Review Article

BIOLOGICAL MODE OF ACTION OF PHOSPHOLIPASE A AND THE SIGNALLING AND PRO AND ANTI INFLAMMATORY CYTOKINES: A REVIEW

Abstract

It is degraded to free triglycerides and fatty acids by the secreted phosphatases of the plant family (sPLA2s). Plants have very few sPLA2s. Plant sPLA2s' molecular, biochemical, and catalytic properties are being studied. Three-dimensional structures are also included when comparing the two groups. Glycine max is used as a benchmark for comparing various organisms, including any herbal plants and small animals. In addition, they can be used as a type of signalling molecular. The functions of SPLa2 enzymes are well understood, however their ligand activities remain a mystery. Since the last review, sPLA2-binding proteins have evolved dramatically. Promiscuous SPLa2 proteins exist in nature for evolutionary reasons that we describe. As sPLA2s have a wide range of roles in the human body, they appear to be suitable therapeutic targets. New diagnostic and therapeutic techniques can be developed by using sPLA2s to interact with other proteins.

Keywords: Mutations, SPLA2, Phospholipase, Clinical Implications, Ligands

1.1 Introduction

Phospholipases A2 (PLA2) are a wide family of enzymes that hydrolyze fats in the body, releasing fatty acids and lysophospholipids [1]. PLA2s are biochemically classified as cytosolic (cPLA2), secretory (sPLA2), or Ca2+-independent (Ca2+-independent) [1, 2]. PLA2 enzymes are important functionally because they synthesise signalling lipids and regulate inflammation. The PLA2-catalyzed fatty acids (eicosanoids) have been linked to many inflammatory diseases [2,3,4] and PLA2. Polymorphonuclear cells (PMNs) are the first line of defence against germs and fungi. Despite their vital involvement in inflammation, neutrophils' relevance in cancer is still debated (1, 2). Despite the new statistics, the traditional opinion says that the high number of neutrophils generated from bone marrow each day (1011) is balanced by their short half-life in the bloodstream (up to roughly 12 hours) (4) . The human neutrophil population (up to 70% of circulating leukocytes) is not represented in mice, where neutrophils range from 10% to 25% of white blood cells (5, 6). PLA2 catalysis produces lysophospholipids and other bioactive lipid molecules [5]. Early studies identified PLA2s as a helpful marker of acute lung injury (ALI) in humans. There has been a lot of research done on PLA2s since then, especially on their role in

regulating inflammation[6]. The lungs can be damaged by direct lung injury (pneumonia), indirect injury (sepsis), or both. Inflammation can be caused by Staph aureus, Strep pneumoniae, influenza, acid (aspiration), or harmful mechanical pressures (such as positive pressure ventilation). As a result of the protein-rich fluid and uncontrolled inflammation, severe hypoxemia and respiratory failure occur. An effort is being made to identify potential therapeutic molecular targets for ALI. In 1961, the Enzyme Commission (EC) classified 3.1.1.4 phospholipase A2 (PLA2) processes. A literature search revealed 28,700 papers on phospholipase A2 [2][3,4]Prof. Ed Dennis and colleagues codified the enzyme class in a naming system based on structural and functional properties after discovering that PLA2 enzyme activity was shared by a wide superfamily of proteins [3,4]. PLA2s, cytosolic PLA2, calcium-dependent PLA2, platelet activating factor acetylhydrolases, and the lysosome-bound PLA2s were all included in this system's classification of active enzymes. Since there are currently nine sPLA2 enzymes that are expressed in the human body (i.e. IB, IIA and IID, IIE and IIF), they are divided into groups IB, IIA and III. Phosphatidylinositol 3-kinase 2 (PIIA)[5] is the subject of this review, and a history of some of the most important findings linked to this enzyme is depicted in Figure 1.

