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 p@mid:12183052, 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 13.

These six peptides are human α-defensins, whose typical structure consists of 29-35 amino acids [14]. (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 [[**???**] ; 1339298 ; 8601627]. 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 14

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 15 . 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 16. Although hBD-1 expression is primarily restricted to epithelium, it has been detected in peripheral blood 17 and was originally isolated from plasma filtrates of patients with end stage renal disease [16,18]

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. 18

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 [19,20]. β-

defensins are preferentially attracted to the negatively charged outer membranes of bacteria, with reported efficacy against bacteria, fungi and enveloped viruses (21). 21.

Mechanism of Action

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