fig. 4A) [14]. FK-16, a fragment of residues 17 to 32 of LL-37, upregulated the expression of LC3-I/II, Atg5 and Atg7, enabling formation of LC3-positive autophagosomes [15]. These observations show that FK-16 triggers caspase-independent apoptosis and autophagy through the p53-Bcl-2/Bax signaling in colon cancer cells (Fig. 4A) [2, 15]. Interestingly, the anti-cancer activity of LL-37 improved when attached to the surface of magnetic nanoparticles (MNPs) [79, 80].

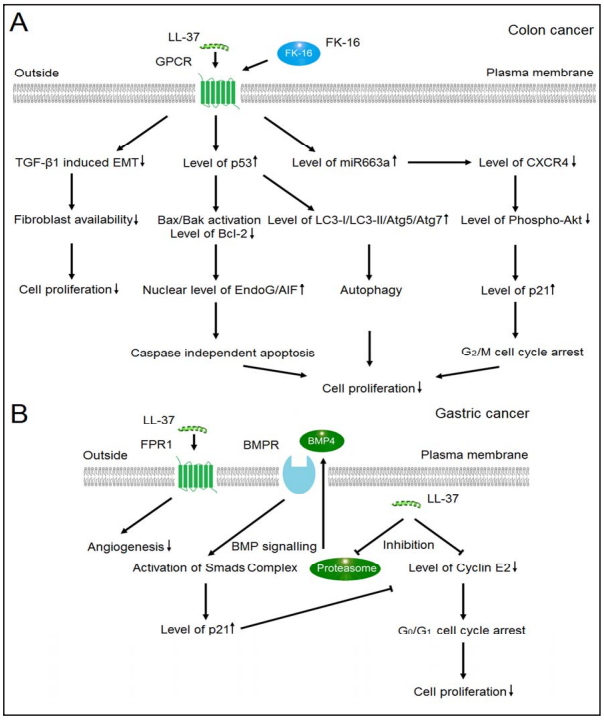

Fig. 4. Proposed anti-cancer mechanism of human cathelicidin LL-37 involvement in colon and gastric cancer cells. (A) Colon cancer. (B) Gastric cancer. Inhibition of proteasome activity induces the upregulation of BMP4, which subsequently activates BMP signaling. GPCR, G protein-coupled receptor. CXCR4, CXC chemokine receptor type 4. TGF-β1, tumor growth factor-β1. EndoG, endonuclease G. AIF, apoptosis inducing factor. FPR1, formyl peptide receptor 1. BMP4, bone morphogentic protein 4. BMPR, bone morphogentic protein receptor.

Cathelicidin LL-37 effectively inhibits tumor growth factor-β1-induced EMT of colon cancer cells and proliferation of fibroblast-supported colon cancer cell (Fig. 4A) [81]. MiR-663a is a miRNA that undergoes major upregulation in HCT116 cells treated with either LL-37 or LL-37 analogue peptide FF/CAP18 (FRKSKEKIGKFFKRIVQRIFDFLRNLV) to drive anti-proliferative effects [82]. The anti-proliferative effect of miR-663a has been attributed to suppressed expression of CXC chemokine receptor type 4 (CXCR4), resulting in the abrogation of Akt phosphorylation and cell cycle arrest in G_2/M via p21 activation in colon cancer cells (Fig. 4A) [82]. Treatment of HCT116 with FF/CAP18 exerts antiproliferative effects via a p53-independent mechanism [83]. The antiproliferative effects of FF/CAP18 are supported by clear-cut alterations in major metabolic pathways such as urine metabolism, glycolysis, and the TCA cycle in FF/CAP18-treated HCT116 cells [84].

Gastric cancer

In gastric cancer tissues, LL-37 expression level is considerably lower than that in non-cancer adjacent tissues [75]. The anti-cancer effect of LL-37 has been proposed to involve

regulation of proteasome activation via bone morphogentic protein (BMP) signaling [75, 85]. The BMP signaling triggers recruitment and phosphorylation of Smad 1/5/8 to form heterodimers with Smad4, and this Smads complex then upregulates the expression level of $p21^{Waf1}$[24, 75]. Using a BMP-independent pathway, lower levels of cyclin E2 can also be induced by LL-37 [75]. The alteration of $p21^{Waf1}$ and cyclin E2 expression levels can trigger G_0/G_1 phase cell cycle arrest (Fig. 4B) [75]. Taken together, these observations indicate that LL-37 inhibits gastric cancer cell proliferation through activation of BMP signaling via a proteasome-dependent mechanism (Fig. 4B) [75]. It has also been reported that the formyl peptide receptor 1 (FPR1) can act as a tumor suppressor in human gastric cancer by inhibiting angiogenesis (Fig. 4B) [86, 87].

