Immunopathologia Persa
http www.immunopathol.com

Defensins usage as novel therapeutic and diagnostic approach

Hamid Nasri[1], Fatemeh Dehghan Shahreza[2*]

[1]Department of Nephrology, Division of Nephropathology, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Clinical Sciences, School of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran

Correspondence to
Fatemeh Dehghan Shahreza;
Email:
f_dehghan66@yahoo.com

Received 6 October 2014
Accepted 27 October 2014
ePublished 28 October 2014

Keywords: Defensines, Antimicrobial effects, Diagnostic usage

Citation: Nasri H, Dehghan Shahreza F. Defensins usage as novel therapeutic and diagnostic approach. Immunopathol Persa. 2015;1(1):e05.

Key point

Defensines are broad spectrum molecules that can become an effectiveness therapeutic and diagnostic agent at cancer and infectious patients.

Introduction

Two essential elements of host defense are innate and adaptive immunity. Innate immunity is highly preserved from fruit flies to human and is the first line of defense against invading pathogens. The secretion of broad-spectrum antimicrobial substances, such as cathelicidins and small cationic polypeptides named defensins is one mechanism of the innate immunity (1,2). Various multicellular organisms defensin antimicrobial peptides conserve against a wide variety of microorganisms, including gram-positive bacteria, gram-negative bacteria, virus and fungi (3). They can disrupt microorganism's membrane integrity and function, which ultimately leads to the lysis of the microorganisms (4). They contain two main subfamilies that differ in length and pairing of the six cysteines. Human alpha-defensins comprise human neutrophil peptides 1 to 4 (HNP1 to HNP4) that are expressed in azurophilic granules and also in B lymphocytes, monocytes and NK cells and human defensin-5 (HD-5) and HD-6 that are expressed primarily in intestinal Paneth cells and epithelial cells of the female urogenital tract (1,5-7). Six members of human beta-defensins include hBD-1 to hBD-6 are expressed in a wide variety of tissues. HBD-1 to HBD-4 are the most abundant b-defensins in human airway secretions (ng/ml range) (5,6). The most important antimicrobial peptide in human epithelia against infection is hBD1 that is expressed constitutive in most tissues. But some instances such as monocytes exposed to LPS, or IFN in uterine and pulmonary gland epithelial cells, hBD-1 expression has been upregulated (1). Bacterial patterns or pro-inflammatory cytokines induce human beta-defensin 2 (hBD-2) and hBD-3. Several diseases, such as inflammatory lung, bowel, and skin diseases are able to upregulate hBD-2 and hBD-3 (8,9). In fact, hBD-2 is mainly present in skin, respiratory, and gastrointestinal tracts, hBD-3 is expressed in epithelial and non-epithelial tissues, such as heart, liver, and skeletal muscle. The testis, gastric antrum, uterus, neutrophils, thyroid gland, lung, and kidney are tissues that express Hbd-4 (1). Bacterial infection can upregulate hBD4 expression but not inflammatory factors that upregulate hBD-2 and hBD-3. While, hBD-5 and hBD-6 have been localized to the epididymis and their antibacterial role in the testis is not yet understood (1,5), however, its attack on the microbial membranes, pore formation, depolarization, blocking of ion channels and effect on microbial intracellular processes, such as inhibiting protein synthesis and the activities of amylases and proteases are antimicrobial mechanisms of defensins (2,10-14).

Recent studies have shown these peptides to have a lot more cellular functions besides their antimicrobial activity such as cell division, attraction and maturation of immune cells, differentiation and reorganization of epithelial tissues, wound healing and tumor suppression (15,16). These large function cause human defensins have been regarded as efficient therapeutic approaches.

These peptides by binding and modulation of host cell surface receptors and disruption of intracellular signaling can inhibit viral fusion and replication. In addition, defensins can present an indirect antiviral mechanism by increasing and altering adaptive im-

mune responses, in this regard they have been considered as source of novel antiviral agents that the most studied have been investigated their antiviral effect on HIV-1 and HAdV-D, HAdV-E, and HAdV-F have been observed (17). Microorganism infection can control by antibiotic usage but organisms like bacteria are able to acquire antibiotic resistance. Antimicrobial properties of defensins have been considered for providing novel antibiotic agents. Recent studies have been checked the sensitivity of drug-resistant bacteria to the antimicrobial activity of human beta defensins such as hBD4. The results suggest that hBDs may represent an effective agent for treatment of infections involving drug-resistant microorganisms and they can be suitable alternative traditional antibiotics (3). However immunonutrients application (arginine, glutamine, dietary nucleotides, and fish oil) up regulate HBD1 expression that augment immune system functions and resulting fewer infectious complications, a fewer antibiotics usage and have a shorter hospitalization (1). Hence several studies have been designed to modify genetically cells like keratinocytes for production biologically active beta defensins that act as local antimicrobial agent and decline drug-resistant microorganisms and improve wound healing (3,18). These peptides also can be used in built of polyelectrolyte multilayer films that provide novel strategy for antimicrobial wound healing (19).

