Inflammation Research (2025) 74:36
https://doi.org/10.1007/s00011-025-02005-8

Inflammation Research

REVIEW

Human antimicrobial/host defense peptide LL-37 may prevent the spread of a local infection through multiple mechanisms: an update

Daniel Svensson[1] · **Bengt-Olof Nilsson**[1]

Received: 21 August 2024 / Revised: 20 January 2025 / Accepted: 26 January 2025

Abstract

Background Human cathelicidin LL-37 shows activity towards both gram-positive and gram-negative bacteria, and it is also active against some types of viruses. Besides its antimicrobial effects, the peptide modulates innate immunity through binding and inactivation of bacterial endotoxins and promoting chemotaxis of immune cells.

Results LL-37 is reported to interact with plasma membrane receptors and mediate import of Ca^{2+}. Importantly, LL-37 has both anti- and pro-inflammatory effects. LL-37 is cytotoxic to many different human cell types, particularly infected cells, when administered to the cells at final concentrations of 1–10 µM. In psoriatic lesions very high concentrations (300 µM) of the peptide are detected, and in periodontitis, gingival crevicular fluid contains about 1 µM LL-37, implying high concentrations of the peptide at the site of infection/inflammation which can affect host cell viability locally.

Conclusions Altogether, LL-37 may inhibit and prevent the infection from spreading by direct anti-bacterial and anti-viral effects, but also via anti- and pro-inflammatory mechanisms, and through killing already infected and weakened host cells at the site of infection/inflammation.

Keywords Antimicrobial peptides (AMPs) · Apoptosis · Cathelicidin/LL-37 · Host cell cytotoxicity · Infection · Inflammation

Introduction

In humans, there are two important families of antimicrobial peptides, cathelicidins and defensins. The human cathelicidin LL-37 is the focus of this review. LL-37 is active against microorganisms and therefore characterized as an antimicrobial peptide, but due to its multiple effects in humans, it is often described as a host defense peptide. The pro-form of LL-37, hCAP18, is secreted by white blood cells and epithelial cells and processed to LL-37 extracellularly through serine protease 3 and kallikrein 5 [1–5]. The formation and processing of hCAP18/LL-37 is depicted in Fig. 1. LL-37 has a rapid turnover, and the systemic levels of LL-37 are low, although elevated levels of LL-37 can be found locally at the infection/inflammation [6–8].

Neutrophils are especially rich in hCAP18, and patients suffering from a congenital severe form of neutropenia (Kostmann syndrome) have extremely low levels/lack LL-37 in blood and saliva [9]. These patients may die from banal infections, if not treated with granulocyte-colony stimulating factor (G-CSF) to elevate their neutrophil contents. Hence, the disease characteristics and symptoms observed in patients with Kostmann syndrome can, at least partly, be caused by lack of sufficient amounts of LL-37, arguing that LL-37 indeed is important in vivo.

LL-37 can interact with many cellular structures, molecules and receptors and shows pleiotropic actions [5]. Importantly, the peptide is active against both bacteria and viruses [4, 10]. It has a direct bactericidal effect through permeabilization of the bacterial cell wall, and indirect anti-bacterial effects via binding and inactivation of bacterial endotoxins such as LPS and LTA, and through its ability to dissolve bacterial biofilms and promote formation of neutrophil extracellular traps (NETs). Moreover, LL-37 modulates innate immunity through both pro- and

Responsible Editor: John Di Battista.

✉ Bengt-Olof Nilsson
bengt-olof.nilsson@med.lu.se

[1] Department of Experimental Medical Science, Lund University, BMC D12, 22184 Lund, Sweden

Published online: 11 February 2025

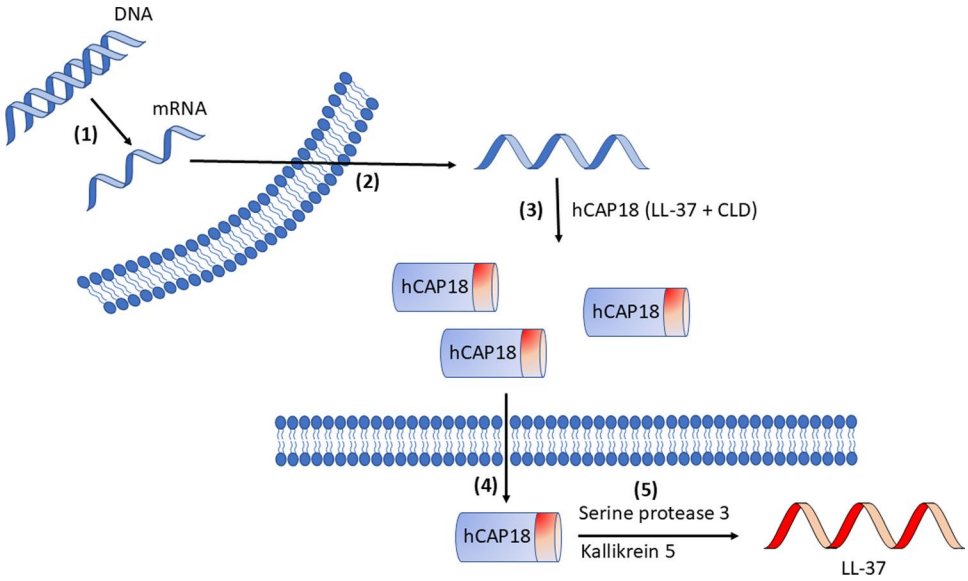

Fig. 1 Production and processing of hCAP18/LL-37. White blood cells and epithelial cells secrete hCAP18 which is cleaved extracellularly to LL-37 by serine protease 3 and kallikrein 5. (1) Transcription of the Cathelicidin AntiMicrobial Protein (CAMP) gene, (2) Export of mRNA, (3) Synthesis of hCAP18, (4) Exocytosis of hCAP18, (5) Cleavage of hCAP18 into biologically active LL-37. hCAP18 = human Cathelicidin Antimicrobial Protein 18, CLD = Cathelin-Like Domain

anti-inflammatory mechanisms and by stimulating recruitment of white blood cells [5, 11]. Last, but not least, LL-37 is cytotoxic to many types of human host cells, which may be recognized as a negative side effect, but importantly there are studies showing that LL-37 primarily kills already infected and weakened cells. Here, LL-37-induced cytotoxicity is extensively reviewed and references provided. Thus, it seems that LL-37 can combat microorganisms and simultaneously destroy and remove host cells locally, probably to reduce/eliminate the spread of a local infection. In this review article, we describe and discuss effects of LL-37 on host cells, and we primarily cover and cite articles presenting data from studies using human cells.

