Role of sPLA2-IIA in Infectious and Inflammatory Diseases

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Host molecules with antimicrobial properties belong to a large family of mediators including type-IIA secreted phospholipase A2 (sPLA2-IIA). The latter is a potent bactericidal agent with high selectivity against Gram-positive bacteria, but it may also play a role in modulating the host inflammatory response. However, several pathogen-associated molecular patterns (PAMPs) or toxins produced by pathogenic bacteria can modulate the levels of sPLA2-IIA by either inducing or inhibiting its expression in host cells.

bacterial toxins sPLA2 host immunity

1. General Biological Functions of sPLA2-IIA

Phospholipase A2 (PLA2) enzymes hydrolyze the sn-2 position of phospholipids, resulting in the production of free fatty acids and lyso-phospholipids [1][2]. These enzymes are classified into two major families: the low molecular weight-secreted PLA2 (sPLA2) and the high molecular weight intracellular PLA2, such as the cytosolic PLA2 (cPLA2) [1][2]. Based on the number and position of their disulfide bridges, sPLA2 can be classified into several different types, one of which is sPLA2-IIA. PLA2 have been shown to release free arachidonic acid (AA), the precursor of proinflammatory eicosanoids, and to bind to specific receptors present on host surface membranes [3][4]. Initially, sPLA2-IIA was suggested to play a role in the development of various inflammatory diseases [5][6]. For example, this enzyme can hydrolyze pulmonary surfactant phospholipids involved in acute respiratory distress syndrome (ARDS). In addition, sPLA2-IIA has been shown to induce neuronal apoptosis in ischemic stroke [7]. Other studies have also shown the involvement of sPLA2-IIA in atherosclerotic lesions [8][9][10], the hydrolysis of mitochondrial membranes released by platelets [11] and plasma lipoproteins [12]. sPLA2-IIA has also been shown to generate lipid mediators from membrane vesicles of platelets and erythrocytes [13].

Thus, it is clear that sPLA2-IIA can be involved in various pathophysiological processes, but its high bactericidal property (especially against Gram-positive bacteria) is now accepted as its most established biological role [5][6][14]. Therefore, it is important to explore the mechanisms by which bacterial toxins can modulate the expression of this enzyme and the pathophysiological consequences of this modulation.

2. PAMPs, Toxins and Innate Immune Response to Bacterial Infections

Pathogen-associated molecular patterns (PAMPs) are microbial motifs that are highly conserved across a wide range of pathogens. They are essential for the survival of these pathogens and their detection by host cells [15]. They include several virulence factors, such as lipopeptides, lipoteichoic acid (LTA) or peptidoglycans (PGN) of Gram-positive bacteria and lipopolysaccharides (LPS), pili or flagellin of Gram-negative bacteria as well as the double-stranded RNA (dsRNA) of certain viruses [16]. Recognition of PAMPs by specialized host cells is the first step in the host immune response, leading to an inflammatory response and elimination of the invading pathogens. This process involves the interactions of PAMPs with cellular receptors called 'pattern recognition receptors', or PRRs.

On the other hand, bacteria also produce a variety of toxins in response to various environmental challenges. These include exotoxins that are actively expressed and secreted into the extracellular media or injected into host cells during the infection process [17][18]. The interaction of pathogens with host cells initiates signaling processes that lead to the production of anti-microbial peptides (AMPs) by these cells. AMPs represent a large family of peptides ranging from 10 to 150 amino acids. In particular, 153 AMPs have been found in humans with net positive charges on the surface of the molecules [19], including defensins, cathelicidin, the type IIA secreted phospholipase A2 (sPLA2-IIA), etc. These antimicrobial molecules interact with bacteria to inhibit the synthesis of bacterial membrane phospholipids, cleave polysaccharides of the bacterial cell wall or increase the permeability of the bacterial membrane [19], which ultimately results in the eradication of the pathogens or the reduction of their proliferation. In particular, sPLA2-IIA has a high net positive charge of +17 [20]. **Table 1** shows the reported effects of some PAMPs and toxins on sPLA2-IIA expression by host cells (**Table 1**).

Table 1. Effects of bacterial PAMPs and toxins on sPLA2-IIA expression by host cells.