Defensins are anti-angiogenesis factor (HNP1-3), immune modulator (chemoattractant) agents for adaptive immunity system and inhibitor of cellular enzymes such as protein kinase C (HADs, HBD) (20,21). HNP1-3 can stimulate the growth of tumor cells or, in high concentration, they have cytotoxic effect and induce tumor cell death (22,23), therefor these defensines's characters make them as tumor suppressor that can provide novel treatment strategy for fighting cancer (20,21). Defensins together with an immune activator agent such as imiquimod to present higher efficiency of antitumor because of overpowering tumor related suppress immunity/immune-tolerance (24).

Defensins can play potent role as vaccine adjuvant, several researches have been done in this context and have been observed enhancement of antigen presentation with using defensins (20-26).

In last years, researchers have search for founding molecules that change their amount in biological fluids and tissues simultaneously occurrence of disease as diagnostic biomarkers, defensins are some of these molecules that can be interested as tumor marker (such as HBD2 and HAD6 as marker of respiratory tract tumors and colon cancer, respectively) (16,27) and infectious marker at synovial fluid (28). In addition, HBD2 and HNPs may be used as prognostic biomarker of resistance to antitumor treatment (29,30).

Conclusion

According mentioned above, defensives are broad spectrum molecules that can become an effectiveness therapeutic and diagnostic agent at cancer and infectious patients.

Authors' contribution

HN and FDS wrote the manuscript equally.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

References

1. Sherman H, Chapnik N, Froy O. Albumin and amino acids upregulate the expression of human beta-defensin 1. Mol Immunol. 2006;43:1617-23.
2. Saito A, Ueda K, Imamura M, Miura N, Atsumi S, Tabunoki H. Purification and cDNA cloning of a novel antibacterial peptide with a cysteine-stabilized alphabeta motif from the longicorn beetle, Acalolepta luxuriosa. Dev Comp Immunol. 2004;28:1-7.
3. Supp DM, Gardner J, Klingenberg JM, Neely AN. Antibiotic resistance in clinical isolates of Acinetobacter baumannii, Pseudomonas aeruginosa, and Staphylococcus aureus does not impact sensitivity to human beta defensin 4. Burns. 2009;35:949-55.
4. Yang D, Biragyn A, Kwak LW, Oppenheim JJ. Mammalian defensins in immunity: more than just microbicidal. Trends Immunol. 2002;23:291-6.
5. Wiesner J, Vilcinskas A. Antimicrobial peptides: the ancient arm of the human immune system. Virulence. 2010;1:440-64.
6. Selsted ME, Ouellette AJ. Ouellette, Mammalian defensins in the antimicrobial immune response. Nat Immunol. 2005;6:551-7.
7. Frye M, Bargon J, Dauletbaev N, Weber A, Wagner TO, Gropp R. Expression of human alpha-defensin 5 (HD5) mRNA in nasal and bronchial epithelial cells. J Clin Pathol. 2000;53:770-3.
8. Fellermann K, Wehkamp J, Herrlinger KR, Stange EF. Crohn's disease: a defensin deficiency syndrome? Eur J Gastroenterol Hepatol. 2003;15:627-34.
9. Claeys S, de Belder T, Holtappels G, Gevaert P, Verhasselt B, van Cauwenberge P, et al. Human defensins and Toll-like receptors in the upper airway. Allergy. 2003;58:748-53.
10. Johnson C, Kleshchenko Y, Furtak V, Nde P, Pratap S, Madison N, et al. Trypanosoma cruzi regulates the defensin alpha-1 interactome network and defensin alpha-1 causes trypanosome membrane pore formation to control the early process of infection. J Immun. 2011;186:56.30.
11. Spelbrink RG, Dilmac N, Allen A, Smith TJ, Shah DM, Hockerman GH. Differential antifungal and calcium channel-blocking activity among structurally related plant defensins. Plant Physiol. 2004;135:2055-67.
12. Yang W, Feng J, Xiang F, Xie Z, Zhang G, Sabatier JM, et al. Endogenous animal toxin-like human β-defensin 2 inhibits own K+ channels through interaction with channel extracellular pore region. Cell Mol Life Sci. 2014;72:1-9.
13. Merriman JA, Nemeth KA, Schlievert PM. Novel antimicrobial peptides that inhibit gram positive bacterial exotoxin synthesis. PLoS One. 2014;9:e95661
14. Wijaya R, Neumann GM, Condron R, Hughes AB, Polya GM. Defense proteins from seed of Cassia fistula include a lipid transfer protein homologue and a protease inhibitory plant defensin. Plant Sci. 2000;159:243-55.
15. Afshar M, Gallo RL. Innate immune defense system of the skin. Vet Dermatol. 2013;24:32-8.
16. Thomas G, Markus D, Beate E, Renate K, Christof WK, Simon P. Human neutrophil a-defensins are associated with adenosine diphosphate-inducible neutrophil-platelet aggregate formation and response to clopidogrel in patients with atherosclerosis.

