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Phospholipases in Bacterial Virulence and Pathogenesis

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Abstract

Phospholipases are ubiquitous hydrolases that catalyze the hydrolysis of phospholipids, a key component of eukaryotic cellular membranes. The metabolites generated after hydrolysis functions as secondary messengers that are further involved in signal transduction, membrane trafficking, cell proliferation, etc. These enzymes are considered as an important virulence factors, as they help the bacterial pathogens in number of ways like host cell invasion, modulating the phospholipid content of their membrane, and so on. Also, these enzymes are crucial for the pathogenesis of certain bacteria because of their role in escape from the host defence mechanism. This review is focused on different diversity of PLs and their role in pathogenesis and virulence in bacterial infection.

Keywords: Phospholipase; Virulence; Pathogenesis; Host cell invasion; Lipid droplet; Phosphatidylcholine; Drug target

Abbreviations: PLA: Phospholipase A; PLB: Phospholipases B; PLD: Phospholipase D; SAM: Sterile Alfa Motif; SG: Src Homology; PMN: Polymorphonuclear Cells

Introduction

Infectious diseases are caused by bacteria, fungi, viruses, or parasites. These may be communicable, acquired from contaminated food or water, or may spread by insect bites, etc. A number of bacteria reside inside the human host harmlessly and some of them are even beneficial, but there are some bacteria that are responsible for causing disease under certain conditions. Few of the bacterial infections are deadliest like tuberculosis [1], acinetobacter infections, memingitis, salmonellosis, etc which claim lives of a number of people every year. Antibiotics are used as the medication for their treatment as they interfere in the processes that are crucial for bacterial survival. But in due course of time, bacteria become resistant to these antibiotics and it becomes difficult to control these infectious diseases [2]. So, by having the complete knowledge of the whole process of bacterial infections and various virulence factors that are responsible for their pathogenesis, it would be easier to combat the disease. These microbial pathogens invade the host defense mechanism by using a number of genetic strategies [3]. The bacteria use multiple virulence factors that enable the bacteria to replicate, colonize, and disseminate within the host. In the process of bacterial pathogenesis, the bacteria have to invade the host cell which can involve enzymes and toxins [4]. Phospholipases (PLs) are reported to be one of the enzymes involved in host cell invasion in a number of diseases [5].

Phospholipids and phospholipases

Phospholipids are the key component of cellular membrane that provides the binding site for both cellular and extracellular proteins. They are derivatives of glycerol-3-phosphate that is esterified at its carbon (sn-1 or sn-2) positions to non-polar fatty acids and at its phosphoryl group to a polar head group composed of nitrogenous base, inositol unit or glycerol [6]. Metabolites such as arachidonic acid (ARA), diglycerol that are generated after the catalysis of phospholipids by PLs can function as lipid mediators or second messengers that are involved in the membrane trafficking, cell proliferation, signal transductiona and apoptotic cell injury [7]. PLs are a ubiquitous group of hydrolases which are involved in the family of lipolytic enzymes that catalyze the hydrolysis of phospholipids into fatty acids and other lipophilic substances.

Phospholipases (PLs) are a heterogeneous group of enzymes which cleaves the ester bonds of phospholipids. They are mainly associated with the cell membranes and membrane-bond vesicles and are responsible for the destabilization of membranes and cell signaling [8,9]. The product release by the hydrolysis of phospholipids by PLs has been reported to play an important role in host cell penetration and cell lysis. Moreover, they are active component of bacterial toxins and also found in arthropod poisons and snake venoms [8]. The various functions

of PLs range from catalysis of nutrients to the formation of bioactive molecules. PLs are critical to life because of their diverse functions [10]. They have been implicated as virulence and pathogenic factors in many pathogenic microorganisms [11-13]. Consequently, PLs of many pathogenic bacteria have also been associated with cell death and exhibits cytotoxic effects on human macrophages [14,15].