LL-37-induced anti-bacterial effects

LL-37 was originally identified as an anti-bacterial peptide, and the mechanisms by which LL-37 exerts this effect have been studied extensively [10]. The peptide shows toxicity towards both gram-negative and gram-positive bacteria, and it acts via permeabilization of the bacterial cell wall [4, 10]. This effect is completely dependent on its helical structure and observed only at sufficient ionic concentrations. The importance of the direct LL-37-induced bactericidal effect has been debated, since relatively high LL-37 concentrations are needed for bacterial clearance. Notably, the sensitivity to LL-37 varies between different bacterial strains, probably because structure and functional characteristics of the bacterial cell wall vary between bacteria [10]. However, LL-37 also has other anti-bacterial effects, besides causing cell lysis, which most likely are of greater biological importance. This includes its ability to dissolve bacterial biofilms at 100-fold lower concentrations than needed to kill the type of bacteria constituting the bacterial component of the biofilm, as well as its chemotactic properties, involved in the recruitment of immune cells to the site of infection [5, 12].

LL-37-induced anti-viral and anti-fungal effects

In accordance with LL-37-induced cytotoxicity in host- and bacterial cells equipped with plasma membrane/cell wall, LL-37 is also able to damage enveloped viruses, such as Influenza A, by disintegration of their envelope, allowing for clearance of viral particles by antibodies [13]. Interestingly, vitamin D shows activity against *Mycobacterium tuberculosis* and inhibits HIV virus replication via LL-37-induced autophagy in macrophages [14].

LL-37 can also function as a fungicide through its ability to disrupt fungal membranes; for the main fungal pathogen in humans, *Candida albicans*, LL-37 kills the fungi at concentrations between 0.8 and 8 µM [15, 16]. Besides this effect, it also suppresses growth of various fungi through different mechanisms involving disruption of ER homoeostasis and induction of oxidative stress [17]. Additionally, LL-37 may bind to carbohydrates in the fungal membrane, and by doing so it attenuates fungal adhesion to host cells, which represents the first step in fungal infections [16].

Anti-inflammatory properties of LL-37

LL-37 shows anti-bacterial and anti-inflammatory capacities also via other mechanisms than direct effects on bacteria and viruses as reviewed previously by Hancock et al. [5]. In Table 1, we summarize LL-37-induced anti- and

Table 1 LL-37-induced pro- and anti-inflammatory mechanisms in different human cell types. Notably, in some types of cells LL-37 shows both pro- and anti-inflammatory effects

Cell type	Pro-inflammatory	Anti-inflammatory	Mechanism	Reference
Erythrocytes, Macrophages		Yes	Binding and inhibition of LPS	[18]
Macrophages, Epithelial cells	Yes	Yes	Pro: Up-regulation of chemokines Anti: Inhibition of bacterial endotoxins	[19]
PBMCs	Yes		Potentiates IL-1β-induced cytokine production	[26]
Monocytes		Yes	Enhances anti-inflammatory IL-10	[22]
Keratinocytes		Yes	Inhibits cytosolic DNA-induced inflammasome	[36]
Bronchial epithelial cells	Yes		Potentiation of poly I:C-induced TLR3 signaling	[29, 30]
Macrophages	Yes		Stimulates activation of the inflammasome	[32, 33]
Keratinocytes	Yes	Yes	Pro: Potentiates poly I:C-induced IL-8 Anti: Inhibits poly I:C-stimulated CCL5 and CXCL10	[31]
Bronchial epithelial cells	Yes		Recruits eosinophils	[24]
Macrophages		Yes	Triggers anti-inflammatory cytokine IL-1RA	[21]
Vascular smooth muscle cells	Yes		Potentiates poly I:C-induced inflammation via up-regulation of TLR3	[28]
Colonic epithelial cells	Yes		Potentiation of LPS-induced IL-8	[25]
Gingival fibroblasts	Yes	Yes	Pro: Stimulation of IL-8 and CXCL1 expression Anti: Inhibition of LPS-induced IL-6 and IL-8	[23]

pro-inflammatory effects and mechanisms of action in various human cell types. The peptide binds and inactivates lipopolysaccharide (LPS) and lipoteichoic acid (LTA) from gram-negative and gram-positive bacteria, respectively. The mechanism behind this effect is regarded to be the direct binding of cationic LL-37 to negatively charged LPS and LTA and thereby inactivation of the endotoxins [18, 19]. LL-37 inhibits TNF-α production induced by LPS from many types of bacteria, such as *S. typhinarium*, *B. cepacia* and *E. coli*, implying that LL-37-induced inactivation of LPS is independent of the bacterial source of LPS [19]. LL-37 inhibits the pro-inflammatory effect of LPS in macrophages and epithelial cells, but also in other human cell types such as periodontal ligament cells, where it has been shown to prevent LPS-induced MCP-1 production [20]. Besides its binding and inactivation of endotoxins and thereby inhibition of endotoxin-mediated inflammation, LL-37 is reported to trigger production of the anti-inflammatory cytokines IL-1RA and IL-10 [21, 22]. Overall, these reports suggest that LL-37 acts anti-inflammatory through multiple mechanisms.

Pro-inflammatory properties of LL-37

In macrophages and gingival fibroblasts, LL-37 has been shown to up-regulate transcripts for chemokines and chemokine receptors [19, 23]. LL-37 triggers chemokine production by airway epithelial cells and colonic epithelial cells, and promotes recruitment of eosinophils to bronchial epithelial cells, implying a significant role for LL-37 in chemotaxis [24, 25]. Yu et al. [26] show that LL-37 potentiates pro-inflammatory IL-1β-induced cytokine and chemokine production (for example the chemokine MCP-1) by peripheral blood mononuclear cells (PBMCs). Furthermore, LL-37 stimulates pro-inflammatory activity and promotes migration of tissue mast cells [27]. Altogether, these data suggest that LL-37 triggers recruitment of immune cells to the inflammatory process.

In vascular smooth muscle cells, LL-37 potentiates the pro-inflammatory effect of synthetic double-stranded RNA (poly I:C) via up-regulation of TLR3, suggesting that LL-37 promotes virus-induced inflammation [28]. Also, in bronchial epithelial BEAS-2B cells, LL-37 enhances poly I:C-induced inflammation [29, 30]. In keratinocytes, LL-37 is reported to amplify poly I:C-induced IL-8 chemokine

expression, whereas it antagonizes poly I:C-stimulated thymic stromal lymphopoietin cytokine and CCL5 and CXCL10 chemokine expressions [31]. In summary, LL-37 seems to potentiate poly I:C-induced inflammation.