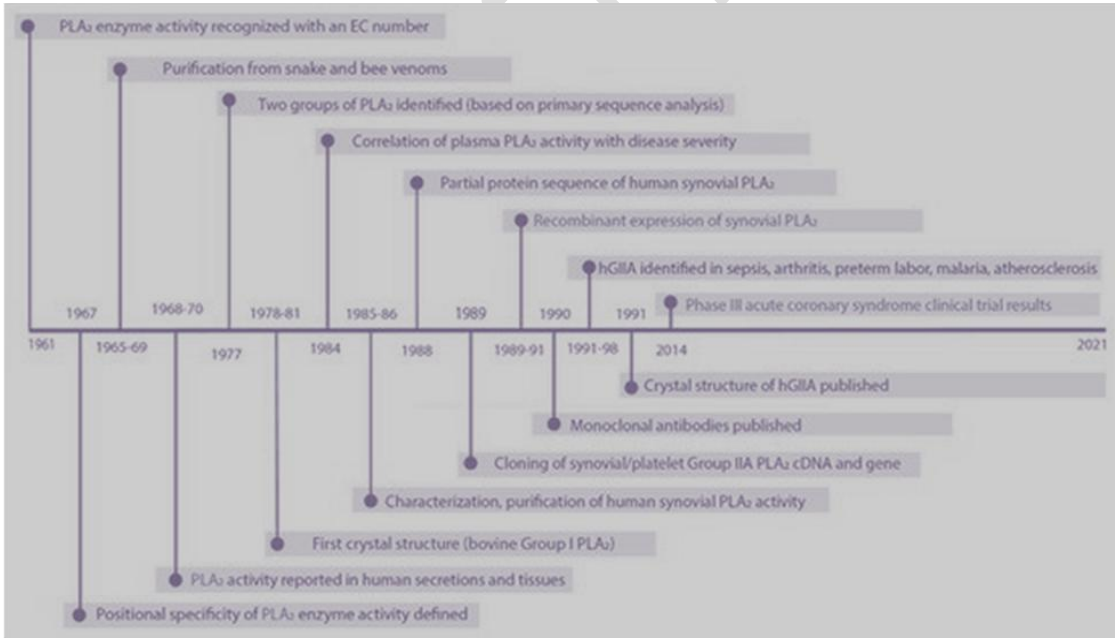

Fig. 1: Timeline of major discoveries in hGIIA drug development [5]

Exosomes, for example, are endosomal-derived vesicles of 30 to 150 nm in diameter that can communicate between cells. When the endosomal membrane fuses with the plasma membrane, they are released into the extracellular area. Antibodies contain specific signals that can affect target cell immunity[9] The PLA2 esterase family hydrolyzes the sn-2 position of glycerophospholipids to produce free fatty acids and lysophospholipids. Except for group III subtype, which has N- and C-terminal extensions, and at least six highly conserved disulfide connections in the N- and C-terminal sections.[10] They have been shown to be highly conserved in all known human sPLA2 proteins (Figure 2). In the active site, Hes48 forms a dyad with Asp99 (His48), which is conserved among subtypes of the enzyme.[11]