The PLs are diverse in the site of action on phospholipids molecules and therefore they are classified into 4 types namely A, B, C and D (Figure 1) (Table 1). Phospholipase A (PLA) is further classified into two subtypes A1 that cleave the acyl ester bond at sn- 1 position and A2 cleaves at sn- 2 position. On the bases of cellular localization the isozymes of PLA1 is divided into two groups i.e. intracellular and extracellular enzymes (Figure 2) [16]. Similarly, PLA2 has been sorted into 5 main types that further contain different groups (group I-XV) (Figure 3) [17]. Some PLs hydrolyze both acyl groups and are termed the phospholipases B (PLB), also known as lysophospholiapse [18]. Enzymes grouped under phospholipase C (PLC) cleaves glycerophosphate bond on the glycerol side, while phospholipase D (PLD) catalyses the removal of base group on the polar side of phospholiapse [19,20]. The PLC and PLD are therefore also known as phosphodiesterases. Till now, 13 PLC isoenzymes have been identified that are grouped into six different subfamilies (Figure 4) [20]. There are two isoforms of PLD (Figure 5). In addition to bacteria, PLD has been reported in many plants, viruses, worms, flies and yeast [21].

Table 1: Types and properties of phospholipases.

S.No	Types	Subtype	EC number	Cleavage site in phospholipids	Product
1	Phospholipase A (PLA)	PLA1	3.1.1.32	SN-1 acyl chain	Fatty acid and lysophospholipd
2		PLA2	3.1.1.4	SN-2 acyl chain	Arachidonic acid and lysophosphatidic acid
3	Phospholipase B (PLB)			Both SN-1 and SN-2 acyl chain	
4	Phospholipase C (PLC)		EC 3.1.4.3	Before phosphate	Diacylglycerol and a phosphate-containing head group
5	Phospholipase D (PLD)		EC 3.1.4.4	After Phosphate	Phosphatidic acid and an alcohol

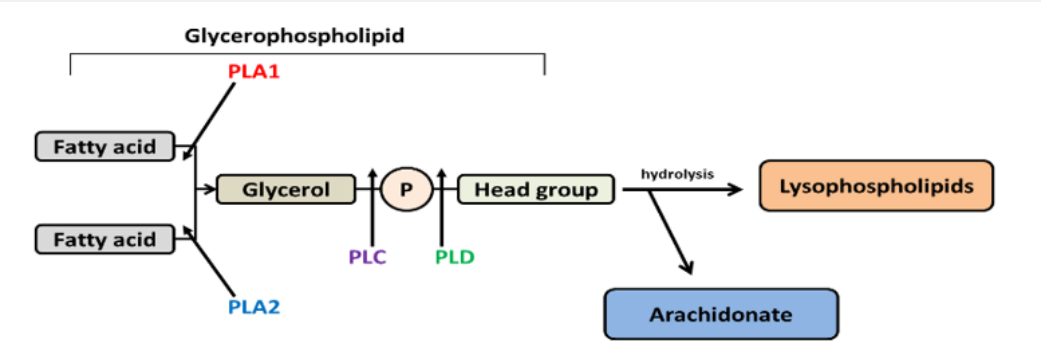

Figure 1: Site of action of different phospholipases in phospholipid molecule.

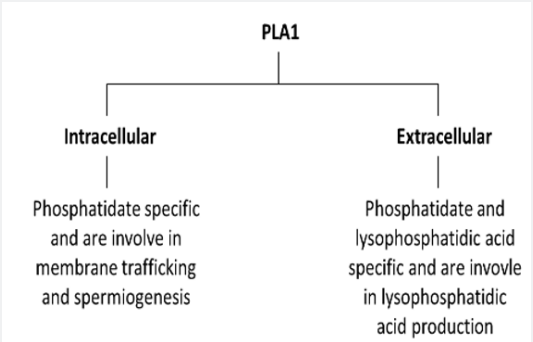

Figure 2: Isoforms of PLA1 and their function.