Table 2 LL-37-induced human host cell cytotoxicity and apoptosis. Here, we present cell types and assays and techniques used to demonstrate LL-37-induced cytotoxicity and pro-apoptotic effects of LL-37. NA = not available

Cell type	Cell viability assay	Cell number/counting assay	Apoptosis assay	Ref
Vascular smooth muscle cells	FITC-annexin V microscopy LDH release	NA	Caspase-3 activity DNA fragmentation ELISA Flow cytometry	[58]
Airway epithelial cells	NA	NA	Cleaved caspase-3 and 9 Cytochrome C release TUNEL staining	[37]
Periodontal ligament fibroblasts	Microscopy of live cells	DNA synthesis Counting in Bürker chamber	Active caspase-3 ELISA	[59]
Airway epithelial cells	MTT assay	NA	Cytochrome C release TUNEL staining Active caspase-3 and 7 PARP cleavage	[52]
Regulatory T cells	NA	NA	DNA fragmentation Chromatin condensation Apoptotic body formation	[54]
MG63 osteoblasts	LDH release MTT assay Microscopy of live cells	NA	NA	[40]
HaCaT keratinocytes	LDH release MTT assay Microscopy of live cells	NA	NA	[40]
MG63 osteoblasts	Microscopy trypan blue	Counting in Bürker chamber	Active caspase-3 ELISA Flow cytometry Annexin V	[49]
Airway epithelial cells	LDH release	NA	TUNEL staining Active caspase-3 Western blot	[60]

LL-37 stimulates the NLRP3-mediated inflammasome in macrophages and induces skin inflammation in mice via activation of the inflammasome [32, 33]. In mice, LL-37 is reported to worsen myocardial injury, and this effect appears to involve activation of the NLRP3 inflammasome [34]. In keratinocytes, LL-37 potentiates UVB radiation-induced inflammasome mediated production of IL-1β [35]. Hence, several studies demonstrate that LL-37 triggers the NLRP3 inflammasome and inflammation. On the other hand, LL-37 has been shown to antagonize cytosolic DNA-induced inflammasome activation through the DNA sensor AIM2, suggesting that LL-37 may interact with the inflammasome and act anti-inflammatory in sterile inflammation caused by DNA [36].

LL-37-induced host cell toxicity

It is well-documented that μM concentrations of exogenous LL-37 cause morphological alterations such as cell shrinkage, increase lactate dehydrogenase (LDH) release and reduce cell viability assessed by for example the MTT assay in various types of human host cells. These effects, which are signs of reduced cell viability and apoptosis in response to LL-37, can be seen in the concentration range 1–10 μM. LL-37-induced cytotoxic and pro-apoptotic effects are observed in cells treated with synthetic LL-37 from different manufacturers, and in concentrations which are relevant for the in vivo situation [6–8]. In Table 2, we present studies reporting reduced cell viability in response to LL-37 in different human cell types, and examples of techniques used to demonstrate LL-37-induced cytotoxicity and apoptosis. Interestingly, Barlow et al. [37] show that LL-37 acts in synergy with *P. aeruginosa* to promote apoptosis in human bronchial epithelial cells, and hence LL-37 seems to trigger apoptosis preferably in infected cells, but LL-37-induced pro-apoptotic effects are also observed in non-infected airway epithelial cells [38]. Thus, LL-37 appears to favor already weak and injured host cells as target cells for LL-37-induced cytotoxicity. On the same theme, Björstad et al. [39] demonstrate that LL-37 primarily permeabilizes the plasma membrane of already apoptotic neutrophils, whereas it has weak or no effect in healthy cells. As pointed out before, LL-37 is a cationic peptide binding to negative moieties of plasma membranes, suggesting that infected and injured cells mobilize and expose negative charges to the outer surface of their plasma membrane. The degree of cytotoxicity caused by LL-37 varies between cell types. For example, LL-37 has a more powerful cytotoxic effect in periodontal ligament cells and osteoblasts compared to keratinocytes and monocytes [40, 41]. In nasal epithelial cells, LL-37 induces cell death via non-apoptotic processes which

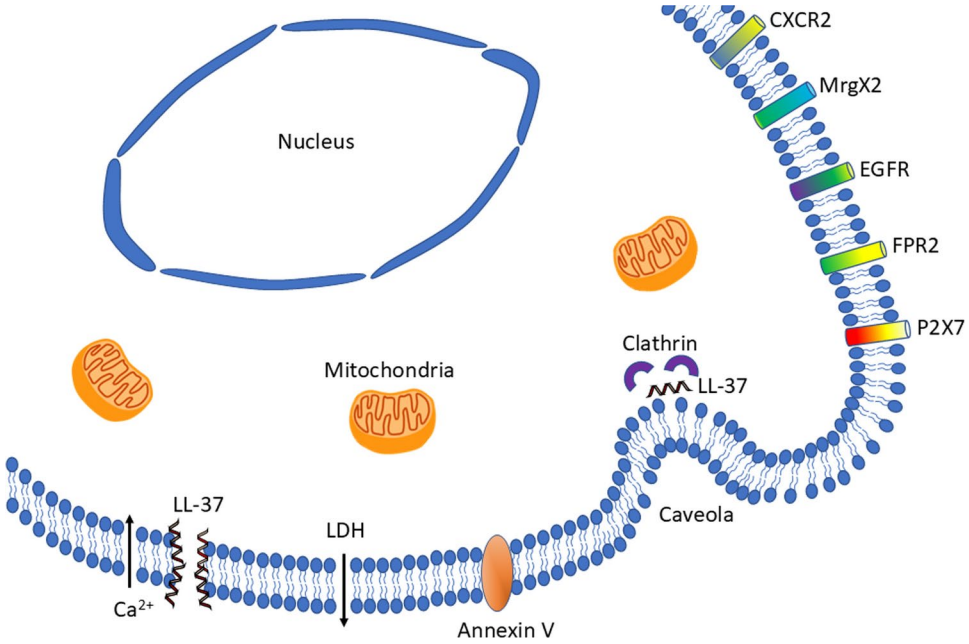

Fig. 2 Interactions of exogenous LL-37 with the plasma membrane of human host cells. LL-37 causes inflow of Ca^{2+}, release of LDH, pore formation and flip of Annexin V indicative of early apoptosis. LL-37 is supposed to be imported via both clathrin- and caveolae-mediated endocytosis. Moreover, LL-37 is believed to exert its effects via G protein-coupled receptors, receptor tyrosine kinases and purinergic receptors as shown in the upper right part of the figure

probably involve cell necrosis, further demonstrating that LL-37 is cytotoxic via different cell specific mechanisms [42]. Thus, LL-37 may cause cell death through different pathways depending on cell type, and likely also concentration and time of exposure to LL-37 are important factors.

