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Review

Role of lipids in the interaction of antimicrobial peptides with membranes

Vitor Teixeira [a,b,*], Maria J. Feio [b], Margarida Bastos [a]

[a] CIQ(UP), Departamento de Química e Bioquímica, FCUP, R. do Campo Alegre, Porto 4169-007, Portugal
[b] REQUIMTE, Departamento de Química e Bioquímica, FCUP, R. do Campo Alegre, Porto 4169-007, Portugal

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ABSTRACT

Antimicrobial peptides (AMPs) take part in the immune system by mounting a first line of defense against pathogens. Recurrent structural and functional aspects are observed among peptides from different sources, particularly the net cationicity and amphipathicity. However, the membrane seems to be the key determinant of their action, either as the main target of the peptide action or by forming a barrier that must be crossed by peptides to target core metabolic pathways. More importantly, the specificity exhibited by antimicrobial peptides relies on the different lipid composition between pathogen and host cells, likely contributing to their spectrum of activity.

Several mechanisms of action have been reported, which may involve membrane permeabilization through the formation of pores, membrane thinning or micellization in a detergent-like way. AMPs may also target intracellular components, such as DNA, enzymes and even organelles. More recently, these peptides have been shown to produce membrane perturbation by formation of specific lipid–peptide domains, lateral phase segregation of zwitterionic from anionic phospholipids and even the formation of non-lamellar lipid phases. To countermeasure their activity, some pathogens were successful in developing effective mechanisms of resistance to decrease their susceptibility to AMPs. The functional and integral knowledge of such interactions and the clarification of the complex interplay between molecular determinants of peptides, the pathogen *versus* host cells dichotomy and the specific microenvironment in which all these elements convene will contribute to an understanding of some elusive aspects of their action and to rationally design novel therapeutic agents to overcome the current antibiotic resistance issue.

Contents

* Corresponding author at: REQUIMTE, Departamento de Química e Bioquímica, FCUP, R. do Campo Alegre, Porto 4169-007, Portugal. Tel.: +351 22 0402511; fax: +351 22 0402659.
E-mail address: vitor.fcup@gmail.com (V. Teixeira).

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1. Introduction

The integrity of any eukaryotic organism depends not only on the proper expression of its genes but also on its ability to resist the action from invading microorganisms. It demands a structured and a functional immune system in constant interaction with the dynamic surrounding environment which in turn determines the ability of the host to prevent an infection.

In order to establish an infection, a pathogen must first overcome many surface barriers, such as physical and mechanical elements like skin, mucous membranes and the epithelia of the respiratory system or the gastrointestinal and genitourinary tracts [1]. In addition, there are also important chemical mediators of the immune system that constitute an effective arsenal to overcome the harmful action of microorganisms. Some of these chemicals and molecules include gastric juices, salivary glycoproteins, lysozyme, **antimicrobial peptides**, the complement system, cytokines and acute-phase proteins which possess antiviral, antifungal, antitumoral and immunomodulatory activities [1–3].

Antimicrobial peptides (AMPs) are a universal feature of the defense systems of virtually all forms of life, with representatives found in organisms ranging from bacteria to plants, fish, amphibians, insects, mammals, and even viruses [1,4–15]. They take part in an ancient, nonspecific innate immune system, which is the main defense mechanism for the majority of living organisms during the initial stages of an infection [1,16,17]. These peptides usually display a broad range activity as they act on bacteria, fungi, metazoans and other parasites, viruses and even cancer cells [18,19]. The importance of these mechanisms to host defense may vary between different sites (skin, oral cavity, gastrointestinal tract, respiratory system) within a particular organism and even between different organisms [1].

Antimicrobial peptides may be expressed constitutively or can be inducibly expressed in response to exposure to foreign microorganisms. Indeed, they may be expressed systemically, as observed for cecropins isolated from the hemolymph of bacteria-challenged moths and flies of the *Lepidoptera* and *Diptera* orders. They can even be localized in specific cell or tissue types in the body, most susceptible to an infection from a particular set of pathogens. For instance, histatins are the main representatives on major salivary glands in humans with bactericidal and fungicidal activities that contribute to the innate defense of the oral cavity and more recently as oral wound healing factors [20–22]. Plant defensins are more abundant on the epidermal cell layer and leaf primordial of the potato tuber, which is consistent with a role in first-line defense of vulnerable tissues [23]. Such compartmentalization has proved to be important according to the type and specificity of the invading organism, which naturally implies not only cell-specific regulation of expression but also a polarity in their distribution on the organism.

Antimicrobial peptides have typically 12–50 amino acids, a molecular mass less than 10 kDa, and possess 2–9 positively charged lysine or arginine residues that confer their overall positive net charge at physiological pH. Only a small number of acidic residues (aspartate and glutamate) are usually found in these peptides, presumably contributing to the increase of amphipathicity when present on the polar face [7,10,14,24]. Moreover, these immunity peptide mediators usually present up to 50% hydrophobic amino acids, contributing to the common amphipatic conformation that they tend to assume at the lipid membrane interface when interacting with the target cell [1,11,24–27].

Although these peptides are mostly recognized by their antibacterial activity, many studies have pointed out an increasingly recognized function as modulators of the innate immune response in higher organisms (Fig. 1) [1,2,28–30]. In fact, a number of properties that modulate the immune response have been attributed to these host defense peptides in many organisms, particularly in mammals. These include epithelial cell proliferation, enhanced wound healing, angiogenesis and the stimulation of chemokine production, regulation of the production of pro-inflammatory cytokines and direct chemotaxis of expression of many types of leukocytes [1] (Fig. 1). It has been known that many cationic peptides,

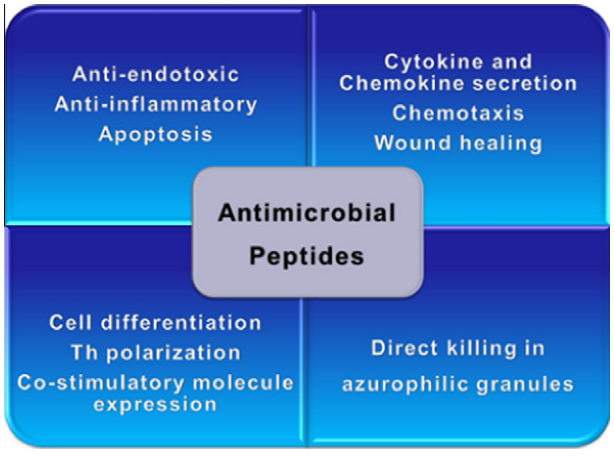

Fig. 1. Biological functions of antimicrobial peptides in immunity. Antimicrobial peptides are mostly recognized by their antibacterial activity (mainly mediated by membrane permeabilization and cell death) but many studies have provided evidence of their immunomodulatory functions in infection, such as chemotaxis, angiogenesis and regulation of the magnitude of the adaptive immune response by modulating the T_h cell polarization.