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Review

The increasing role of phosphatidylethanolamine as a lipid receptor in the action of host defence peptides

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ABSTRACT

Host defence peptides (HDPs) are antimicrobial agents produced by organisms across the prokaryotic and eukaryotic kingdoms. Many prokaryotes produce HDPs, which utilise lipid and protein receptors in the membranes of bacterial competitors to facilitate their antibacterial action and thereby survive in their niche environment. As a major example, it is well established that cinnamycin and duramycins from Streptomyces have a high affinity for phosphatidylethanolamine (PE) and exhibit activity against other Gram-positive organisms, such as Bacillus. In contrast, although eukaryotic HDPs utilise membrane interactive mechanisms to facilitate their antimicrobial activity, the prevailing view has long been that these mechanisms do not involve membrane receptors. However, this view has been recently challenged by reports that a number of eukaryotic HDPs such as plant cyclotides also use PE as a receptor to promote their antimicrobial activities. Here, we review current understanding of the mechanisms that underpin the use of PE as a receptor in the antimicrobial and other biological actions of HDPs and describe medical and biotechnical uses of these peptides, which range from tumour imaging and detection to inclusion in topical microbicidal gels to prevent the sexual transmission of HIV.

Contents

1. Introduction

The production of host defence peptides (HDPs) as a defence and survival strategy is practiced by organisms across the prokaryotic [1,2] and eukaryotic kingdoms [3,4]. HDPs from bacteria, more generally known as bacteriocins, inhibit the growth of similar or closely related bacterial strains and it is well established that many of these peptides utilise lipid and protein receptors in the

Abbreviations: AD, Alzheimer's disease; DMPE, 1,2-dimyristoyl-*sn*-glycero-3-phosphoethanolamine; HDPs, host defence peptides; HIV, human immunodeficiency virus; IAPPs, islet amyloid polypeptides; LPS, lipopolysaccharide; MD, molecular dynamic; PE, phosphatidylethanolamine.

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membranes of target bacteria to facilitate their antibacterial action [5–8]. For example, class I bacteriocins, or lantibiotics, such as nisin from *Lactococcus lactis*, are commonly used as food preservatives and are produced by a large number of Gram-positive bacteria to attack other Gram-positive bacteria [9,10]. These peptides commonly target lipid II, which is a major cell wall precursor, to exert their antimicrobial action through pore formation in target membranes and/or the inhibition of cell wall biosynthesis [11,12]. Other receptors, which promote the activity of bacterial HDPs are increasingly being reported [5–8] with most recent examples, including: the maltose ABC transporter for the class IIc bacteriocin, garvicin ML [13]; a Zn-dependent metallopeptidase for the class IId bacteriocin LsbB [14]; and an undecaprenyl pyrophosphate phosphatase for the class IIb bacteriocin lactococcin G [15].

HDPs produced by eukaryotic organisms are evolutionarily conserved, multi-functional components of innate immune systems that show potent activity against a wide spectrum of microbes [16–19] and cancer cells [20,21]. Numerous studies have shown that in the vast majority of cases, this activity involves membrane interactive mechanisms but in contrast to bacterial HDPs, the prevailing view has long been that these mechanisms do not require the use of membrane receptors [20–23]. However, this view has been increasingly questioned in the light of recent studies [20] and several investigations have suggested that the antibacterial mechanisms of a number of HDPs may utilise protein receptors to facilitate membrane translocation and interaction with cytoplasmic targets [24–26]. There is also increasing evidence that eukaryotic HDPs utilise lipid receptors in their antimicrobial mechanisms [23]. For example, it has been recently shown that lipoprotein in the outer membrane of Gram-negative bacteria serves as a cell surface receptor to promote the action of a number of HDPs against these organisms [27], including SMAP-29 from sheep [28], and CAP-18, and LL-37 from humans [29,30]. It has also recently been shown that interaction with microbe-specific lipid receptors is a key step in the antimicrobial action of a number of defensins [31–33], which are HDPs found across eukaryotes [34–42]. For example, lipid II has been shown to promote the inhibition of cell wall biosynthesis and antibacterial activity of some defensins [31–33], including: Cg-Defh1, Cg-Defh2, and Cg-Defm from the oyster, *Crassostrea gigas* [43], and plectasin from the fungus, *Pseudoplectania nigrella* [44]. However, when fungi are the targets of defensins, it has been demonstrated that fungal-specific sphingolipids can promote the activity of a number of defensins [31–33], as in the case of RsAFP2 from the plant, *Raphanus sativus*, whose interaction with glucosylceramides promotes fungal death by a variety of mechanisms, including membranolysis and apoptosis induction [45].