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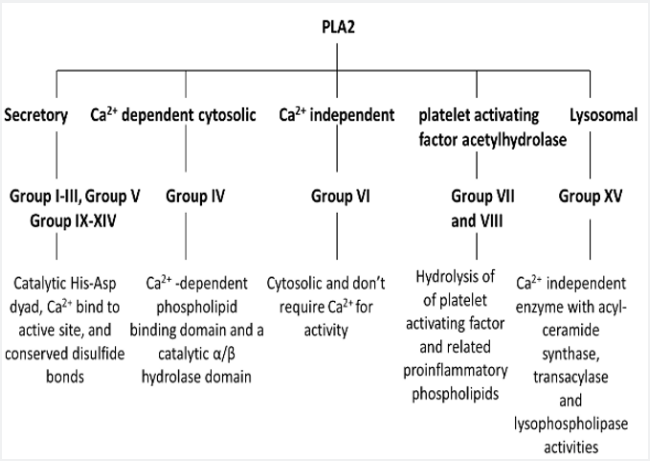

Figure 3: Types of PLA2 and their role.

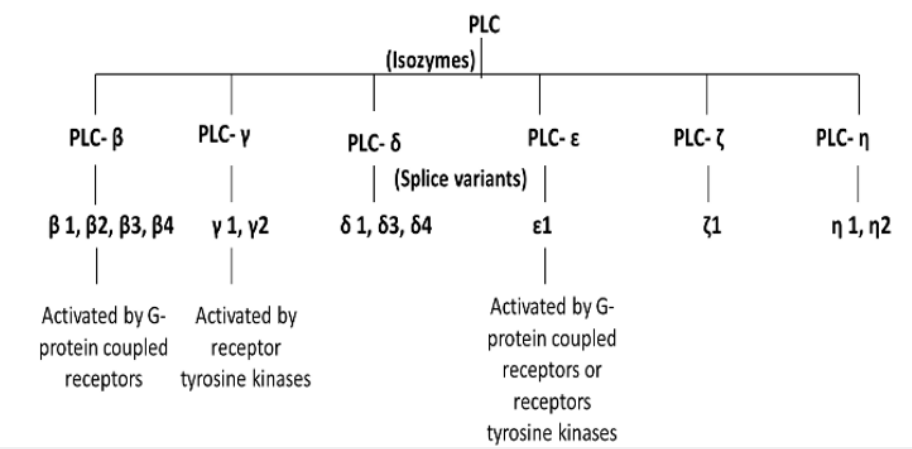

Figure 4: Isozymes and different splicing variants of PLC.

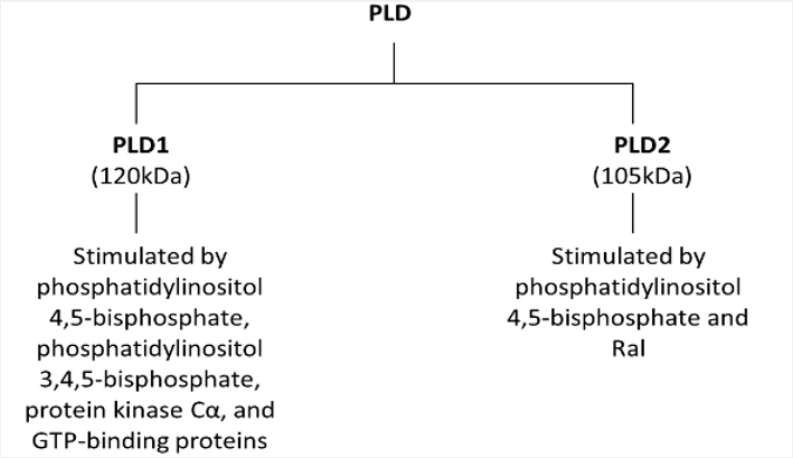

Figure 5: Isoforms of mammalian PLD.