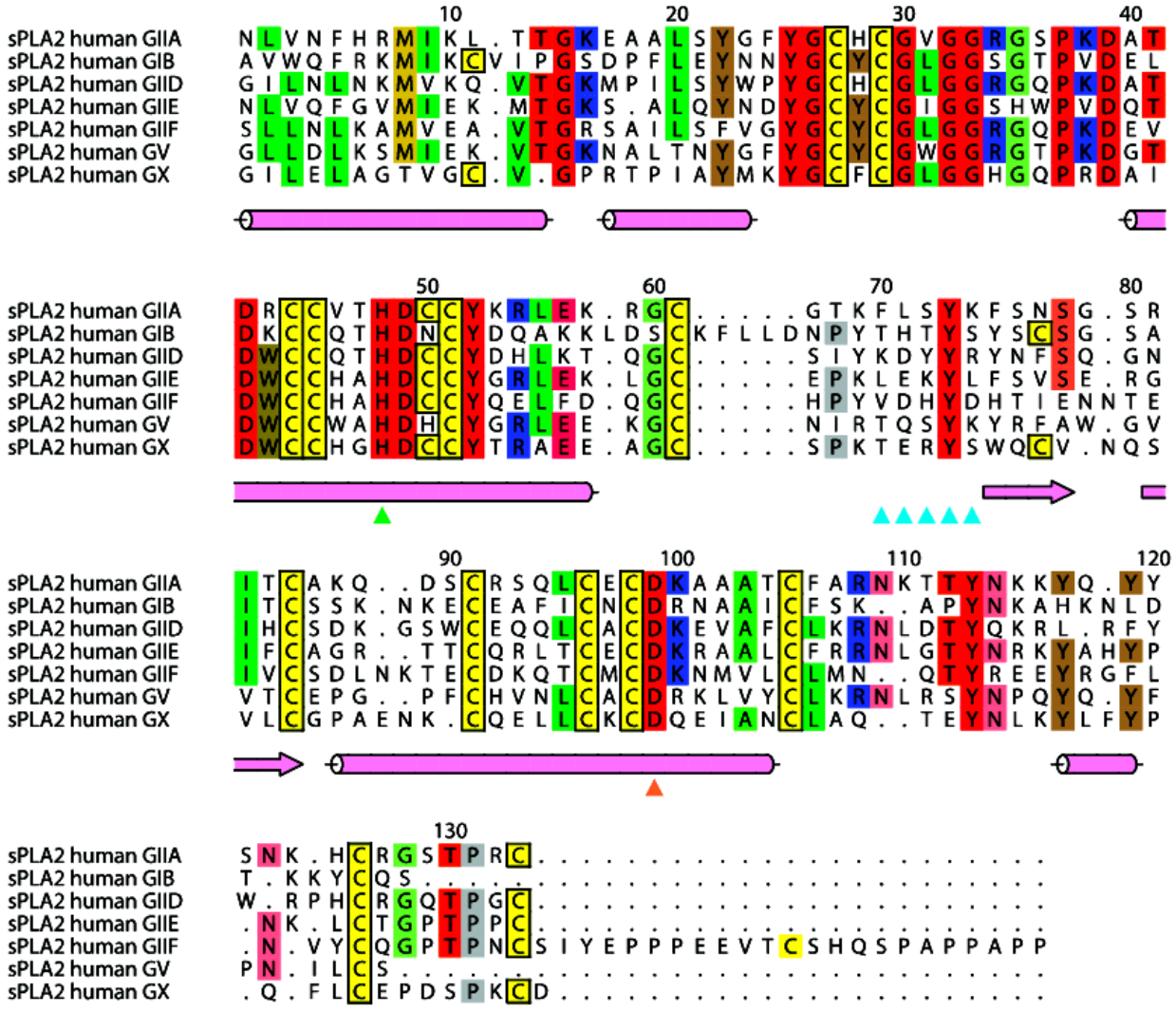

Fig: 2 Seven secreted phospholipases A2 were compared. The active site, calcium binding, and disulfide bond have high sequence conservation. All Cys are highlighted in yellow, while the proteins as a whole are marked in red to show complete conservation. Disulfide bonding Cys are boxed. Other amino acids with four or more identities are highlighted and coloured by amino acid type. There are several important locations in the sequence highlighted with triangles: catalytic HIS (green), catalytic ASP (orange), calcium binding loop (blue) (cyan) (cyan). The position of the FLSYK is represented with blue triangles. Renetseder et al. [4] adopted this numbering scheme for hGIIA, but it cannot be relied upon for the other entries. Assembled with ALINE

1.2. PLA2 Secretary Structure

The secreted PLA2 (sPLA2) families contain about a third of the isoforms. (IB, IIA, IIC, IIE, IIF, III, V, X, XIIA, and XIIB) are all calcium-dependent isoforms found in mammals. The bulk of secretory [12] PLA2s are sub-20 kDa proteins. Protein sequence identity separates Groups III and XII. As shown in Figure 3, all sPLA2s have the same calcium binding domain and the same disulfide-stabilized tertiary structure.[13]