Hematologic malignancy

The LL-37 expression level in the neutrophils of healthy individuals is significantly lower than that of patients with acute myeloid leukemia at the protein level, but not at the mRNA level [75]. Notably, recombinant LL-37 treatment reportedly kills Jurkat T leukemia cells by activating apoptosis that is caspase-independent but calpain- and AIF-dependent as shown by BAX activation and translocation to mitochondria (Fig. 5) [2, 88]. Although LL-37 targeted receptor in Jurkat cells has not yet been reported, it is known that FPRL1, a LL-37-targeted GPCR is expressed in T lymphocytes [89].

Cathelicidin secreted from inflammatory M1 macrophages has been shown to directly induce cell death by targeting mitochondria of high-grade lymphatic malignancies such as Burkitt's lymphoma (BL) cells [90]. Conversely, anti-inflammatory M2 macrophages and M2-like tumor-associated macrophages (TAMs) in BL affect vitamin D signaling, resulting in downregulation of hCAP-18/LL-37 and consequently, in inability to kill BL cells (Fig. 5) [90]. Mechanistically, the induction of the vitamin D signaling pathway activates TAM antitumor activity and improves the efficacy of antibody-dependent cellular cytotoxicity (ADCC) against BL cells (Fig. 5) [90]. Moreover, cathelicidin knockout mice ($Camp^{-/-}$) exhibit quicker tumor growth than wild types in two xenograft tumor mouse models (murine melanoma cell line B16.F10 and RMA-S cell line derived from T cell lymphoma of C57BL/6). NK cells derived from $Camp^{-/-}$ as compared to the wild types show impaired cytotoxic action toward tumor targets [91]. The findings indicate the significance of cathelicidin to NK cell function and *in vivo* tumor defense (Fig. 5) [91].

Oral Squamous Cell Carcinoma (OSCC)

Immunohistochemical analyses show that low expression of LL-37 in OSCC tissues compared to the normal oral mucosa tissues is related to histological differentiation and lymph node metastasis [77]. These results suggest that LL-37 might act as a tumor suppressor in OSCC [77]. The regulation of hCAP-18 expression in several oral cancer cell lines involves DNA methylation status at human *CAMP* promoter region [77]. It had also been shown that incubation of a C-terminal domain peptide of human CAP18 (109-135) induces caspase-independent apoptosis in OSCC SAS-H1 cells but not in human gingival fibroblasts or HaCaT cells [92].

Recent reports indicate that some cancer cells have cholesterol-rich lipid rafts, which could also be a key factor governing LL-37 selectivity for different cancer cells, thus providing a novel possibility besides the anti-cancer mechanisms of LL-37 already mentioned [1, 5, 93, 94].

Roles of vitamin D-dependent induction of cathelicidin in cancer progression

1, 25-Dihydroxyvitamin D3 [1, $25(OH)_2D_3$], the biologically active form of vitamin D induces expression of human *CAMP* [93-95]. The induction occurs via a consensus vitamin D response element (VDRE) in human *CAMP* promoter that is activated by vitamin D binding to the vitamin D receptor (VDR) [93-97]. Microorganisms such as *Mycobacterium tuberculosis*, induce expression of the VDR and vitamin D-1-hydroxylase genes in human macrophages, leading to the generation of more 1, $25(OH)_2D_3$, which in turn upregulates of hCAP18/LL-

37 [98]. It has been reported that the VDR *Bsm*I G/A gene variant might be a moderate risk factor for ovarian cancer in the European population [99]. The polymorphisms of vitamin D receptor gene *Bsm*I and *Fok*I may be related to ovarian cancer risk in Polish population [100]. The protective effects of vitamin D and VDR on colorectal cancer and the association of vitamin D deficiency with the high risk of colorectal cancer have been also reported [101-105]. These findings suggested possible roles of vitamin D-dependent induction of cathelicidin in cancer progression. Indeed, such roles have been reported in a recent publication, which indicated that the vitamin D signaling pathway activation in human macrophages induces the anti-cancer activity of TAMs and enhances the efficacy of ADCC for high-grade lymphatic malignancies such as BL (Fig. 5) [90]. Another report also showed that the versican V1 derived from tumor cells enhances hCAP18/LL-37 expression in macrophages through the activation of TLR2 and subsequent vitamin D-dependent mechanisms to promote ovarian cancer progression *in vitro* [42]. Taken together, these findings strongly support the critical roles of vitamin D-dependent induction of cathelicidin in cancer progression.