Structural analysis

It is very important to understand the three dimensional structure of enzyme to examine its significant role in the pathophysiology of the microorganisms in disease. PLA1 contains the lipase consensus sequence (Gly-x-Ser-x-Gly), a catalytic triad (Ser-Asp-His) with serine at its active site and shares a multiple conserved motifs. Intracellular PLA1 mainly contains DDHD domain and some of them have a sterile alfa motif (SAM) which is important for the binding of enzyme to the intracellular membrane [22]. Extracellular PLA1 contains surface loops known as lids, β5 loops and β9 loops. Subfamilies present in secretary PLA1 mainly varies due to the length of lids

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and β9 loops. Notably, PLA1 that posses triacylglycerol hydrolase activity generally have long lids (22-23 amino acids) and long β9 loops (18-19 amino acids), whereas PLA1-α and PLA1- β that do not exhibits triacylglycerol hydrolase activity contain short lids (7-12 amino acids) and β9 loops (12-13 amino acids) [23].

PLA2 belongs to the α/β hydrolse family. β- sheets are generally present in the enzyme core whose strands are interconnected by α- helices and catalytic serine is present in tight turn between α/β strand. Secreted PLA2 contains His-Asp catalytic diad and a Ca2+ binding site, whereas cytosolic PLA2 contains Ca2+ dependent phospholipid domain and its active site is covered by the cap region [24]. Plasma platelet activating factor-acetylhydrolase and Lysosomal PLA2 contains lipase motif (Gly-x-Ser-x-Gly), the catalytic Ser-Asp-His triad, and serine active site. They also contains the N-glycolation site and an N-terminal signal sequence [25].

PLC contains X and Y catalytic domain that comprise highly conserved amino acid regions in isozymes. They are located between EF-hand motif which is a helix-turn-helix structural domain that binds Ca2+ ions and C2 domain that also contains three to four Ca2+ binding sites and regulates the enzyme activity. It has been shown that plekstrin homology (PH) domain is located in the N- terminal region and it provides the passage onto the membrane surface [20]. PLC- β and PLC-γ contains an additional COOH- terminal and SH domain respectively that is responsible for the membrane attachment and in mitogenic signaling [20]. PLD contains the sequence motif HXK(X)4D, which is found twice without exception in all known isoforms of enzyme and denoted as HKD motif [21]. This motif has been involved in signal transduction and lipid biosynthesis in many pathogenic bacteria [26]. Phox consensus sequence (PX), the (PH) domain is the other highly conserved regions which are involved in lipid binding [27].

Mechanism of action

The PLA gene family member shares a multiple conserved motif that includes G-X-S-X-G motif, a catalytic triad and cysteine residues that moderated disulphide bond formation. It contains the N-terminal signal sequence followed by catalytic triad with Ser154, Asp178, and His249. Glycosylation is critical for the catalytic activity and four acceptors sequences of N-glycosylation sites are present at amino acid 50, 58, 66 and 357 positions [28]. The catalytic action of PLA2 proceeds through the Serine–acyl intermediate that is present in a pentapeptise sequence G-L-L-G-S using serine-228 as nuclephilic residue. This catalytic serine residue is termed as "nucleophilic elbow". It has been reported that in addition to Serine-288, Asp-549 and Arg-200 is also found to be essential for the activity [24].

The X and Y structural domain of PLC are responsible for the catalytic activity of the enzyme. Based on the structural analysis it has been reported that Lysine-438, Lysine-440, Serine-522 and Arginine-549 are present at active site which are implicated in the binding with the phosphate group [20]. PH domain moderates the binding of enzyme to phospholipids. PLC-γ contains the long amino acid sequence that contain Src homology (SG) domain which mediated the interaction with other proteins [29]. Phospholipase D crystal structure reveals that it contain two motif from single active site and the histidine residue from one motif acts as a nucleophile in the catalytic mechanism of the enzyme forming an intermediate of phosphoenzyme whereas, the histidine residue of second motif cleaves the phosphodiester bond [26]. PH and PX domain also plays an important role in the catalysis of enzyme. PH domain helps in the localization of the protein whereas; PX domain is thought to mediate the protein- protein interaction. The lysine residue conserved in the structure is involved in phosphate binding [27].

