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Review Article

Performance evaluation of antimicrobial peptide ll-37 and hepcidin and β-defensin-2 secreted by mesenchymal stem cells

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ABSTRACT

Peptides are secreted by different cell types and are trendy therapeutic agents that have attracted attention for the treatment of several diseases such as infections. Antimicrobial peptides exert various mechanisms such as changing cell membrane permeability which leads to inhibition or death of bacterial cells. mesenchymal stem cells (MSCs) are key to produce antimicrobial peptides and to inhibit the growth of pathogens. These cells have been shown to be capable of producing antimicrobial peptides upon exposure to different bacteria. As a result, antimicrobial peptides can be considered as novel agents for the treatment of infectious diseases. The purpose of this review was to investigate the targets and mechanisms of antimicrobial peptides secreted by MSCs.

1. Introduction

Antibiotics are used to treat bacterial infections through either inhibiting or killing the target bacteria. The first antibiotic was discovered by Alexander Fleming in 1928, called penicillin and saved the lives of millions of people. However, the discovery of penicillin as a modern medication was preceded by the management of microbial infections in Egypt, Greece and ancient China [1]. Shortly after the discovery of penicillin, the bacterial resistance to this antibiotic became one of the challenges in the treatment of bacterial infections. Therefore, new generation of beta-lactam antibiotics was developed to overcome antibiotic resistance and to treat bacterial infections. However, the first case of methicillin-resistant *Staphylococcus aureus* (MRSA) was reported in England in 1962 [2,3]. The production and discovery of new antibiotics continue to this day and new antibiotics are marketed to counteract the drug resistance problem. Yet, the point should be raised that one day antibiotics can no longer affect bacteria and will no longer be able to control bacterial infections. Consequently, in recent years, researchers have devised other means to treat bacterial infections. One of such approaches is the use of antimicrobial peptides (AMPs) or "peptide antibiotics" to kill pathogenic bacteria and to treat bacterial infections [4]. Over the past decades, antimicrobial peptides (peptide antibiotics) have been shown to be effective in innate immunity of various species, such as plants, invertebrates and vertebrates.

The intrinsic immune system is the first line of defense against the attack of microorganisms, among which the antimicrobial peptide molecules are the most important ones. The cathelicidin family is important antimicrobial agents in mammals [5, 6]. These peptides are mainly stored in lysosomes of macrophages (MQ) and polymorphonuclear neutrophils (PMNs) [7]. Cathelicidins have been isolated from many cell types including neutrophils to coordinate the immune system, but have been found in other immune cells such as epithelial cells and macrophages and have been shown to combat against bacteria, viruses and fungi. Cathelicidins have a variety of sizes (12–80 amino acids) and also have a wide range of structures [8]. The molecular mechanism of antimicrobial peptides has been investigated [9]. Stem cells have been the focus of research because they have shown good potential in the field of therapy [10]. One of the features of the stem cells referred to in this review is antimicrobial activity of mesenchymal stem cells that perform this action through antimicrobial peptides such as ll-37, Hepcidin and β-Defensin-2 [11]. The purpose of this study is to briefly review mesenchymal stem cells and antimicrobial peptides and how these peptides function.

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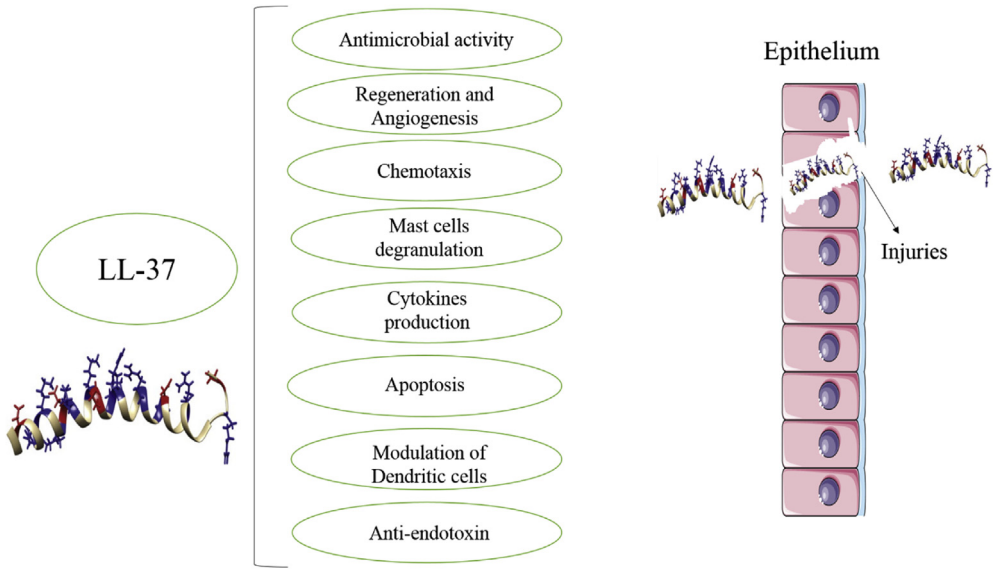

