

Defensin

S.Priyanka

First year BDS, Saveetha dental college and hospitals

Abstract:

Defensin is a small amino acid (cysteine) rich cationic proteins. The another name for defensin is HUMAN NEUTROPHIL PEPTIDES (HNP). They are found in both vertebrates and invertebrates and also in plants. Defensins are endogenous antimicrobial peptides (AMPs) produced by phagocytes and epithelial cells. They have multiple functions in host defence. The other activities such as chemoattraction of a range of different cell types to sites of inflammation. They are classified into alpha, beta, theta defensins. They play a role in mucosal defense. They act as natural inhibitors of HIV-1 infection. They are antibiotic peptides.

Key words:

Epigenetics, DNA methylation, Defensin gene expression

INTRODUCTION:

The human genome encodes as a minimum of 35 different defensin peptides which belong to two structurally different subfamilies, α - and β -defensins [1,2]. Human α -defensin genes and several β -defensin genes are clustered on the short arm of chromosome 8. Four of the six human α -defensin peptides, human neutrophil peptides (HNPs) 1–4, are found chiefly in neutrophils and other leukocytes. The other two, human α -defensin 5 and 6 (HD5 and HD6), are expressed in the small intestine by paneth cell [3]. HD5 is also produced in female genital tract by epithelial cells [4]. Defensins are universal antimicrobial peptide products of neutrophils (α -defensins) and epithelia (β -defensins) [5,6]. Defensins are 4kDa cationic peptides with a characteristic six cysteine/three disulfide bridge pattern and three domains present in a flexible aminoterminal loop, a central α -helix and a carboxy-terminal antiparallel β sheet [7].

hBD-3 is an antimicrobial peptide which contains chemotactic and immunomodulatory properties [8-12]. α -Defensins are cationic molecules produced by epithelial cells; these molecules have antimicrobial, as well as immunomodulatory activity [13-16]. Of the first three hBDs hBD-1, hBD-2, and hBD-3—hBD-3 has the greatest positive charge, the widest range of antimicrobial activity, and is the most salt-tolerant [17, 18]. hBD-3, like other AMPs, it does not damage host cell membranes while inflicting fatal membrane interruption to bacterial cells. The outer leaflet of bacterial membranes contains high numbers of negatively charged phospholipids, whereas eukaryotic outer leaflets contain neutral phospholipids as well as cholesterol [19]. These differences may no less than partially, account for the capacity of AMPs to kill microbes but not host cells [20].

STRUCTURE:

Defensins are crystal in structure, based on a central, three-stranded β -sheet core in spite of different sizes, residue distributions, and cysteine-pairing schemes. In mammalian peptides, the structures of various α -defensins and BDs have been determined, and it appears that each group represents a conserved scaffold, where the folding is apparently determined by the formation of the disulfides. This conserved, tertiary-structure scaffold allows the molecules to display considerably different surfaces and a

remarkable variation of cationicity, which ranges from neutral in mouse BD-2 to 11 in human BD-3. They reflect on their quaternary structure; some defensins form dimeric or oligomeric structures and monomeric [21]. The mature peptides of defensins are 30–45 amino acids in length and are amphipathic. Their net positive surface charge implies an initial electrostatic interaction between the peptide and negatively charged components of the bacterial cell wall, e.g. lipopolysaccharide or teichoic acid [22]. Four of these peptides, called human BD1 (hBD1; DEFB1), hBD2 (DEFB4), hBD3 (DEFB103A), and hBD4 (DEFB104), are mainly expressed by respiratory, gastrointestinal, and urogenital epithelial cells [23]. All four hBDs are cationic and 36 to 45 amino acids long and show similar folding and an invariable six-cysteine motif that gives rise to three disulfide bonds [24-28].

SIGNIFICANCE:

Once activated, most of the cells involved in both innate and cognate immune responses secrete soluble factors, including cytokines, chemokines, antibiotic peptides, which can directly irritate infectious microorganisms and/or contribute to the recruitment and activation of other immune cells [29,30]. In HIV infection, various host-derived soluble factors with antiviral activity have been described, which act by both specific and nonspecific mechanisms. These include chemokines such as RANTES, MIP-1 α , and MIP-1 β [31]. Cytokines such as the interferons, IL-10, IL-13, IL-16 [32]. Neutrophilic granulocytes are the major producers of α -defensins, which are stored at very high concentration in their azurophilic granules [33]. Neutrophils, the most abundant leukocytes in the circulation, are the first cells to infiltrate inflammatory sites and prominent components of inflammatory responses induced by viral infections [34-36]. The potential for hBD-3 to mediate APC activation may be important in bridging innate and adaptive defense mechanisms; hBD-3 also has antiviral effects, including an ability to cause down-modulation of HIV coreceptor (CXCR4) expression and to neutralize viruses directly [37-39]. Microbial products which cross the gut barrier are found at a higher concentration in plasma of HIV-infected persons compared with healthy donors [40-42]. Defensins can provide chemotactic signals to a variety of cells, including APCs at nanomolar concentration [43-45].

ROLE OF DEFENSINS IN HUMAN HEALTH:

Monocytes are recruited into inflamed tissues where these cells mature and mediate effect or functions[46,47]. hBD-3, at nanomolar concentrations, recruits monocytes via CCR2. hBD-3 induces maturation of these cells at micromolar concentration [48]. In certain diseases, i.e., psoriasis [49] and solid tumors [46], hBD-3 is found at high concentrations which cause the effects that may include membrane disruption leading to repair or death, as determined by the concentration of peptide. The role of antimicrobial peptides in bridging innate and adaptive defenses is becoming increasingly recognized. HBD-3 is expressed in the basal layer of the epithelium, there it may have greater access to submucosal tissues. At nanomolar concentration, HBD-3 causes chemotaxis via CCR2 interactions [50,51], and at higher concentrations, hBD-3 can mediate antimicrobial activity [52 -54] and APCs [55,56]

CONCLUSION:

Defensins are cationic proteins with multiple functions in host defence. Further research is required to investigate the properties and biological significance of defensins to give a broader and clear picture of its role in host defence.

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