In summary, LL-37 reduces viability and causes apoptosis in most human cell types, although its impact differs between cell types. To our knowledge, LL-37-induced anti-apoptotic effects have only been observed in keratinocytes, dermal fibroblasts, and neutrophils, suggesting that this effect is coupled to specific properties of these cell types and/or experimental conditions [38, 43–45]. In neutrophils, LL-37 reduces cell turnover by causing secondary necrosis demonstrated by flow cytometry of cells stained with propidium iodide (PI) and annexin V. Here, LL-37 rapidly converts the neutrophils from PI-negative, annexin V-positive cells to PI-positive cells, i.e., transform them into necrotic cells, and this effect does not seem to be pro-inflammatory to macrophages [46, 47].

LL-37 induces caspase-independent apoptosis

In Fig. 2, we depict how exogenous LL-37 may interact with the plasma membrane in human host cells. LL-37 causes pore formation, allows for inflow of Ca^{2+}, promotes LDH release and enhances the proportion of annexin V positive cells [40, 48–50]. Moreover, LL-37 is believed to be imported via both clathrin- and caveolae-mediated endocytosis as described in Fig. 2, and hereby it may bind and interact with intracellular binding partners [51]. LL-37-induced flip of annexin V indicates early apoptosis, and moreover TUNEL positive cells are seen in response to LL-37, showing that LL-37 causes DNA fragmentation, and late stage apoptosis. LL-37-induced apoptosis is not associated with caspase-3 activation or PARP cleavage in Jurkat cells, airway epithelial cells and osteoblast-like cells (MG63 cells), suggesting that LL-37 causes caspase-independent apoptosis in these cell types [37, 50, 52]. In oral squamous carcinoma cells, a C-terminal domain of hCAP18 ($hCAP18_{109-135}$) has been reported to trigger caspase-independent apoptosis [53]. Although LL-37 induces apoptosis that is not associated with caspase activity in healthy epithelial cells, it may cause caspase-3 activation in epithelial cells infected with bacteria [37]. In regulatory T cells, LL-37 causes both caspase-dependent and caspase-independent apoptosis, suggesting that both processes may occur in this cell type [54]. Mader et al. [55] show that LL-37-induced apoptosis is dependent on apoptosis-inducing factor (AIF) released from mitochondria in Jurkat cells, implying that LL-37 directly and/or indirectly interacts with mitochondria and thereby triggers AIF-dependent apoptosis. In colon cancer cells, LL-37 causes caspase-independent apoptosis and translocation of AIF from cytosol to nucleus, and in mitochondria isolated from MG63 cells, LL-37 releases AIF, providing further evidence that AIF from mitochondria is responsible for LL-37-induced apoptosis [56, 57]. Although, results of many studies imply that caspase-independent apoptosis caused by mitochondrial AIF is responsible for LL-37-induced cell death, further studies are needed to clarify the importance and involvement of caspase-dependent apoptosis, caspase-independent apoptosis, necrosis and other alternative mechanisms in cell death of human host cells caused by LL-37.

In Table 2, we include additional studies, not discussed in the text, reporting cell death in response to treatment with exogenous LL-37 [58–60].

LL-37 signaling through plasma membrane receptors

Besides LL-37-induced permeabilization of the plasma membrane allowing for influx of Ca^{2+} from the extracellular space as discussed before, LL-37 is also believed to interact with the host cell plasma membrane via G protein-coupled receptors (GPCRs), receptor tyrosine kinases and purinergic receptors as illustrated in Fig. 2. Although LL-37 is suggested to exert its action via plasma membrane receptors, it is unclear if this represents a direct interaction with the extracellular ligand-binding domain of the receptor, or if the peptide acts through indirect mechanisms, e.g., by interaction with the cytoplasmic portion of the receptor and/or through its pore forming capacity [61]. Treatment with pertussis toxin, causing disruption of GPCR signaling, has been reported to inhibit LL-37-induced apoptosis in colon cancer cells, implying that this effect is mediated by a GPCR [56]. Over the years, a considerable number of different GPCRs are suggested to mediate LL-37 downstream effects. In mast cells, the GPCR, Mas-related gene X2 (MrgX2), is reported to mediate LL-37-evoked mast cell degranulation [62]. CXCR2 is a GPCR that acts as a receptor for the chemokine interleukin 8, and LL-37 is reported to act as a functional ligand for this receptor in human neutrophils [63]. The formyl peptide receptor 2 (FPR2) is a GPCR expressed by many different human cell types including white blood cells. The arachidonic acid metabolite lipoxin A4 as well as bacterial/viral derived peptides are proposed to act as FPR2 ligands which upon binding trigger, for example chemotaxis. LL-37 has been reported to activate MAPK via FPR2 in cancer cells, and FPR2 is also suggested to play a role in LL-37-stimulated chemoattraction of white blood cells [64–66]. Recently, Lou et al. [67] show that LL-37 upregulates FPR2, activates opening of mitochondrial permeability transition pores, and stimulates formation of NETs in neutrophils. Interestingly, LL-37 increases synthesis of FPR2 in human mesenchymal stem cells (hMSC), allowing for FPR2-mediated chemokine/cytokine production and accumulation of hMSCs in atherosclerotic plaques [68]. LL-37 promotes phagocytosis by human macrophages, and this effect is also suggested to be mediated through FPR2 [69]. Moreover, LL-37 has been reported to promote wound healing and epithelial cell proliferation of airway epithelium through activation of EGFR, belonging to tyrosine kinase membrane receptor family [70].