Fig. 1. LL-37 activities [35].

2. Main text

2.1. Mesenchymal stem cells (MSCs)

In recent years, stem cells have been widely used in the treatment of many diseases. One of the most important stem cells is mesenchymal stem cells (MSCs) that have been shown to play a role in regulating the immune system and suppressing deleterious properties. MSCs have the ability to differentiate into mesenchymal tissues such as cartilage, bone, muscle and fat. MSCs have been obtained from bone marrow, umbilical cord, blood, placenta, skeletal muscle and adipose tissue. Recent studies have found that MSCs play an important role in the treatment of diseases, including infections, by producing antimicrobial peptides [12, 13, 14].

Table 1
Molecular targets of LL-37.

Target	Cell Types	Reference
EGFR	Lung carcinoma cell line, bronchial epithelial cell line, keratinocyte	[17, 27]
ERP2	293 cells stably transfected with FPRL1, eosinophils, neutrophils, umbilical vein endothelial cells, lung cancer cell lines	[19]
P2X	Breast cancer cell lines	[28]
ERBb2	Monocyte	[28]

2.2. Antimicrobial peptides (AMP)

Cathelicidin is a carrier that has a wide range of functional molecules (i.e. cysteine or non-cysteine). The presence of this peptide has been proven in cattle, rabbits, pigs and humans [15].

Due to the unique characteristics of antimicrobial peptides, these peptides are one of the main candidates in the treatment of bacterial diseases and are effective on antibiotic resistant strains and even cancer cells. These properties include rapid killing and a wide range of activity that perform antimicrobial action by pore-forming the cell membrane [16]. But these peptides can also be toxic to the cells of the body, so using peptides with a wide range of lethality and low side effects can help cure bacterial infections [17].

2.3. LL-37 antimicrobial peptides

In 1995, Agerberth et al [18] based on the protected section of cathepsin, derived human bone marrow cDNA clones from an unspecified antibacterial peptide named FA-LL-37. The peptide constitutes of 39