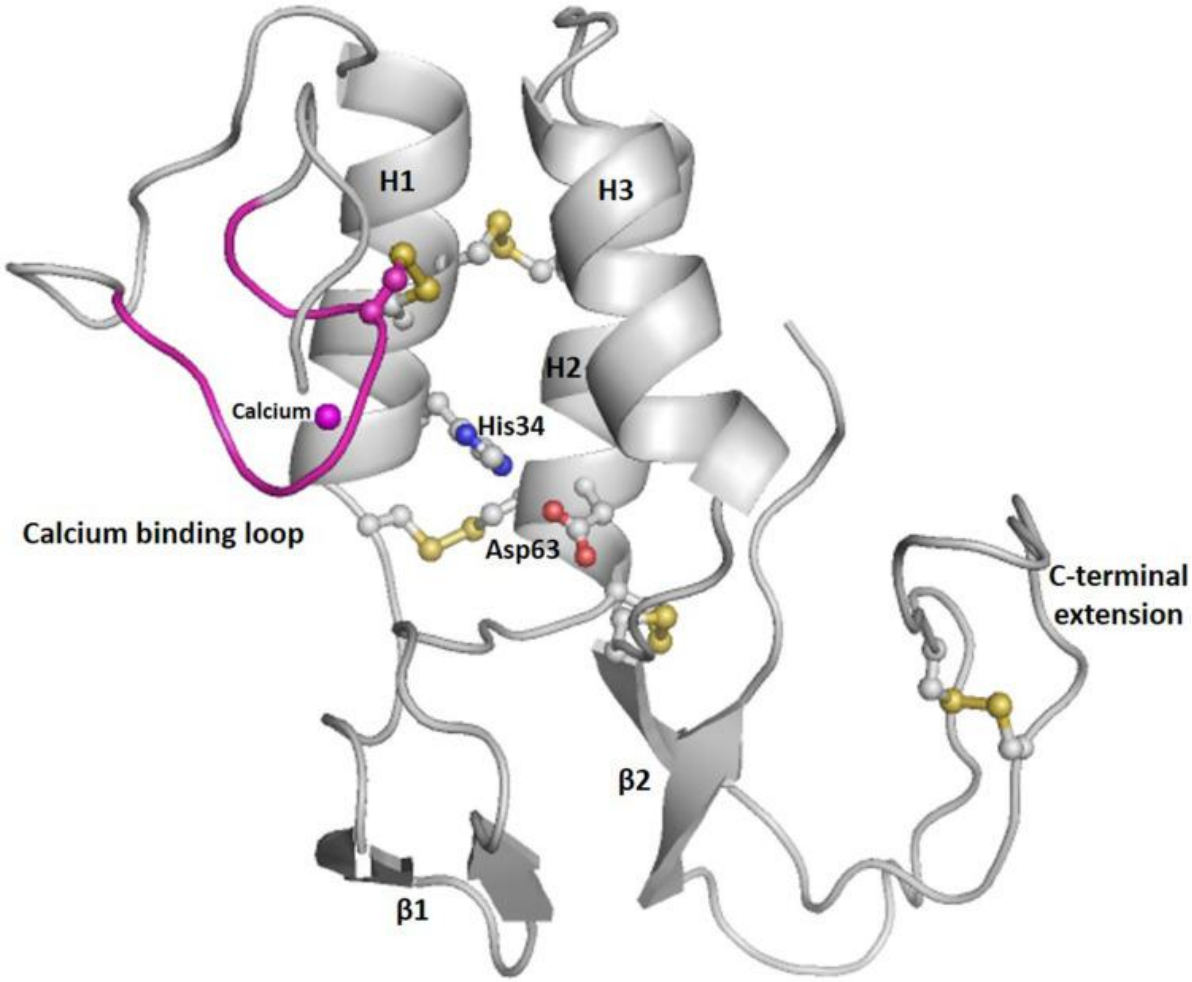

Fig 3: The human sPLA2 prototype (group III PLA2) is shown as a ribbon. Calcium binding loop (pink) with both calcium (sphere in magenta); active site to residues histidine 34 and aspartic acid 63; C-terminal extension; and stabilised by five disulfide bonds (yellow) (yellow). The structure of the human group III PLA2 sequence (Q9NZ20) is shown on Pymol[13]

The stereochemical mechanism of sPLA2 is similar to that of serine proteases. [14] A conserved water molecule acts as an attacking nucleophile on the sn-2 bond. A conserved histidine in PLA2's active region removes a proton from the N1 water molecule. The histidine's positive charge is maintained by a large hydrogen-bonded network that contains aspartic acid carboxylate and tyrosine phenolic groups. Keep in mind that the sPLA2 enzyme family includes nonanalogous backbone positions for aspartate and tyrosine at the active site. The sPLA2 catalytic residues are histidine, aspartate, and single/dual tyrosine. This type of catalytic machinery is found in most sPLA2 groups, including I, II, IV, V, X, and XII. [15–18] In the human

group III sPLA2 (human), the phenylalanine's aromatic ring fails to form hydrogen bonds with either the histidine or the aspartate nearby. Thus, tyrosine is not required for the stabilisation of the aspartic acid residue at the active site of PLA2. 7 sPLA2 from the liver fluke parasite exhibits standard histidine-aspartic acid-tyrosine hydrogen bond forming hallmarks. [19] To build unique therapeutic drugs against the parasite Clonorchis sinensis, this structural divergence between the target enzyme and the housekeeping human isoform can be exploited. [20]

However, stable multichain complex forms observed in reptiles and scorpions, including homodimers, homotrimers, and heterodiglycans, lack quaternary conformations.[21,22] Scorpion sPLA2 has a disulfide connection connecting it to the primary enzyme subunit, while human GIII sPLA2 has a comparable C-terminal extension.[12,13] However, bisindole compounds and anionic molecules have been shown to promote dimerization in certain sPLA2.[23,24]

