Defensins usage as novel therapeutic and diagnostic approach

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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 kidney. 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-

Key points

Defensines are broad spectrum molecules that can become an effectiveness therapeutic and diagnostic agent at cancer and infectious patients.
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 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 defensins’ 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 can improve efficiency of antivirus because of overpowering tumor related suppress immunity/immune-tolerance (24). Defensins can play poten 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 synoval fluid (28). In addition, HBD2 and HNP5 may be used as prognostic biomarker of resistance to antitumor treatment (29,30).

Conclusion

According mentioned above, defensins 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.

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