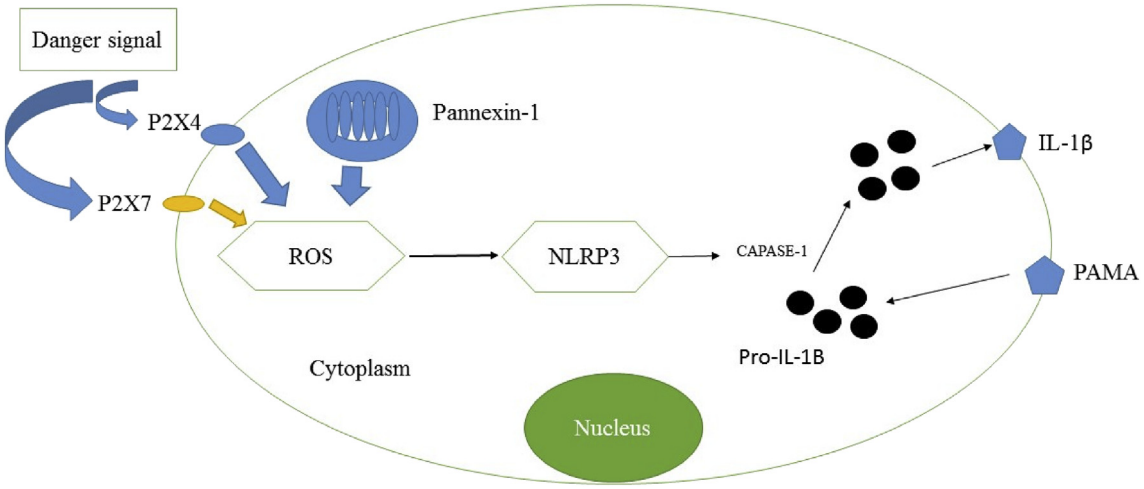

Fig. 2. Effect of LL-37 peptide on P2X7 purine receptor and stimulation of IL-1β production [35].

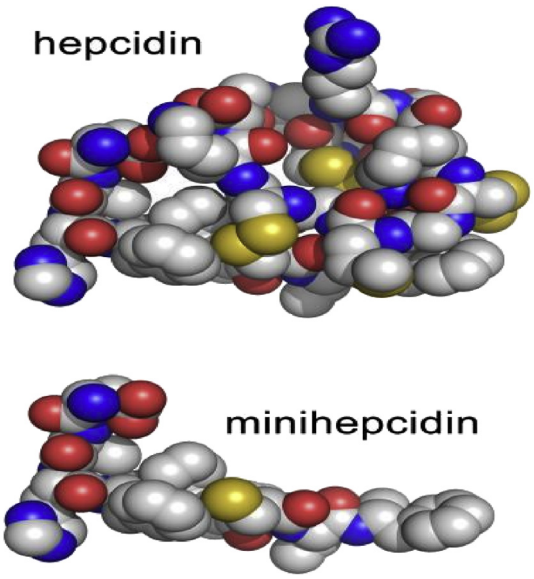

Fig. 3. Hepcidine structure. Structure of the human hormone hepcidin (top panel) and the portion used for the minihepcidin design (bottom panel) [38].

amino acids whose N-terminal is FALL and the name of the peptide was coined for FALL. The helical structure of this peptide was investigated in a saline environment containing vitamin E upon synthesis and antibacterial activity was investigated [9]. The peptide is specifically secreted in the secondary granules of neutrophils. It is also produced by many types of cells, including macrophages, natural killer (NK) cells, epithelial cells of the skin, airways, eyes and intestinal tract. Also, the expression of the peptide LL-37 is controlled by inflammatory pathways, similar to the pathway of vitamin D [19].

In addition to antimicrobial activity, this peptide has immunomodulatory roles. For example, exposure to 10 μg/ml of LL-37 peptide during a monocyte-macrophage differentiation leads to a positive inflammatory response, resulting in a decrease in the level of interleukin 10 and an adjustment of 12p40. In addition, the peptide LL-37 leads to the phenotype M1, which suggests that this peptide has an important role in the development of macrophages and cytokine production [20].

Other chemical properties of LL-37 is as follows: migration of neutrophils and eosinophils through the formyl-peptide receptor; transactivation of the epidermis growth factors by the peptide causes the migration of keratinocytes, which results in wound healing; MCP-1CCL-2 is a monocyte extraction factor that is secreted by LL-37 after stimulation. In addition, transforming growth factor beta (TGFβ) released from the epithelial cells of the intestine after exposure to LL-37 has an effect on the migration of epithelial cells and improved response. It is concluded that the peptide LL-37 is spread at the site of the infection, causing inflammatory response and wound healing [20, 21, 22].

LL-37 peptide has different activities, all of which lead to antimicrobial activity. These include regeneration and angiogenesis, which is done by the formyl-peptide receptor-like 1 expressed on the endothelial cells [23]. Chemotaxis is also one of the activities of this peptide, which causes the migration of mast cells to the environment [24]. In addition, degranulation of mast cells and the release of inflammatory mediators takes place by the LL-37 peptide [25]. LL-37 peptide, on the other hand, induces many cytokines and induces the production of antibodies [26]. LL-37 peptide from primary human keratinocytes and human keratinocytes (HaCaT) cells protect from apoptosis [27]. The results have shown that fluid membrane-associated peptides increases the plasma membrane of the subcutaneous glandular cells [28]. This peptide also considered as an endotoxin, which inhibits the responses of inflammatory proteins to the bacterial lipopolysaccharides (LPS) in human cells (Fig. 1) [29].

