FEBS Letters 580 (2006) 5572–5579

Minireview

About lipids and toxins

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Received 6 July 2006; revised 8 August 2006; accepted 9 August 2006

Available online 28 August 2006

Edited by Bernd Helms

Abstract Many mono or multicellular organisms secrete soluble proteins, referred to as protein toxins, which alter the behavior of foreign, or target cells, possibly leading to their death. These toxins affect either the cell membrane by forming pores or modifying lipids, or some intracellular target. To reach this target, they must cross one of the cellular membranes, generally that of an intracellular organelle. As described in this minireview, lipids play crucial roles in the intoxication process of most if not all toxins, by allowing/promoting binding, endocytosis, trafficking and/or translocation into the cytoplasm.

Keywords: Toxins; Anthrax; Pore-forming; Cholera toxin; Lysenin; Raft

1. Introduction

Many pathogenic organisms produce protein toxins to kill or modify the behavior of their target eukaryotic host. These organisms include bacteria and parasites but also eukaryotes such as sea anemones. The mode of action of toxins can be very diverse. Some affect the plasma membrane by puncturing holes while other have lipase activity, such as sphingomyelinases or phospholipases, and thus modify the lipid composition of membrane and can lead to the production of second messengers such as ceramide. More of half of the known bacterial toxins however carry an enzymatic activity that is aimed at modifying a cytosolic target. These activities include ADP-ribosyl transferases, glucosylating enzymes, proteases, adenylate cylases. The targets are equally diverse and are general molecules that carry out or regulate key cellular functions such as protein synthesis, organization of the actin cytoskeleton, signaling or regulated membrane fusion. Although there might not always be a direct apparent link between these proteins and lipids, lipids or lipid domains play essential roles in the intoxication process of most if not all toxins. In the present minireview we will restrict ourselves to protein toxins, thus excluding peptides and venoms. Lipid modifying toxins (lipases) will also be excluded. A hand-full of well-characterized toxins have been selected to illustrate the importance of lipids in mediating toxin binding, multimerization when necessary, signalling, endocytosis and intracellular trafficking.

2. Brief description of selected toxins

Most of the minireview will be focused on the large family of pore-forming toxins (PFTs), the Anthrax toxin, Cholera and Shiga toxins and the vacuolating toxin VacA of *Helicobacter pylori*. The bird eye view of their respective mode of action is as follows. PFTs are produced by organisms as diverse as bacteria, parasite and sea anemones [1]. Although initially soluble, they have the capacity to form channels in target cell membranes, leading to the permeabilization to small ions and sometimes proteins. Examples include aerolysin from *Aeromonas hydrophila*, listerolysin O from *Listeria monocytogenes*, actinoporins from the sea anemones or lysenin from the earthworm *Eisenia fetida* (Table 1).

The other toxins dealt with in this minireview are so-called AB toxins. These toxins are either multidomain or multisubunit proteins, where the A subunit carries the enzymatic activity and the B subunit is responsible for target cell binding and escorting the A subunit to its final destination, generally the cytoplasm. Some of the relevant features of the AB toxins discussed in this review are summarized in Table 2. Cholera toxin is formed by a pentameric B subunit and an A subunit endowed with an ADP-ribosyltransferase activity that modifies the stimulatory Gsα subunit of heterotrimeric G proteins thereby interfering in the cAMP signaling in the cell, the consequence of which is an increased Cl^- secretion followed by water efflux leading to secretory diarrhea [2]. The B subunit of Shiga toxin is similarly pentameric, but its A subunit has an *N*-glycosidase activity capable of modifying the 28S rRNA thus impairing binding of elongation factors and inhibiting protein synthesis [3]. The B subunit of the Anthrax toxin, called the protective antigen or PA, is initially monomeric but undergoes heptamerization after a cellular surface proteolytic activation step. Heptameric PA subsequently acts as the receptor of the two enzymatic subunits: the lethal factor (LF), a metalloprotease that cleaves MAP kinase kinases, and edema factor (EF), a calmodulin dependent adenylate cyclase [4]. Finally *VacA*, is also thought of as an AB toxin because the protein is composed of two domains separated by a cleavage motif. No enzymatic activity has however been found for the A subunit which surprisingly has the ability to form anion selective transmembrane channels [5].

3. Lipids in toxin binding

Lipids allow or contribute to the binding of a wide range of toxins in a variety of ways. Some toxins use lipids as their

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0014-5793/$32.00
doi:10.1016/j.febslet.2006.08.033

Table 1
Toxin–lipid interactions

Toxin	Organism	Lipid	Interaction required for	References
Pore-forming				
α-toxin	*Clostridium septicum*	GPI-APs	Binding Oligomerization	[12] [13]
Actinoporins	Sea anemones	Rafts	Binding	[35]
Aerolysin	*Aeromonas hydrophila*	GPI-APs Rafts	Binding Oligomerization	[74] [33]
Cry11Aa	*Bacillus thuringiensis*	GPI-APs	Binding	[18]
Cry1A	*Bacillus thuringiensis*	Rafts	Binding	[37]
Cry 5B	*Bacillus thuringiensis*	Glycolipids	Binding	[11]
Intermedilysin	*Streptococcus Intermedius*	GPI-APs (CD59)	Binding Pore-formation	[29] [8]
Listeriolysin O	*Lysteria monocytogenes*	Rafts	Binding Oligomerization Signaling	[36] [40]
Lysenin	*Eisenia fetida*	Sphingomyelin Rafts	Binding Oligomerization Signaling	[10] [75] [41]
Perfringolysin O	*Clostridium perfringens*	Cholesterol Rafts	Binding Oligomerization pore-formation	[34] [29]
Streptolysin O	*Streptococcus pyogenes*	Cholesterol Rafts	Binding Pore-formation	[29]
Enzymatically active toxins				
Anthrax toxin	*Bacillus anthracis*	Rafts	Oligomerization Endocytosis Signaling	[57] [19]
Cholera toxin	*Vibrio cholerae*	GM1, rafts	Binding Endocytosis Signaling Trafficking	[6] [76]
Iota toxin	*Clostridium perfringens*	Rafts	Oligomerization Endocytosis	[77] [62] [63]
Shiga toxin	*Escherichia coli*	Gb3, rafts	Binding Endocytosis Signaling Trafficking	[7] [44] [39]
Tetanus toxin	*Clostridium tetani*	Rafts	Oligomerization Endocytosis	[16]
VacA	*Helicobacter pylori*	Rafts	Oligomerization Trafficking	[67–70] [78]

specific receptors. This is the case of Cholera toxin that binds to the ganglioside GM1 [6], Shiga toxin that binds the globoside Gb3 [7], the cholesterol dependent toxins (CDTs, such as streptolysin O, listeriolysin O and pneumolysin), which with some exceptions (see below, [8]) bind cholesterol [9] and finally the earthworm PFT lysenin which binds to sphingomyelin [10]. It was recently shown that glycolipids in *C. elegans* also act as receptors for the *Bacillus thuringiensis* pore-forming toxin Cry 5B, a toxin that specifically affects nematodes [11].

Other toxins use lipid-anchored proteins, namely glycosylphosphatidyl anchored proteins (GPI-APs), as receptors. Interestingly some toxins, such as the β-PFTs aerolysin and *Clostridium septicum* α-toxin, bind to the glycan core of the GPI-anchor, that separates the lipid moiety from the protein