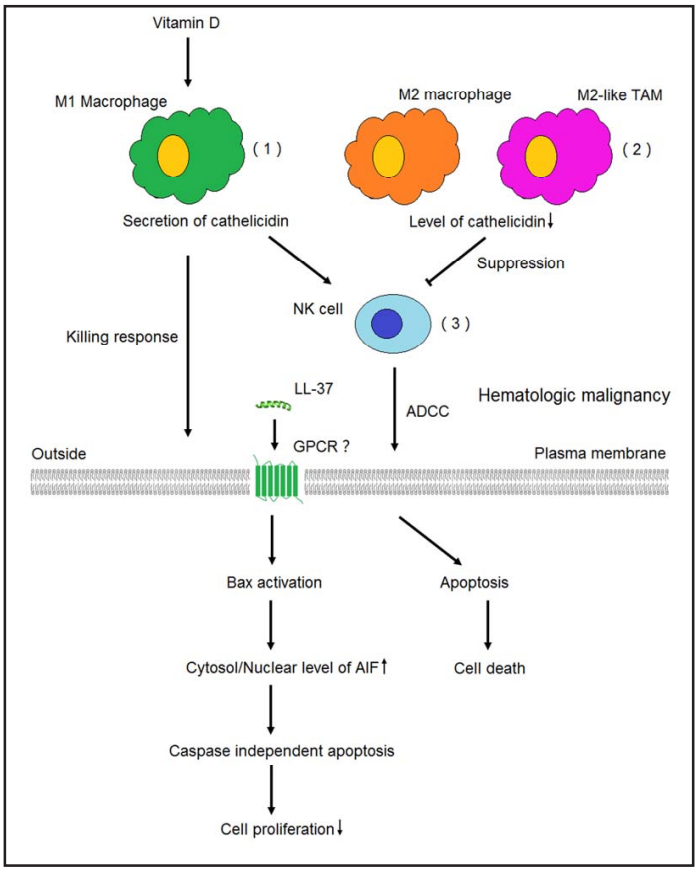

Fig. 5. Proposed anti-cancer mechanism of human cathelicidin LL-37 involvement in hematological malignancy cells. (1) M1 macrophages kill hematological malignancy cells by releasing cathelicidin in a vitamin D–dependent fashion. (2) M2 macrophages and M2-like TAMs with altered vitamin D metabolism result in low expression of cathelicidin and consequent ADCC suppression. (3) Cathelicidin secreted from macrophages enhances ADCC and cathelicidin in NK cell is also important for its function. GPCR?, G protein-coupled receptor, not yet reported. TAM, tumor-associated macrophage. ADCC, antibody-dependent cellular cytotoxicity. AIF, apoptosis inducing factor. NK, natural killer.

Conclusions and future perspectives

Current research about the roles and mechanisms of LL-37 in human cancer mainly focuses on molecular and cellular levels. These investigations indicate that LL-37 can either be pro-tumorigenic or an anti-cancer agent for different cancers. Currently, it is difficult to fully understand the molecular basis for LL-37 effects in different cellular settings. However, available data indicate that LL-37 can act as a ligand for various membrane receptors thus explaining its tissue-specific effects in different cancers. Although mouse models of cancer for studying the mechanism of CAMP/LL-37 have been used [30, 41, 43, 62, 64, 81, 91, 106, 107], the promoter of murine cathelicidin gene lacks of VDRE. Thus, the signaling of vitamin D-dependent induction of cathelicidin does not work effectively in mouse cells [95, 108]. Differences in tissue-specific and developmental expression of cathelicidin between human

and mouse also exist [109, 110]. Due to the problems and differences, it can be concluded that results obtained from mouse models are defective to explain the roles of CAMP/LL-37 in human cancer progression. Based on the growing number of novel proposed mechanisms of tumorigenic and anti-cancer effects induced by LL-37, it is reasonable to conclude that LL-37 exerts multiple and complex effects on various cancer cells. In some cancers, there are both tumorigenic and anti-cancer effects induced by LL-37, and the final effect depends on the combined effects of these involved mechanisms.

More and more tumor types are now associated with LL-37, and we suggest the need for further exploration of the relationship between LL-37 and other cancers not yet investigated. Considering the fact that the expression of LL-37 in various cells is inducible, the relationship between these inducible factors and tumorigenesis needs to be considered and investigated. The anti-cancer effect of vitamin D in several cancers is intriguing and promising. The detailed mechanisms of vitamin D-dependent induction of cathelicidin that can impact cancer progression need to be further clarified. As a result of the elucidation of the roles and mechanisms of LL-37 in human cancer, it is expected that the research of LL-37 on therapeutic purpose for cancers will increase.

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Disclosure Statement

No conflict of interests exists.

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