2.4. *LL-37 peptide function*

This peptide performs its actions by connecting to cell receptors (Table 1). As previously mentioned, LL-37 is actively involved in physiological responses to eukaryotic cells, which is essentially an antimicrobial peptide. This peptide is effective in people whose immune system is low, so that through transactivation of EGFR and angiogenesis by FPRL1 receptor and chemotaxis causes cell migration [30].

In addition, the expression of transgenic LL-37 leads to a significant increase in proliferation of corpuscular cells in HaCaT and HEK 293 [33]. With the presence of lymph node metastases in estrogen-receptor positive or ER positive cancer, clinical trials have shown an increase in Erb-B2 receptor tyrosine kinase 2 ($ERBB_2$) signaling, indicating an increase in peptide LL-37 activity, which plays an important role in the treatment of cancer [34].

This peptide also interacts with P_2X7 purinoceptor, which is expressed mainly in monocytes, macrophages and dendritic cells (DCs) and stimulates and releases cytokine IL-1β in human gingival fibroblasts (Fig. 2) [35]).

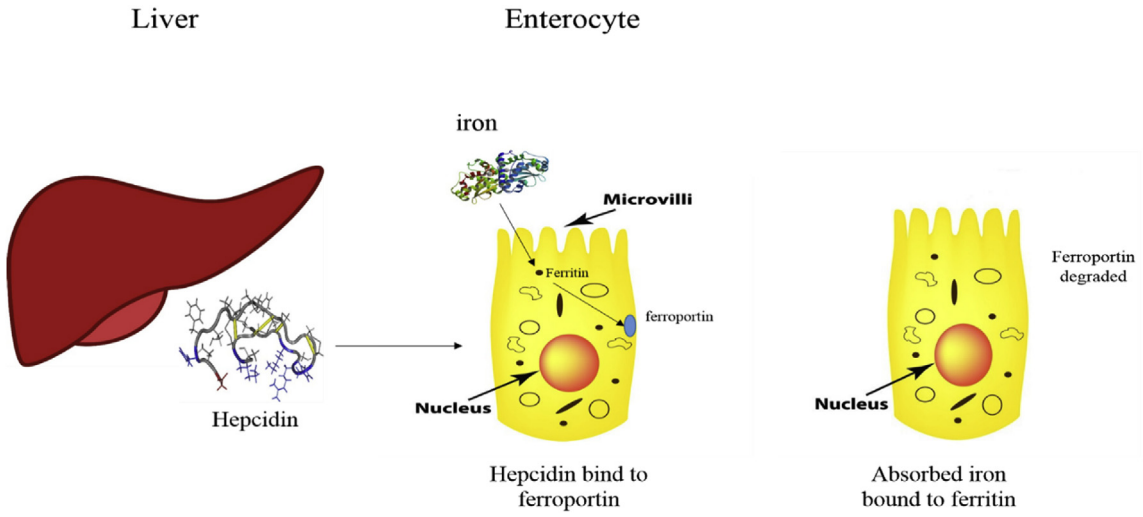

Fig. 4. After expressing the hepcidin in the cell, ferritin is transmitted to the macrophage and is degraded by lysozyme, resulting in the storage of iron inside the cell [40, 51].

Table 2
Defensin types [43, 44, 45].

		Gene name	Protein name	Description
Defensins	α-Defensin	alpha 1	Neutrophil Defensin 1	Primarily expressed in neutrophils, as well as in NK cells and some T lymphocyte subsets.
		alpha 1B	alpha 1	
		alpha 3	Neutrophil Defensin 3	
		alpha 4	Neutrophil Defensin 4	
		alpha 5	Defensin-5	
		alpha 6	Defensin-6	
	β - Defensin	β 1	β-Defensin 1	Secreted by leukocytes and epithelial cells of many kinds.
		β 2	β-Defensin 2	
		β 3	β-Defensin 3	
		β 103B	β-Defensin 103	
		β 106A	β-Defensin 106A	
		β 106B	β-Defensin 106B	
		β 107A	β-Defensin 107	
		β 110	β-Defensin 110	
		β 136	β-Defensin 136	
	Θ - Defensin	1 pseudogene	Not expressed in humans	Have been found only in the leukocytes of the rhesus macaque and the olive baboon, Papio anubis, being vestigial in humans and other primates.