1.3. The Function of sPLA2-IIA in ALI

Many clinical and preclinical studies indicate sPLA2-IIA function in ALI/ARDS [11, 19]. Multiple studies have indicated higher sPLA2-IIA mRNA and protein expression in ARDS patients' BAL fluid and plasma [20–23] Recently, sPLA2-IIA levels were found to be elevated in COVID-19 patients' plasma and associated to disease severity [25]. Many ALI-pathogenic cells, including alveolar macrophages and epithelial cells, generate sPLA2-IIA when stimulated with inflammatory mediators including endotoxins and TNF [20, 26]. In vivo, sPLA2-IIA increases ALI-induced respiratory distress and surfactant PG hydrolysis when directly injected into the lungs [27, 28]. This link between sPLA2-IIA and ALI development prompted research into the therapeutic potential of inhibiting this enzyme. LY315920Na/S-5920, a small molecule that specifically inhibits sPLA2-IIA, has been shown to reduce lung injury in animal models of ALI and sepsis[29, 30]. As previously stated, sPLA2-IIA has significant bactericidal effects and protects against infections [14]. sPLA2-IIA inhibition may thereby impair the host's defence against bacterial infections, worsening bacterial-induced ALI. Despite extensive research on sPLA2-IIA, additional research is required to understand its pro- and anti-inflammatory effects in regulating ALI. An isoform of the sPLA2-II family, sPLA2-IID (or PLA2G2D), may be involved in the spread of respiratory infections. Aged CD11c+ cells (alveolar macrophages and respiratory dendritic cells) produce sPLA2-IID, whereas middle-aged mice lacking sPLA2-IID are protected

from SARS-CoV infection[32]. Lung damage was minimised, and survival increased in the absence of sPLA2-IID. SPLA2-IID expression increased in lung CD11c+ cells, resulting in increased eicosanoids involved in the initial immune response [33].

1.4. An Enzymatic Activity of PLA_2

Clinical and preclinical studies show that sPLA2-IIA may play a significant role in the development of ALI/ARDS.[34] Patients with ARDS and patients with early ARDS both have sPLA2-IIA protein and transcripts in their bronchoalveolar lavage (BAL) fluid, according to independent investigations. Researchers have discovered that the presence of high levels of plasma sPLA2-IIA in COVID-19 patients correlates with a more severe form of the disease. For now, it's evident that more research is needed to better understand how sPLA2-IIA controls ALI in terms of its pro-and anti-inflammatory effects.[35] Despite this, it's clear that further research is needed. Since EVs are well-established vehicles for long-range transmission of mRNA across tissues and cell types, we wondered if sPLA2-IIA mRNA was also present in the BAL fluid of early ARDS patients linked with exosomal type EVs.[36] In this study, QRT-PCR was used to determine sPLA2-IIA (sPLA2-IIA) mRNA levels in the BAL fluid of early, late, and non-ARDS patients.[37]