PAMPs	Bacterium	Host PRRs	Effect on sPLA2-IIA Expression		References
			gpAMs	BECs	
LPS	G−	TLR4 [a]	Upregulation [b]	No effect [c]	a [21], b [22], c [23]
Peptidoglycan	G+; G−	NOD1 [a], NOD2 [a]	Upregulation [b]	/	a [24], [25], b [26]
Lipoteichoic acid	G+	TLR2 [a]	No effect [b]	/	a [27], b [28]
Flagellin	G−	TLR5 [a]	No effect [b]	No effect [c]	a [29], b our unpublished data, c [28]
Pili	G+; G−	CD46, CD48, CD55, etc [a]	Upregulation[b]	No effect [c]	a [30], b [31], c [23]
HSP60	G+; G−	TLR2, TLR4 [a]	/	/	a [32]
CpG DNA	G+, G−	TLR9 [a]	/	No effect [b]	a [33], b [23]

PAMPs	Bacterium	Host PRRs	Effect on sPLA2-IIA Expression		References
			gpAMs	BECs	
HSL	G−	/	/	No effect [a]	a [23]
ExoS	G−	/	/	Upregulation [a]	a [23]
Adenosine	G+	Adenosine receptor [a]	downregulation [b]	/	a [34], b [28]
AC-Hly	G−	CD11b/CD18 integrin [a]	downregulation [b]	/	a [35], b [28]
Edema toxin	G+	CMG2 [a], TEM8 [a]	downregulation [b]	/	a [36], [37], b [26]
Lethal toxin	G+	CMG2 [a], TEM8 [a]	downregulation [b]	/	a [36], [37], b [26]

/: not tested; gAMs: guinea pig alveolar macrophages; BECs: bronchial epithelial cells. a–c: indicate the corresponding references in the table.

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The bactericidal activity of sPLA2-IIA is related to its ability to efficiently penetrate the cell wall of Gram-positive bacteria. This particular property is due to the high net positive charge of sPLA2-IIA (+17) [20], whereas Gram-positive bacteria have high net anionic charges due to the presence of the D-alanyl moiety covalently linked to lipoteichoic acid (LTA) [38], which is a major membrane component of Gram-positive bacteria. Thus, the highly efficient and rapid binding of sPLA2-IIA to LTA by electrostatic interaction promotes the penetration of sPLA2-IIA into the peptidoglycan layer, another major wall component of Gram-positive bacteria. This leads to efficient hydrolysis of bacterial membrane lipids and subsequent bacterial killing [14]. One study has reported a classification of mouse and human sPLA2 based on their ability to kill the Gram-positive bacterium *Staphylococcus aureus* [39] and showed that sPLA2-IIA is the most bactericidal sPLA2 type. Indeed, the concentration of sPLA2-IIA in human tears of healthy subjects exceeds 30 µg/mL, and only 15–80 ng/mL of this protein is sufficient to kill *S. aureus* [40]. Additionally, concentrations of sPLA2-IIA rapidly increase in host biological fluids as a result of inflammation or bacterial infection [4][41][42], as discussed in Part 4 of this section. These concentrations are virtually sufficient to kill all Gram-positive bacteria that may invade the host. Thus, sPLA2-IIA can be considered a major player in the host's innate immunity.

4. Role of the sPLA2-IIA in the Gut Microbiota–Lung Axis

Given its potent and selective antibacterial activity against Gram-positive bacteria, it is tempting to speculate that sPLA2-IIA might be involved in shaping the gut and pulmonary microbiota [43][44]. Indeed, two recent studies have investigated the influence of sPLA2-IIA on the gut microbiota [43][44]. Using gain- or loss-function assays, sPLA2-IIA was shown to play a central role in the composition of the gut microbiota by reducing the proportion of Gram-positive strains [43][44]. Most importantly, sPLA2-IIA-driven changes in the gut microbiota contributed to alterations in local and extra-intestinal immune responses, leading to increased susceptibility to cancer and arthritis [43][44]. This evidence suggests that intestinal sPLA2-IIA has profound effects on the host immune response through

modulation of the gut microbiota and it may also have an impact on the pulmonary immune response by influencing the airway microbiota. Interestingly, there is a privileged relationship and communication between the lung and the gut (known as the gut–lung axis) that is mediated by the microbiota [45], and the gut microbiota has been associated with immunity to viral and bacterial infections [45][46][47][48]. Therefore, future studies are needed to better address the specific role of sPLA2-IIA in microbiota changes and the associated effects on the gut microbiota–lung axis.

5. sPLA2-IIA Levels in Biological Fluids of Infectious and Inflammatory Diseases

sPLA2-IIA was originally identified in synovial fluid from patients with rheumatoid arthritis [49], suggesting its involvement in excessive inflammatory conditions, such as autoimmunity. Subsequent studies have reported elevated levels of sPLA2-IIA in biological fluids from inflammatory diseases, including ARDS [50], pancreatitis, sepsis, cardiovascular disease [4][41][42] and in nasal fluids from patients with allergic rhinitis [51]. ARDS is defined as a life-threatening lung injury characterized by non-cardiogenic pulmonary edema and arterial hypoxemia [50]. The alteration of pulmonary surfactant is a hallmark of ARDS, accounting for increased surface tension at the air–liquid interface, resulting in impaired gas exchange and alveolar collapse.

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