defensins and cancer

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Abstract

In humans, endogenous Antimicrobial peptides (AMP) are part of the immune system and act against pathogens. Defensins compose a class of AMPs that have activity against gram-positive and -negative bacteria and viruses.their role in innate immunity as microbicidal and immunoregulatory agents that orchestrate cross-talk with the adaptive immune system, and, most recently, their association with cancer. Defensins produced by cells in the course of innate host defence serve as signals which initiate, mobilise, and amplify adaptive immune host defences. Linkage of defensins to weak tumour antigens potentiates their immunoadjuvant effects. Defensins use multiple cellular receptors, which endows them with the capacity to marshall adaptive host defences against microbial invaders recently, findings related to specific activation pathways of some of defensins have led investigators to associate them with pro-tumoral activity, contributing to a tumorigenic microenvironment. This review summarizes current knowledge of defensins to discuss their role in tumour growth, tumour monitoring and cancer treatment, is substantial interest in the identification of circulating human tumor-derived proteins in serum for the purposes of early cancer diagnosis

Introduction

The AMP are polypeptides of fewer than 100 amino acids contain a positive net charge (from +2 to +9), high lysine and arginine content, and a significant number of hydrophobic residues (≥30%) 1.

These properties permit the peptides to fold into amphipathic conformations upon contact with cell membranes, and the positively charged polar face help the molecules bind to the membrane through electrostatic interaction with the negatively charged head groups of phospholipids 2.

AMP have been isolated and characterized from a wide range of animal, plant and bacterial species and are known to play important roles in the host defence system and innate immunity 3

The history of AMPs dates back to 1922 with the discovery of lysozyme by Alexander Flemming. The first reported animal originated AMP is defensin, which was isolated from rabbit leukocytes in 1956 4. at the same time, it was also proven that human leukocytes contain AMPs in their lysosomes.

for mammals, there are two main genetic categories for AMP, have been implicated in antimicrobial activity of phagocytes, inflammatory and epithelial secretions. Defensins are widely distributed in epithelial cells and phagocytes, 5. Cathelicidins are structurally and evolutionarily distinct antimicrobial peptides that are similar to defensins in abundance and distribution 6

The great diversity of AMP differs from one animal species to another. In this review I will focuson on defensins because, defensins are particularly prominent in humans, as evidenced by the large number of expressed human genes 6 , the various forms that are present in human tissues, and the ubiquitous occurrence of defensins in inflamed or infected human tissues 1.

Subclasses and antimicrobial activity defensins

Mammalian defensins are cationic AMP, with relatively arginine-rich nonglycosylated peptides with a molecular mass of 3.5–4.5 kDa. Their structure typically contains three intramolecular disulphide bridges between six cysteine residues 7. As mentioned for AMP in general, the classification of defensins is based on their structure, which divides them into three groups: **α**-defensins, β-defensins, and θ-defensins. In **α**-defensins, intramolecular bonding occurs between cysteines 1-6, 2-4, and 8, whereas in β-defensins it is between 1-5, 2-4, and 3-6 9. Human defensins are produced in leukocytes and are also secreted by different epithelial cells and mucosal tissues. These human peptides have antimicrobial activity against a large number of gram-positive and -negative bacteria, fungi, and viruses 10. (table 1)

Although these disulfide bonds in cytheins appear to have a close relationship with microbial activity, it has been reported that the three disulfides or the order of connectivity is not an essential characteristic for activity in defensins, since even if cytokines defend them they still have antimicrobial activity 11.

α-Defensins	**sequence**
HNP-1	ACYCRIPACIAGERRYGTCIYQGRLWAFCC
HNP-2	CYCRIPACIAGERRYGTCIYQGRLWAFCC
HNP-3	DCYCRIPACIAGERRYGTCIYQGRLWAFCC
HNP-4	VCSCRLVFCRRTELRVGNCLIGGVSFTYCCTRVD
HNP-5	ATCYCRTGRCATRESLSGVCEISGRLYRLCCR

α-Defensins	sequence
HNP-6	TCHCR-RSCYSTEYSYGTCTVMGINHRFCCL

β-defensins	sequence
hBD-1	GNFLTGLGHRSDHYNCVSSGGQCLYSACPIFTKIQGTCYRGKAKCCK
hBD-2	GIGDPVTCLKSGAICHPVFCPRRYKQIGTCGLPGTKCCKKP
hBD-3	GIINTLQKYYCRVRGGRCAVLSCLPKEEQIGKCSTRGRKCCRRKK
hBD-4	EFELDRICGYGTARCRK-KCRSQEYRIGRCPN-TYACCLRKWDESLLNRTKP

α-defensins

The α-defensins were described, which have been isolated from the granules of polymorphonuclear neutrophil leukocytes. Because of their distribution in the granules of the leucocytes, they were named human neutrophil peptides 1-4 (HNP1-4) 12 They are constitutively produced by myeloid precursor cells. However, recent reports suggest that their production can be induced by activated CD8 T cells as well 13, in contrast, HD-5 and HD-6 are enteric defensins stored in the granules of Paneth cells, processing of 'pro-HD-5' is mediated by one or more isoforms of Paneth cell trypsin 24 . Although the main sites of human α-defensins production are leukocytes and Paneth cells, the human famale reproductive tract expresses HD-5, When induced to degranulate, neutrophils and Paneth cells release these α defensins locally 14.