2.5. Human antimicrobial peptide hepcidin

Another antimicrobial peptide produced by MSCs is called hepcidin, which plays an important role in the clearance of pathogens. This antimicrobial peptide is rich in cysteine, the precursor of which is secreted by the liver (Fig. 3). Hepcidin is present in three forms of prehormone (84 amino acids), prohormone (60 amino acids) and hormones (25 amino acids) [36]. This peptide was discovered in 2000 and was called LEAP 1, but after a while due to presence in the liver, the peptide was named "hepcidin". This peptide is effective on a wide range of fungi, bacteria and viruses. One of the most important effects of hepcidin in the body is the regulation of iron hemostasis. This peptide prevents iron absorption from the small intestine and releases iron from reticuloendothelial cells. In infectious diseases, macrophages and bacteria compete to absorb iron [37]. Macrophages interfere with the absorption of iron by bacteria. Eventually, the pathogen does not grow and replenish. Factors that cause hepcidin production are increased in bone marrow and anemia. Other factors that increase the production of hepcidin are iron accumulation and inflammation [38].

2.6. Mechanism of hepcidin

Hepcidin is effective on iron transfer from macrophages. In the presence of hepcidin, ferritin is transmitted into the macrophage and is destroyed by lysosomes, resulting in storage of iron inside the cell. In low concentrations of hepcidin, ferritin is present in the cell membrane, allowing the release of iron. After leaving the cell, iron oxide is rapidly oxidized by ceruloplasmin, a copper-rich ferroxidase and converted into ferric iron and then bound to transferrin [39].

Hepcidin is bound to plasma alpha-2 macroglobulin (alpha 2M). Evidence suggests that other cells may express the hepcidin mRNA at a much lower level than the hepatocytes; the biological significance of the extra hepatic production of hepcidin remains uncertain. Plasma hepcidin is freely treated through glomeruli and in animals with normal kidney activity it quickly passes through the urine. In addition, a part of hepcidin is cleansed through degradation along with ferritin [40] (Fig. 4).

2.7. Defensins

Cysteine-rich cationic proteins are found in vertebrates, invertebrates and plants, which range from 18 to 145 amino acids [41]. The role of these peptides is to defend the host against bacteria, fungi and viruses. These peptides play a role in destroying the bacterial cell membrane. Defensins were discovered for the first time in 1980. The basic genes produced by these peptides are highly polymorphic. Generally, defensins are classified in three main groups of alpha, beta and theta, each of which has different genetic symbols and is produced from different cells [42], as shown in Table 2.

In immature individuals, defensins (present in breast milk) play a very important role in protecting the disease due to the weak immune system. The Defensin is produced by epithelial cells and leukocytes, as indicated in Table 2. Alpha defensin exists only in mammals, while beta defensin exists in many vertebrates, invertebrates and plants, but theta