The ionotropic P2X7 receptor belongs to the family of purinergic receptors, and it is activated by ATP. However, P2X7 receptors are also suggested to mediate LL-37 signaling. In this paragraph, we present examples of LL-37-induced responses in human cells reported to involve the P2X7 receptor. In human macrophages, LL-37-induced stimulation of thromboxane A_2 and leukotriene B_4 formation, and LL-37-stimulated ERK phosphorylation, are reported to involve P2X7 [71]. Furthermore, LL-37 is suggested to be internalized by macrophages through clathrin- and caveolae-mediated endocytosis via activation of P2X7 receptors [33, 51]. In human monocytes, Rekha et al. [72] show that the P2X7 receptor antagonist KN62 inhibits LL-37-stimulated autophagy, suggesting that P2X7 may be involved in this effect. A recent study reports that LL-37-induced autophagy is dependent on post-translational modification of LL-37, and interestingly this effect is observed at low concentrations of LL-37 (2 μg/ml = 0.44 μM), where no obvious cytotoxic effects of LL-37 are observed [40, 73]. In human gingival fibroblasts, P2X7 receptors seem to be involved in LL-37-induced stimulation of interleukin-8 expression [74]. Stiffening of endothelial cells induced by LL-37 may represent an anti-inflammatory mechanism, and this effect is suggested to be blocked by P2X7 receptor antagonists, arguing that LL-37-evoked endothelial cell stiffening is dependent on P2X7 receptor signaling [75]. In human neutrophils, LL-37 has been reported to exert an anti-apoptotic effect as discussed previously, and this effect is suggested to be mediated via FPR2 and P2X7 receptors [45]. Finally, P2X7 has been implicated in LL-37-induced IL-1β production by monocytes [76]. Hence, the P2X7 receptor is reported to mediate various LL-37-induced effects in many different cell types.

Conclusions

LL-37 combats bacteria and viruses, both directly through permeabilization of their cell wall/envelope, and indirectly via binding and inactivation of bacterial endotoxins and stimulation of inflammation. In μM concentrations, LL-37 permeabilizes cell membranes and is cytotoxic to human host cells, especially infected and injured cells, and it also induces apoptosis. Therefore, LL-37 may kill tissue cells, at the site of infection/inflammation, where the local concentration of the peptide is high. The main purpose of this review is to summarize these diverse effects of LL-37 and highlight that they may act in synergy to combat pathogens. More information about systemic and local levels of LL-37 in healthy individuals and in patients with inflammatory/infectious diseases represents an important topic for future studies. Another important matter is to better clarify

LL-37-evoked signaling pathways and their complex downstream effects and importance in inflammation. In local infections, LL-37 may thus eliminate infected host cells and thereby cause local tissue destruction and loss of functionality. However, on the systemic level, these mechanisms can help the patient avoid a spread of the infection and life-threatening sepsis. Importantly, there is no direct evidence that LL-37-induced cytotoxicity is beneficial. Therefore, it is important to examine the multiple actions of LL-37 in complex experimental set-ups, such as co-culture systems with many cell types, and of course in vivo, to get a more complete picture of its integrated and systemic role.

Acknowledgements Authors are supported by a grant from the Gyllenstiernska Krapperup Foundation (Grant No. KR2024-0001).

Author contributions Daniel Svensson and Bengt-Olof Nilsson had the idea for this article. Both authors performed the literature search and drafted and critically revised the work.

Funding Open access funding provided by Lund University.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Sorensen OE, Follin P, Johnsen AH, Calafat J, Tjabringa GS, Hiemstra PS, et al. Human cathelicidin, hCAP18, is processed to the antimicrobial peptide LL-37 by extracellular cleavage with proteinase 3. Blood. 2001;97:3951–9. https://doi.org/10.1182/blood.v97.12.3951.
2. Zanetti M. The role of cathelicidins in the innate host defenses of mammals. Curr Issues Mol Biol. 2005;7:179–96.
3. Yamasaki K, Schauber J, Coda A, Lin H, Dorschner RA, Schechter NM, et al. Kallikrein-mediated proteolysis regulates the antimicrobial effects of cathelicidins in skin. FASEB J. 2006;20:2068–80. https://doi.org/10.1096/fj.06-6075com.
4. Cederlund A, Gudmundsson GH, Agerberth B. Antimicrobial peptides important in innate immunity. FEBS J. 2011;278:3942–51. https://doi.org/10.1111/j.1742-4658.2011.08302.x.
5. Hancock RE, Haney EF, Gill EE. The immunology of host defence peptides: beyond antimicrobial activity. Nat Rev Immunol. 2016;16:321–34. https://doi.org/10.1038/nri.2016.29.
6. Ong PY, Ohtake T, Brandt C, Strickland I, Boguniewicz M, Ganz T, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. N Engl J Med. 2002;347:1151–60. https://doi.org/10.1056/NEJMoa021481.
7. Puklo M, Guentsch A, Hiemstra PS, Eick S, Potempa J. Analysis of neutrophil-derived antimicrobial peptides in gingival crevicular fluid suggests importance of cathelicidin LL-37 in the innate immune response against periodontogenic bacteria. Oral Microbiol Immunol. 2008;23:328–35. https://doi.org/10.1111/j.1399-302X.2008.00433.x.
8. Turkoglu O, Emingil G, Eren G, Atmaca H, Kutukculer N, Atilla G. Gingival crevicular fluid and serum hCAP18/LL-37 levels in generalized aggressive periodontitis. Clin Oral Investig. 2017;21:763–9. https://doi.org/10.1007/s00784-016-1834-z.
9. Pütsep K, Carlsson G, Boman HG, Andersson M. Deficiency of antibacterial peptides in patients with morbus Kostmann: an observation study. Lancet. 2002;360:1144–9. https://doi.org/10.1016/S0140-6736(02)11201-3.
10. Kai-Larsen Y, Agerberth B. The role of the multifunctional peptide LL-37 in host defense. Front Biosci. 2008;13:3760–7. https://doi.org/10.2741/2964.
11. Mookherjee N, Brown KL, Bowdish DM, Doria S, Falsafi R, Hokamp K, et al. Modulation of the TLR-mediated inflammatory response by the endogenous human host defense peptide LL-37. J Immunol. 2006;176:2455–64. https://doi.org/10.4049/jimmunol.176.4.2455.
12. Overhage J, Campisano A, Bains M, Torfs EC, Rehm BH, Hancock RE. Human host defense peptide LL-37 prevents bacterial biofilm formation. Infect Immun. 2008;76:4176–82. https://doi.org/10.1128/IAI.00318-08.
13. Barlow PG, Svoboda P, Mackellar A, Nash AA, York IA, Pohl J, et al. Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. PLoS ONE. 2011;6:e25333. https://doi.org/10.1371/journal.pone.0025333.
14. Campbell GR, Spector SA. Vitamin D inhibits human immunodeficiency virus type 1 and Mycobacterium tuberculosis infection in macrophages through the induction of autophagy. PLoS Pathog. 2012;8:e1002689. https://doi.org/10.1371/journal.ppat.1002689.
15. den Hertog AL, van Marle J, van Veen HA, Van't Hof W, Bolscher JG, Veerman EC, et al. Candidacidal effects of two antimicrobial peptides: histatin 5 causes small membrane defects, but LL-37 causes massive disruption of the cell membrane. Biochem J. 2005;388:689–95. https://doi.org/10.1042/BJ20042099.
16. Tsai PW, Yang CY, Chang HT, Lan CY. Human antimicrobial peptide LL-37 inhibits adhesion of *Candida albicans* by interacting with yeast cell-wall carbohydrates. PLoS ONE. 2011;6:e17755. https://doi.org/10.1371/journal.pone.0017755.
17. Memariani M, Memariani H. Antifungal properties of cathelicidin LL-37: current knowledge and future research directions. World J Microbiol Biotechnol. 2023;40:34. https://doi.org/10.1007/s11274-023-03852-5.
18. Larrick JW, Hirata M, Balint RF, Lee J, Zhong J, Wright SC. Human CAP18: a novel antimicrobial lipopolysaccharide-binding protein. Infect Immun. 1995;63:1291–7. https://doi.org/10.1128/iai.63.4.1291-1297.1995.
19. Scott MG, Davidson DJ, Gold MR, Bowdish D, Hancock RE. The human antimicrobial peptide LL-37 is a multifunctional modulator of innate immune responses. J Immunol. 2002;169:3883–91. https://doi.org/10.4049/jimmunol.169.7.3883.
20. Aidoukovitch A, Anders E, Dahl S, Nebel D, Svensson D, Nilsson BO. The host defense peptide LL-37 is internalized by human periodontal ligament cells and prevents LPS-induced MCP-1