Currently, a major focus of research into the role of lipid receptors in the antimicrobial action of HDPs is phosphatidylethanolamine (PE), which is present at high levels in the membranes of Gram-negative bacteria and is also found in some Gram-positive bacteria [46]. PE is also ubiquitous in eukaryotic membranes, and is predominantly a constituent in the inner leaflet of the plasma membrane [47,48]. However, emerging evidence has shown that in addition to serving as a structural element in the bilayer, PE is translocated or redistributed across the membrane in a number of biological events [49,50] such as apoptosis and malignant transformation where membrane asymmetry is compromised and the lipid is exposed to the extracellular milieu [51]. Here, we review current understanding of HDPs that utilise PE as a receptor in their antimicrobial and other biological actions.

2. Amyloid-forming HDPs

It is well established that human Aβ40 and Aβ42 are the major amyloid forming peptides associated with Alzheimer's disease (AD) but currently, their normal physiological functions are unknown [52]. However, a major recent study presented strong evidence to suggest that this function may be to serve as HDPs in protecting the human brain against microbial infection [53]. Several authors have proposed that the ability of Aβ40 and Aβ42 kill bacteria involves binding to this lipid and the induction of amyloid-mediated membrane pore formation [54,55]. In addition to Aβ40 and Aβ42, a number of major amyloid forming peptides involved in neurodegenerative and other diseases are known to possess antimicrobial activity [55]; it has been proposed that PE-binding may also be involved in membrane pore formation by at least some of these peptides [56,57]. For example, the human islet amyloid polypeptides (IAPPs), which are involved in type II diabetes, have recently been shown to possess antibacterial activity that is associated with the ability of these peptides to oligomerise and thereby induce the disruption of bacterial membranes [58]. IAPPs have been shown to induce leakage in bacterial membranes using nucleation-dependent mechanisms of membrane pore formation that show many similarities to those of amyloidogenic HDPs [55,59]. Moreover, IAPPs were found to exhibit full cross-cooperativity with magainin 2, which is an amphibian AMP shown to form amyloid fibrils [60], in the induction of membrane leakage and inhibition of bacterial growth [59]. Studies on the membrane interactions of IAPPs found that their monomers had a weak affinity for membranes containing PE but amyloid fibres of the peptide interacted strongly and specifically with this lipid to induce high levels of membrane disruption *via* a pore-type mechanism [56].

3. Lantibiotics

Amongst the first PE-binding HDPs to be described were cinnamycin, duramycin, duramycin B and duramycin C, which are structurally related, class I, type B lantibiotics (Fig. 1A) [61,62]. These peptides are produced by some strains of the Gram-positive bacteria, *Streptomyces*, and exhibit weak activity against other Gram-positive organisms, such as species of *Bacillus*, which appears to involve the compromise of membrane integrity and/or function [61,63–65]. It is well established that cinnamycin and the duramycins have a high affinity and specificity for PE [61,62,66–70] and there is evidence to suggest that this affinity plays a role in the antibacterial activity of these peptides although this role has, as yet, not been fully elucidated [61,63–65]. However, consistent with this role for PE, it has been shown that the lipid is absent from the membranes of species of *Bacillus subtilis* and *Bacillus firmus* with resistance to duramycin [71,72]. One study suggested that this resistance mechanism is underpinned by the replacement of PE in bacterial membranes by its plasmalogen form, plasmenylethanolamine [73] but more recent studies have suggested that both duramycin and cinnamycin have a general ability to bind PE-lipids, including its plasmalogen form [74]. In addition, these HDPs also show a number of PE-mediated activities against eukaryotic cells [70,75–78], which contrasts to most lantibiotics whose activity is generally limited to bacterial cells [79,80], For example, cinnamycin possesses haemolytic ability [81] and appears to promote this ability by inducing the transbilayer movement of PE from the inner leaflet of erythrocyte membranes to be exposed on the outer surface of these cells [82]. More recent studies have suggested that duramycin also promotes the transbilayer movement of the lipid [74] and that binding of the peptide to PE exposed on the surface of pancreatic tumour cells led to the death of these cells *via* the disruption of the structure and/or function of the cancer cell membrane [83,84].

Cinnamycin and duramycin are by far the best characterised of the PE-binding, lantibiotics, in part, because they are one of the very few examples of small peptides with a three-dimensional

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