Transl Res. 2014;164:202-8.
17. Wilson SS, Wiens ME, Smith JG. Antiviral Mechanisms of Human Defensins. J Mol Biol. 2013;425:4965-80.
18. Smiley AK, Gardner J, Klingenberg JM, Neely AN, Supp DM. Expression of human beta defensin 4 in genetically modified keratinocytes enhances antimicrobial activity. Burn Care Res. 2007;28:127-32.
19. Gácser A, Tiszlavicz Z, Németh T, Seprényi G, Mándi Y. Induction of human defensins by intestinal Caco-2 cells after interactions with opportunistic Candida species. Microbes and Infection. 2014;16:80-5.
20. Suarez-Carmona M, Hubert P, Delvenne P, Herfs M. Defensins:"Simple' Antimicrobial Peptides Or broad-spectrum molecules?. Cytokine Growth Factor Rev. 2015;26:361-70.
21. Winter J, Wenghoefer M. Human defensins: potential tools for clinical applications. Polymers. 2012;4:691-709.
22. Schaefer AS, Richter GM, Nothnagel M, Laine ML, Rühling A, Schäfer C, et al. A 3' UTR transition within DEFB1 is associated with chronic and aggressive periodontitis. Genes Immun. 2010;11:45-54.
23. Lichtenstein A, Ganz T, Selsted ME, Lehrer RI. In vitro tumor cell cytolysis mediated by peptide defensins of human and rabbit granulocytes. Blood. 1986;68:1407-10.
24. Tewary P, de la Rosa G, Sharma N, Rodriguez LG, Tarasov SG, Howard OM, et al. β-Defensin 2 and 3 promote the uptake of self or CpG DNA, enhance IFN-α production by human plasmacytoid dendritic cells, and promote inflammation. J Immunol. 2013;191:865-74.
25. Park HJ, Qin H, Cha SC, Sharma R, Chung Y, Schluns KS, et al. Induction of TLR4-dependent CD8+ Tcell immunity by murine beta-defensin2 fusion protein vaccines. Vaccine. 2011;29:3476-82.
26. Chen Y, Xu X, Hong S, Chen J, Liub N, Underhill CB, et al. RGD-tachyplesin inhibits tumor growth. Cancer Res. 2001;61:2434-8.
27. Arimura Y, Ashitani J, Yanagi S, Tokojima M, Abe K, Mukae H, et al. Elevated Serum beta-defensins concentrations in Patients with lung cancer. Anticancer Res. 2004;24:4051-7.
28. Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Combined measurement of synovial fluid α-Defensin and C-reactive protein levels: highly accurate for diagnosing periprosthetic joint infection. J Bone Joint Surg Am. 2014 3;96:1439-45.
29. Etienne G, Dupouy M, Costaglioli P, Chollet C, LagardeV, Pasquet JM, et al. α-defensin 1-3 and α-defensin 4 as predictive markers of imatinib resistance and relapse in CML patients. Dis Markers. 2011;30:221-7.
30. Jansen PA, Rodijk-Olthuis D, Hollox EJ, Kamsteeg M, Tjabringa GS, de Jongh GJ, et al. Beta-defensin-2 protein is a serum biomarker for disease activity in psoriasis and reaches biologically relevant concentrations in lesional skin. PLoS One. 2009;4:e4725.