These six peptides are human α-defensins, whose typical structure consists of 29-35 amino acids. (Table1) demonstrates the difference in structure between α- and b-defensins.

α-defensins are synthesized as inactive prepro-α-defensins whose maturation requires the cleavage of a signal peptide to produce pro-α-defensins. Then, the NH2-terminal neutralizing pro fragment is cleaved by cellular proteases [**???**,15,16]. Mature HNP-1, HNP-2 and HNP-3 appear to have similar bioactivities.

Mature HNP-1 3 are 3 kDa peptides comprising 6 characteristic, highly conserved cysteine residues and 3 intra-molecular disulfide bonds. HNP-2 is the smallest human defensin (29 amino-acids) and differs from HNP1 and HNP3 by the absence of only one, N-terminal amino-acid residue in HNP-1 is alanine and aspartate in HNP3 17

β-defensins

b-defensins are phylogenetically older and new family members continue to be identified, with approximately 40 potential coding regions on the human genome 18 . A computational search strategy identified 28 new human β-defensin genes in five syntenic chromosomal regions. At least 26 of the predicted genes were found to be transcribed. [**???**]: 23060878. hBD-1 was the first b-defensin discovered 19. Although hBD-1 expression is primarily restricted to epithelium, it has been detected in peripheral blood 20 and was originally isolated from plasma filtrates of patients with end stage renal disease [19,21]

Actualy the platelets express and release hBD-1 protein in response to S. aureus-derived toxins. Platelets have also recently been shown to express and release hBD-3 protein. 21

β-defensins were traditionally viewed as exclusively antimicrobial molecules, as their induction in response to diverse bacterial, viral, parasitic and fungal infections was widely reported [22,23]. β-

defensins are preferentially attracted to the negatively charged outer membranes of bacteria, with reported efficacy against bacteria, fungi and enveloped viruses. 24.

##Mechanism of Action

The classical mechanism of action of cationic AMPs, such as defensins, is the disruption of the anionic bacterial membrane 25 . This way, bacterial destruction occurs by the interaction between the electrostatic forces of positively charged amino acids and the negatively charged cell surface [8,26] .

Bacterial membranes are rich in negatively charged phospholipids, such as phosphatidyl-glycerol (PG), cardiolipin (CL), and phosphatidylserine (PS); these are 2þ 2þ stabilized by bivalent cations such as Mg+2 and Ca+2. Gram-negative bacteria have an additional lipopolysaccharide rich outer membrane, which stands as a barrier to the cytoplasmic membrane. On the other hand, human cells are rich in neutrally charged phospholipids, such as phosphatidylethanolamine (PE), phosphatidylcholine (PC), and sphingomyelin (SM). In humans, the interaction with AMPs is even less likely because of the presence of cholesterol, which affects the fluidity of phospholipids in the membrane and increases its stability [49].

As for the membrane-permeabilizing mechanism, different models of interaction have been proposed (a) Barrel- stave pore model, in which the HDPs form dimers or multi- mers that cross the membrane forming barrel-like channels (Matsuzaki et al. 1991; Ben-Efraim and Shai 1997); (b) Toroidal pore model, in which the peptide forms a monolayer by con- necting the outer and the inner lipid layers in the pore (Mor and Nicolas 1994); (c) Carpet model, where HDPs form a carpet-like structure covering the outer surface of the membrane acting like detergents disrupting the bacterial membrane (Oren and Shai 1998)

In a recent work, Mathew and Nagaraj proposed the ability of HD5 to strongly bind DNA as the basis of its mechanism of action, suggesting that this interac- tion may inhibit essential processes associated with DNA repli- cation, transcription or translation of important genes

the defensisn has more impliction, Defensin binding to viral attachment proteins could disrupt receptor interactions critical for viral entry into the cell. HNP1-3, HD5, and hBD-3 bind a recombinant viral glycoprotein (gB) of both HSV-1 and HSV-2, which correlates with the ability of these defensins to inhibit HSV-1 and HSV-2 entry and adhesion 27

Viral infection can also induce defensin expression. For example, human rhinovirus induces hBD-2 in primary human epithelial cell cultures, although hBD-2 has no direct antiviral effect on the virus 28. Another example of how defensins can not only attack the pathogen, but can also induce the response of the immune system is β-Defensins exert regulatory activity in host innate and adaptive immune responses. For example, mouse β-defensin 2 activates Immature dendritic cells (DCs) via Toll-like receptor (TLR4), triggering a Th1 lymphocytes response, and human β-defensin 3 activates Ag-presenting cells (APCs) via TLR1 and TLR2 in an NF-κB-dependent manner [29,30]

Now a day we continue to discover new functions of the defensins, and therefore the mechanisms of action have not yet been fully elucidated, for example studies report that the use of human defenses to regulate host metabolism and mitigate dyslipidemia, and non alcoholic fatty liver disease NAFLD pmid:30860877. however, hard work is still being done to try to understand all the functions of the defensins, as well as their mechanisms of action.

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