production. J Periodontal Res. 2019;54(6):662–70. https://doi.org/10.1111/jre.12667.
21. Hemshekhar M, Choi KG, Mookherjee N. Host defense peptide LL-37-mediated chemoattractant properties, but not anti-inflammatory cytokine IL-1RA production, is selectively controlled by Cdc42 Rho GTPase *via* G protein-coupled receptors and JNK mitogen-activated protein kinase. Front Immunol. 2018;9:1871. https://doi.org/10.3389/fimmu.2018.01871.
22. Mookherjee N, Hamill P, Gardy J, Blimkie D, Falsafi R, Chikatamarla A, et al. Systems biology evaluation of immune responses induced by human host defence peptide LL-37 in mononuclear cells. Mol Biosyst. 2009;5:483–96. https://doi.org/10.1039/b813787k.
23. Lappin MJ, Dellett M, Mills KI, Lundy FT, Irwin CR. The neutralising and stimulatory effects of antimicrobial peptide LL-37 in human gingival fibroblasts. Arch Oral Biol. 2023;148:105634. https://doi.org/10.1016/j.archoralbio.2023.105634.
24. Jiao D, Wong CK, Tsang MS, Chu IM, Liu D, Zhu J, et al. Activation of eosinophils interacting with bronchial epithelial cells by antimicrobial peptide LL-37: implications in allergic asthma. Sci Rep. 2017;7:1848. https://doi.org/10.1038/s41598-017-02085-5.
25. Holani R, Babbar A, Blyth GAD, Lopes F, Jijon H, McKay DM, et al. Cathelicidin-mediated lipopolysaccharide signaling via intracellular TLR4 in colonic epithelial cells evokes CXCL8 production. Gut Microbes. 2020;12:1785802. https://doi.org/10.1080/19490976.2020.1785802.
26. Yu J, Mookherjee N, Wee K, Bowdish DM, Pistolic J, Li Y, et al. Host defense peptide LL-37, in synergy with inflammatory mediator IL-1beta, augments immune responses by multiple pathways. J Immunol. 2007;179:7684–91. https://doi.org/10.4049/jimmunol.179.11.7684.
27. Agier J, Różalska S, Wiktorska M, Żelechowska P, Pastwińska J, Brzezińska-Błaszczyk E. The RLR/NLR expression and pro-inflammatory activity of tissue mast cells are regulated by cathelicidin LL-37 and defensin hBD-2. Sci Rep. 2018;8:11750. https://doi.org/10.1038/s41598-018-30289-w.
28. Dahl S, Cerps S, Rippe C, Swärd K, Uller L, Svensson D, et al. Human host defense peptide LL-37 facilitates double-stranded RNA pro-inflammatory signaling through up-regulation of TLR3 expression in vascular smooth muscle cells. Inflamm Res. 2020;69:579–88. https://doi.org/10.1007/s00011-020-01340-2.
29. Lai Y, Adhikarakunnathu S, Bhardwaj K, Ranjith-Kumar CT, Wen Y, Jordan JL, et al. LL37 and cationic peptides enhance TLR3 signaling by viral double-stranded RNAs. PLoS ONE. 2011;6:e26632. https://doi.org/10.1371/journal.pone.0026632.
30. Singh D, Vaughan R, Kao CC. LL-37 peptide enhancement of signal transduction by toll-like receptor 3 is regulated by pH: identification of a peptide antagonist of LL-37. J Biol Chem. 2014;289:27614–24. https://doi.org/10.1074/jbc.M114.582973.
31. Chen X, Takai T, Xie Y, Niyonsaba F, Okumura K, Ogawa H. Human antimicrobial peptide LL-37 modulates pro-inflammatory responses induced by cytokine milieus and double-stranded RNA in human keratinocytes. Biochem Biophys Res Commun. 2013;433:532–7. https://doi.org/10.1016/j.bbrc.2013.03.024.
32. Kahlenberg JM, Carmona-Rivera C, Smith CK, Kaplan MJ. Neutrophil extracellular trap-associated protein activation of the NLRP3 inflammasome is enhanced in lupus macrophages. J Immunol. 2013;190:1217–26. https://doi.org/10.4049/jimmunol.1202388.
33. Yoon SH, Hwang I, Lee E, Cho HJ, Ryu JH, Kim TG, et al. Antimicrobial peptide LL-37 drives rosacea-like skin inflammation in an NLRP3-dependent manner. J Invest Dermatol. 2021;141:2885–94. https://doi.org/10.1016/j.jid.2021.02.745.