Role in virulence and pathogenesis: Several bacteria and fungi produce extracellular phospholipases, which helps them to invade the host by damaging its cell membrane [8,30,31]. The presence of their activity is generally associated to the virulence of the pathogen. The strains of Candida albicans with highest phospholipase activity showed the greatest mortality in mice [8]. Also, only phospholipase activity was predictive of mortality among a number of candidate factors in C. albicans [32]. It has been reported that Aspergillus fumigatus was able to produce different type of phospholipases like PLA, PLB, PLC, and PLD [33]. Different phospholipases that play an important role in bacterial virulence and pathogenesis are mentioned in Table 2.

Table 2: Different bacteria possessing different type of phospholipases.

Organism	Phospholipase type	Function of enzyme	References
Pseudomonas aeruginosa	PLC	Colonization of tissues	[45]
C. perfringens	PLC (alpha toxin)	Host tissue invasion	[34]
Clostridium novyi	PLC (gamma toxin)	Hemolytic activity	[46]
L. monocytogenes	PLC	Bacterial escape from phagosomes	[37]
Pseudomonas cepacia	PLC	Hemolytic activity	[47]
Staphylococcus aureus	PLC (beta toxin)	Hemolytic activity	[48,49]
Bacillus cereus	PLC	Protects against phagocytosis	[50]
M. tuberculosis	PLD, PLA, PLC	Role in virulence and pathogenesis	[38,51,52]
Rickettsia prowazekii	PLA	Host cell invasion	[53,54]

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Arcanobacterium haemolyticum	PLD	Virulence determinant	[55]
Cryptococcus neoformans	PLB	Necessary for central nervous system infection	[56]
Yersinia enterocolitica	PLA2	Promoting colonization	[57]
Campylobacter coli	PLA	Haemolytic activity	[58]
Yersinia pseudotuberculosis	PLA	Host cell invasion	[59]
Helicobacter pylori	PLA1	Host cell membrane disruption during invasion	[60]
Campylobacter jejuni	PLA	Promoting colonization	[61]
Legionella pneumophila	PLA	Bacterial detoxification of lysophospholipids	[62]
Legionella pneumophila	PLB, PLC, PLD	virulence	[63,64]
Campylobacter concisus	Membrane bound PLA	Haemolytic activity	[65]
Neisseria meningitides, N. gonorrhoeae	Outer membrane associated PL	Autolysin	[66]
A. baumannii	PLD	Virulence and Host cell invasion	[36]
Plasmodium falciparum	PLA2	Brain swelling	[67]
B. melitensis	PLA1	Polymyxin resistance and pathogenicity	[35]
S. pneumoniae	PLA2	Pulmonary inflammation	[39]
Vibrio vulnificus	PLA2	Lysis and necrotic death of epithelial cells	[68]

Phospholipases are important virulence factors as they are able to cleave phospholipids in eukaryotic membranes and the products might act as signaling molecules, which ultimately leads to a number of events to occur favorable for the pathogen [14]. They help the bacterial pathogens to invade the host cells by destroying the phospholipids of cell membranes. The role of α-toxin (PLC) was confirmed when α-toxin mutant from a virulent strain of Clostridium perfringens was unable to cause tissue damage and necrosis in mice hind limbs after inoculation [34]. Also, they modulates phospholipid content of cell envelope of certain bacteria, which would be helpful for the pathogenesis of bacteria like PLA1 of Brucella melitensis is responsible for the resistance against polymyxin B and also contributed to host-pathogen interactions [35]. There are three PLDs in Acinetobacter baumannii and are major virulence factors as they are required for host cell invasion. All three PLDs were necessary for the full invasion and virulence as they work in concerted manner, confirmed when the inactivation of all three pld genes leads to the minimum invasion efficiency [36]. Moreover, they play an important role in pathogenesis of intracellular pathogens as they help the bacteria to escape from phagosomes in certain cases. Two PLC were found in Listeria monocytogenes which aid the bacterial escape from phagosomes as this was confirmed by creating its mutants. The individual mutants of plcA or plcB were two and 20 fold, respectively, less virulent, but a double mutant was 500-fold less virulent in mice deciphering the significance of this enzyme for the virulence and pathogenesis of the bacteria [37].