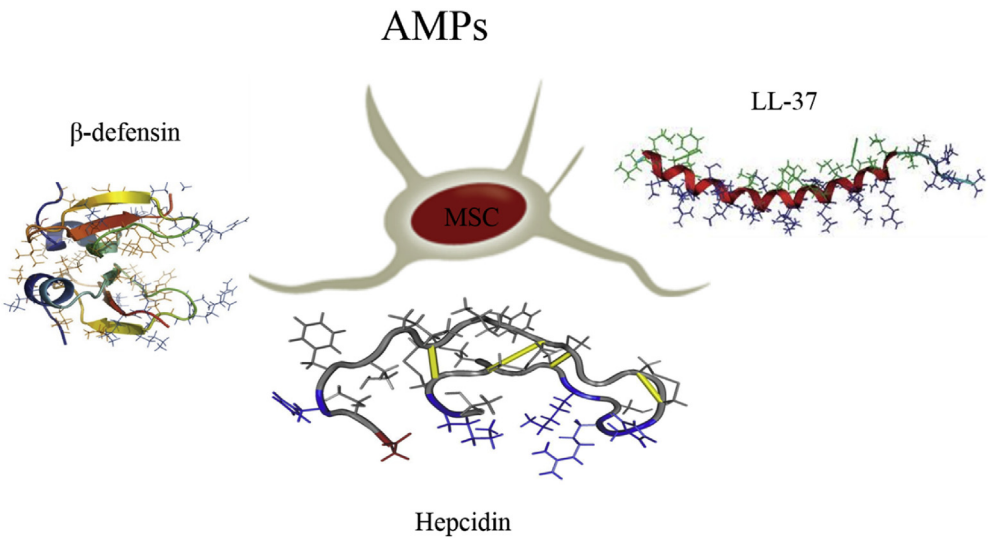

Fig. 5. MSCs produce microbial peptides including hepcidin, LL-37 and β-defensin to fight against bacteria. As shown in the figure above, the antimicrobial peptide LL-37 is effective against *Staphylococcus aureus* and *Escherichia coli* bacteria, while the effect of β-defensin peptide on the bacteria of *Escherichia coli* has been proven [14].

defensin has been found in several species of ancient monkeys, but not in humans and other primates. The important point is that the mRNA manages to denote the theta defensin, but the mutations cause the end codon to stop peptide production. One of the key characteristics of defensins is their antimicrobial activity, which is active against Gram-positive and Gram-negative bacteria, fungi and viruses [46].

In addition to antimicrobial activity, defensin exerts other functions that includes chemical absorption for monocytes, cytokines production by monocytes and epithelial cells, angiogenesis activity and response to hormones. Antimicrobial effect on Gram-positives is different from Gram-negative bacteria. The reason is that, first, the cell wall structure of Gram-positive bacteria is different from Gram-negatives (the cell wall of Gram-negative bacteria is rich in lipopolysaccharide (LPS), which has a negative charge, while in Gram-positive bacteria the cell wall have teichoic acids (TA) with less negative charge. Secondly, the peptidoglycan layer is thick in Gram-positive bacteria and the formation of pores by defensin on the surface of the Gram-positive cells requires more time. Therefore, defensin has weaker anti-microbial activity in Gram-positive bacteria [46].

Defensin functions on the bacterial cells via the L-arginine cationic chain that are attached by electrostatic absorption to the membrane's anionic structure, then defensin is introduced into the membrane by using the electromotive force of the membrane, creating channels inside the membrane. Ultimately, materials that are surrounded by membranes are leaked outside or inside the cell and causes bacterial cell lysis [46].

2.8. The role of MSCs in destroying pathogenic bacteria

Attempts to design novel treatment strategies as alternatives for the current treatment of diseases such as sepsis, bacteremia, bloodstream infections and other bacterial infections have become a major challenge. One of the most important treatments used to kill pathogenic bacteria is the use of antibiotics, which has some disadvantages in addition to its benefits. Antibiotic resistance is one of the biggest treatment problems with antibiotics. Antibiotic resistance is on the rise and the number of resistant are constantly circulating in the communities and it can be said that it will not last long as antibiotics will no longer be effective against bacteria [47, 48]. An emerging approach to treat infections is the use of antimicrobial peptides produced from various cells, including MSCs. Research has shown that MSCs have antimicrobial properties and this property is related to the production of antimicrobial peptides (Fig. 5) [14].

There are several barriers to using stem cells in treatment, such as the immune response to stem cells that can reduce the function of these cells, as well as their use may cause infection, poisoning, cancer and even death [49]. As a result, it is better to use mesenchymal stem cells in treatment if the treatments that have been used so far are no longer effective. On the other hand, the use of mesenchymal stem cells as a treatment has many benefits, one of which is the lack of damage that is usually caused by chemical treatments on the body. The use of mesenchymal stem cells in the treatment of bacterial infections can reduce the spread of antibiotic resistance [50].

3. Conclusion

In conclusion, MSCs are very capable of eliminating bacterial infections. The use of these cells and their antimicrobial products can be a potential alternative to current treatments, while bacterial resistance can be avoided.

Declarations

Author contribution statement

Reza Esfandiyari, Raheleh Halabian, Elham Behzadi, Hamid Sedighian, Ramezan Jafari, Abbas Ali Imani Fooladi: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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