34. Wu Y, Zhang Y, Zhang J, Zhai T, Hu J, Luo H, et al. Cathelicidin aggravates myocardial ischemia/reperfusion injury via activating TLR4 signaling and $P2X_7R$/NLRP3 inflammasome. J Mol Cell Cardiol. 2020;139:75–86. https://doi.org/10.1016/j.yjmcc.2019.12.011.
35. Salzer S, Kresse S, Hirai Y, Koglin S, Reinholz M, Ruzicka T, et al. Cathelicidin peptide LL-37 increases UVB-triggered inflammasome activation: possible implications for rosacea. J Dermatol Sci. 2014;76:173–9. https://doi.org/10.1016/j.dermsci.2014.09.002.
36. Dombrowski Y, Peric M, Koglin S, Kammerbauer C, Göss C, Anz D, et al. Cytosolic DNA triggers inflammasome activation in keratinocytes in psoriatic lesions. Sci Transl Med. 2011;3:82ra38. https://doi.org/10.1126/scitranslmed.3002001.
37. Barlow PG, Beaumont PE, Cosseau C, Mackellar A, Wilkinson TS, Hancock RE, et al. The human cathelicidin LL-37 preferentially promotes apoptosis of infected airway epithelium. Am J Respir Cell Mol Biol. 2010;43:692–702. https://doi.org/10.1165/rcmb.2009-0250OC.
38. Barlow PG, Li Y, Wilkinson TS, Bowdish DM, Lau YE, Cosseau C, et al. The human cationic host defense peptide LL-37 mediates contrasting effects on apoptotic pathways in different primary cells of the innate immune system. J Leukoc Biol. 2006;80:509–20. https://doi.org/10.1189/jlb.1005560.
39. Björstad A, Askarieh G, Brown KL, Christenson K, Forsman H, Onnheim K, et al. The host defense peptide LL-37 selectively permeabilizes apoptotic leukocytes. Antimicrob Agents Chemother. 2009;53:1027–38. https://doi.org/10.1128/AAC.01310-08.
40. Svensson D, Wilk L, Mörgelin M, Herwald H, Nilsson BO. LL-37-induced host cell cytotoxicity depends on cellular expression of the globular C1q receptor (p33). Biochem J. 2016;473:87–98. https://doi.org/10.1042/BJ20150798.
41. Aidoukovitch A, Bankell E, Svensson D, Nilsson BO. Vitamin D triggers hCAP18/LL-37 production: Implications for LL-37-induced human osteoblast cytotoxicity. Biochem Biophys Res Commun. 2024;712–713:149962. https://doi.org/10.1016/j.bbrc.2024.149962.
42. Thomas AJ, Pulsipher A, Davis BM, Alt JA. LL-37 causes cell death of human nasal epithelial cells, which is inhibited with a synthetic glycosaminoglycan. PLoS ONE. 2017;12:e0183542. https://doi.org/10.1371/journal.pone.0183542.
43. Chamorro CI, Weber G, Grönberg A, Pivarcsi A, Ståhle M. The human antimicrobial peptide LL-37 suppresses apoptosis in keratinocytes. J Invest Dermatol. 2009;129:937–44. https://doi.org/10.1038/jid.2008.321.
44. Kim HJ, Cho DH, Lee KJ, Cho CS, Bang SI, Cho BK, et al. LL-37 suppresses sodium nitroprusside-induced apoptosis of systemic sclerosis dermal fibroblasts. Exp Dermatol. 2011;20:843–5. https://doi.org/10.1111/j.1600-0625.2011.01327.x.
45. Nagaoka I, Tamura H, Hirata M. An antimicrobial cathelicidin peptide, human CAP18/LL-37, suppresses neutrophil apoptosis via the activation of formyl-peptide receptor-like 1 and P2X7. J Immunol. 2006;176:3044–52. https://doi.org/10.4049/jimmunol.176.5.3044.
46. Zhang Z, Cherryholmes G, Shively JE. Neutrophil secondary necrosis is induced by LL-37 derived from cathelicidin. J Leukoc Biol. 2008;84:780–8. https://doi.org/10.1189/jlb.0208086.
47. Li HN, Barlow PG, Bylund J, Mackellar A, Björstad A, Conlon J, et al. Secondary necrosis of apoptotic neutrophils induced by the human cathelicidin LL-37 is not proinflammatory to phagocytosing macrophages. J Leukoc Biol. 2009;86:891–902. https://doi.org/10.1189/jlb.0209050.
48. Burton MF, Steel PG. The chemistry and biology of LL-37. Nat Prod Rep. 2009;26:1572–84. https://doi.org/10.1039/b912533g.
49. Säll J, Carlsson M, Gidlöf O, Holm A, Humlén J, Ohman J, et al. The antimicrobial peptide LL-37 alters human osteoblast Ca^{2+} handling and induces Ca^{2+}-independent apoptosis. J Innate Immun. 2013;5:290–300. https://doi.org/10.1159/000346587.