The intracellular lung pathogen, Mycobacterium tuberculosis also possessed phospholipases which are important for its virulence and pathogenesis too. There are four genes (plcA, plcB, plcC, plcD) that encode PLC enzyme. Mutation studies demonstrated that all four genes were required to encode a functional PLC. The expression of these genes was upregulated during first 24 hr of infection suggesting the role of PLC in the virulence of the bacteria [38].

Sometimes, they are very crucial to the pathogens that without them bacteria would be unable to survive in the host. One such example is the PLA2 enzyme of Streptococcus pneumoniae which elicits pulmonary inflammation during infection and is also required for lethal systemic infection [39]. PLA2 enzyme inhibitors almost blocked (diminished by >80%) the polymorphonuclear cells (PMN) transepithelial migration in vitro [40]. Also, PLA2-deficient mice were survived from S. pneumoniae bacteremia challenge which was otherwise lethal to wild-type mice [41]. The byproducts of this enzyme catalysis lead to the formation of certain metabolites that aid in the inflammatory processes and in that case phospholipase inhibition could be a more effective anti-inflammatory approach [42]. Like bacteria, snake venom is enormously rich in these enzymes and their inhibitors could prevent skeltel muscle necrosis and permanent injuries in snakebite victims [43].

They also play anabolic roles. There are two PLA2 that are pivotal in lipid droplet formation in case of Hepatitis C virus infection (HCV). Their knockdown studies showed that their function were irreplaceable and could not be restored even on complementation with each other and lipid droplet formation activity was also found to be impaired. These two PLA2 were found to be play an important role in HCV replication and pathogenesis and they could be a target for an anti-HCV drug [44-68].

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Conclusion

Phospholipids are key components of cell membrane of all eukaryotes. The pathogens vary in their preference for the usage of carbon sources during host colonization like mucus sugars, amino acids, lactic acid and many more [69]. In human host, phospholipids are abundant as they are the major building blocks of biological membranes. So, they serve as good candidate for carbon and energy source for the pathogens. Among them, phosphatidylcholine accounts for 50% of all phospholipids and its prevalence is upto 80% in the lungs [70,71]. During lung infections by pathogens like A. baumannii, P. aeruginosa, M. tuberculosis; phosphatidylcholine serve as nutrient source [72,73]. The pathogens must possess certain enzymes for the utilization of these phospholipids and phospholipases are such enzymes. The role of phospholipases in the virulence and pathogenesis of the disease is equally diverse as they are a diverse group of enzymes. These enzymes are involved in various processes like host cell membrane disruption [10], promote colonization [57], detoxification of toxic lipids [62], cell signaling, etc. They also help bacteria in various ways to cause disease in host and in some infections, these are the key enzymes. So, phospholipases could be used as probable drug targets to combat different bacterial infections.

The different approaches may include the development of vaccines, identification of various enzyme inhibitors, and identification of agents that inhibit the production of enzyme. In today's world, high throughput screening of small molecular inhibitors could also be possible in very short time [74]. As phospholipases are critical to some bacterial pathogens, their inhibition by various inhibitors could lead to the diminished virulence and they could be used as probable drug targets to combat the bacterial infections in future.

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