50. Bankell E, Dahl S, Gidlöf O, Svensson D, Nilsson BO. LL-37-induced caspase-independent apoptosis is associated with plasma membrane permeabilization in human osteoblast-like cells. Peptides. 2021;135:170432. https://doi.org/10.1016/j.peptides.2020.170432.
51. Tang X, Basavarajappa D, Haeggström JZ, Wan M. P2X7 receptor regulates internalization of antimicrobial peptide LL-37 by human macrophages that promotes intracellular pathogen clearance. J Immunol. 2015;195:1191–201. https://doi.org/10.4049/jimmunol.1402845.
52. Aarbiou J, Tjabringa GS, Verhoosel RM, Ninaber DK, White SR, Peltenburg LT, et al. Mechanisms of cell death induced by the neutrophil antimicrobial peptides alpha-defensins and LL-37. Inflamm Res. 2006;55:119–27. https://doi.org/10.1007/s00011-005-0062-9.
53. Okumura K, Itoh A, Isogai E, Hirose K, Hosokawa Y, Abiko Y, et al. C-terminal domain of human CAP18 antimicrobial peptide induces apoptosis in oral squamous cell carcinoma SAS-H1 cells. Cancer Lett. 2004;212:185–94. https://doi.org/10.1016/j.canlet.2004.04.006.
54. Mader JS, Ewen C, Hancock RE, Bleackley RC. The human cathelicidin, LL-37, induces granzyme-mediated apoptosis in regulatory T cells. J Immunother. 2011;34:229–35. https://doi.org/10.1097/CJI.0b013e318207ecdf.
55. Mader JS, Mookherjee N, Hancock RE, Bleackley RC. The human host defense peptide LL-37 induces apoptosis in a calpain- and apoptosis-inducing factor-dependent manner involving Bax activity. Mol Cancer Res. 2009;7:689–702. https://doi.org/10.1158/1541-7786.MCR-08-0274.
56. Ren SX, Cheng AS, To KF, Tong JH, Li MS, Shen J, et al. Host immune defense peptide LL-37 activates caspase-independent apoptosis and suppresses colon cancer. Cancer Res. 2012;72:6512–23. https://doi.org/10.1158/0008-5472.CAN-12-2359.
57. Bankell E, Liu X, Lundqvist M, Svensson D, Swärd K, Sparr E, et al. The antimicrobial peptide LL-37 triggers release of apoptosis-inducing factor and shows direct effects on mitochondria. Biochem Biophys Rep. 2021;29:101192. https://doi.org/10.1016/j.bbrep.2021.101192.
58. Ciornei CD, Tapper H, Bjartell A, Sternby NH, Bodelsson M. Human antimicrobial peptide LL-37 is present in atherosclerotic plaques and induces death of vascular smooth muscle cells: a laboratory study. BMC Cardiovasc Disord. 2006;6:49. https://doi.org/10.1186/1471-2261-6-49.
59. Jönsson D, Nilsson BO. The antimicrobial peptide LL-37 is anti-inflammatory and proapoptotic in human periodontal ligament cells. J Periodontal Res. 2012;47:330–5. https://doi.org/10.1111/j.1600-0765.2011.01436.x.
60. Lau YE, Bowdish DM, Cosseau C, Hancock RE, Davidson DJ. Apoptosis of airway epithelial cells: human serum sensitive induction by the cathelicidin LL-37. Am J Respir Cell Mol Biol. 2006;34:399–409. https://doi.org/10.1165/rcmb.2005-0170OC.
61. Xhindoli D, Pacor S, Benincasa M, Scocchi M, Gennaro R, Tossi A. The human cathelicidin LL-37-A pore-forming antibacterial peptide and host-cell modulator. Biochim Biophys Acta. 2016;1858:546–66. https://doi.org/10.1016/j.bbamem.2015.11.003.
62. Subramanian H, Gupta K, Guo Q, Price R, Ali H. Mas-related gene X2 (MrgX2) is a novel G protein-coupled receptor for the antimicrobial peptide LL-37 in human mast cells: resistance to receptor phosphorylation, desensitization, and internalization. J Biol Chem. 2011;286:44739–49. https://doi.org/10.1074/jbc.M111.277152.
63. Zhang Z, Cherryholmes G, Chang F, Rose DM, Schraufstatter I, Shively JE. Evidence that cathelicidin peptide LL-37 may act as functional ligand for CXCR2 on human neutrophils. Eur J Immunol. 2009;39:3181–94. https://doi.org/10.1002/eji.200939496.
64. Li Y, Cai L, Wang H, Wu P, Gu W, Chen Y, et al. Pleiotropic regulation of macrophage polarization and tumorigenesis by formyl peptide receptor-2. Oncogene. 2011;30:3887–99. https://doi.org/10.1038/onc.2011.112.
65. Yang D, Chen Q, Schmidt AP, Anderson GM, Wang JM, Wooters J, et al. LL-37, the neutrophil granule- and epithelial cell-derived cathelicidin, utilizes formyl peptide receptor-like 1 (FPRL1) as a receptor to chemoattract human peripheral blood neutrophils, monocytes, and T cells. J Exp Med. 2000;192:1069–74. https://doi.org/10.1084/jem.192.7.1069.
66. Tjabringa GS, Ninaber DK, Drijfhout JW, Rabe KF, Hiemstra PS. Human cathelicidin LL-37 is a chemoattractant for eosinophils and neutrophils that acts via formyl peptide receptors. Int Arch Allergy Immunol. 2006;140:10312. https://doi.org/10.1159/000092305.
67. Lou X, Chen H, Chen S, Ji H, He T, Chen H, et al. LL37/FPR2 regulates neutrophil mPTP promoting the development of neutrophil extracellular traps in diabetic retinopathy. FASEB J. 2024;38:e23697. https://doi.org/10.1096/fj.202400656R.
68. Egea V, Megens RT, Santovito D, Wantha S, Brandl R, Siess W, et al. Properties and fate of human mesenchymal stem cells upon miRNA let-7f-promoted recruitment to atherosclerotic plaques. Cardiovasc Res. 2023;119:155–66. https://doi.org/10.1093/cvr/cvac022.
69. Wan M, van der Does AM, Tang X, Lindbom L, Agerberth B, Haeggström JZ. Antimicrobial peptide LL-37 promotes bacterial phagocytosis by human macrophages. J Leukoc Biol. 2014;95:971–81. https://doi.org/10.1189/jlb.0513304.
70. Shaykhiev R, Beisswenger C, Kändler K, Senske J, Püchner A, Damm T, et al. Human endogenous antibiotic LL-37 stimulates airway epithelial cell proliferation and wound closure. Am J Physiol Lung Cell Mol Physiol. 2005;289:L842–8. https://doi.org/10.1152/ajplung.00286.2004.
71. Wan M, Soehnlein O, Tang X, van der Does AM, Smedler E, Uhlén P, et al. Cathelicidin LL-37 induces time-resolved release of LTB4 and TXA2 by human macrophages and triggers eicosanoid generation in vivo. FASEB J. 2014;28:3456–67. https://doi.org/10.1096/fj.14-251306.
72. Rekha RS, Rao Muvva SS, Wan M, Raqib R, Bergman P, Brighenti S, et al. Phenylbutyrate induces LL-37-dependent autophagy and intracellular killing of Mycobacterium tuberculosis in human macrophages. Autophagy. 2015;11:1688–99. https://doi.org/10.1080/15548627.2015.1075110.
73. Rekha RS, Padhi A, Frengen N, Hauenstein J, Vegvari A, Agerberth B, et al. The di-leucine motif in the host defense peptide LL-37 is essential for initiation of autophagy in human macrophages. Cell Rep. 2024;44:115031. https://doi.org/10.1016/j.celrep.2024.115031.
74. Montreekachon P, Chotjumlong P, Bolscher JG, Nazmi K, Reutrakul V, Krisanaprakornkit S. Involvement of P2X(7) purinergic receptor and MEK1/2 in interleukin-8 up-regulation by LL-37 in human gingival fibroblasts. J Periodontal Res. 2011;46:327–37. https://doi.org/10.1111/j.1600-0765.2011.01346.x.
75. Byfield FJ, Wen Q, Leszczynska K, Kulakowska A, Namiot Z, Janmey PA, et al. Cathelicidin LL-37 peptide regulates endothelial cell stiffness and endothelial barrier permeability. Am J Physiol Cell Physiol. 2011;300:C105–12. https://doi.org/10.1152/ajpcell.00158.2010.

76. Elssner A, Duncan M, Gavrilin M, Wewers MD. A novel P2X7 receptor activator, the human cathelicidin-derived peptide LL37, induces IL-1 beta processing and release. J Immunol. 2004;172:4987–94. https://doi.org/10.4049/jimmunol.172.8.4987.