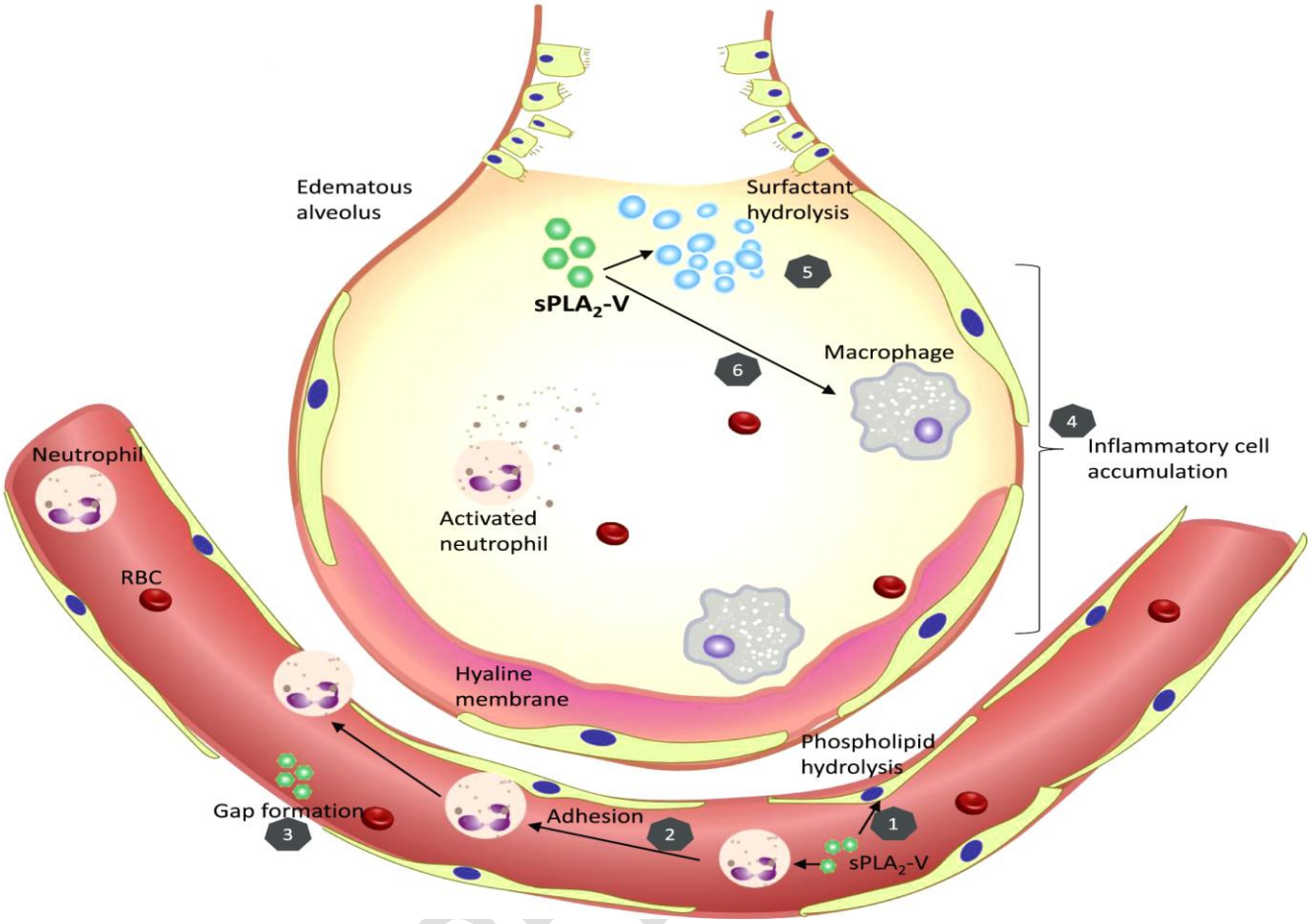

Fig. 4: sPLA2-V plays a role in acute lung injury. The lung endothelium expresses sPLA2-V (green hexagons), which directly hydrolyzes phospholipids to promote inflammatory processes (1) These include neutrophil activation, lung EC adhesion, and migration into the interstitium and alveolar space (2). sPLA2-V also causes gap development and increased vascular permeability in the lungs (3). sPLA2-V is raised in the alveolar space during ALI, contributing to alveolar damage, hyaline membrane formation, edoema fluid buildup, and inflammatory cell recruitment (4, 5). sPLA2-V may also influence macrophage phagocytosis (6). (online drawing in full colour)[34]

2.1. $sPLA_2$ Mutations and Weight Loss in Patients with Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic inflammatory disease that causes coughing, dyspnea, and wheezing.[35] Cardiovascular failure, anaemia, GERD, sadness, anxiety, osteoporosis, and weight loss can all be caused by the disease's impact on heart and air exchange function. [36] Cachexia is a loss of muscle and fat tissue caused by systemic inflammation in COPD. [37] It is clinically significant since it impacts a patient's everyday activities, quality of life, and prognosis. TNF and

interleukins are pro-inflammatory mediators related with weight loss.Patients with COPD, on the other hand, had varying weight loss and pro-inflammatory mediator levels. [38,39] In other words, systemic pro-inflammatory stimuli increase the production of the sPLA2 GIID protein in different tissues, including the lung. [40] G80S is a missense mutation in a loop that generates the IBS. Due to its open conformation, the mutant enzyme has a greater affinity for the M-type receptor than the wild-type sPLA2. [41] Thus, the G80S mutation in human sPLA2 GIID increases the production of cytokines like (IL-1, IL-6, and TNF) may be involved in weight loss.[42]

2.2. Other Diseases Caused by $sPLA_2$ Mutations

This gene encodes a phospholipase A2 enzyme, which catalyses fatty acid release from phospholipids.[43] Transmembrane ion flux in glucose-stimulated B-cells, leukotriene and prostaglandin production, and phospholipid remodelling may all be impacted by the encoded protein. Secretory phospholipase A2 IIA (sPLA2) is one of the most well-studied inflammatory proteins. Despite its association with neurodegenerative diseases, no direct proof of its expression in diseased human brains has been found.[44] In this study, Alzheimer's disease patients' brains had higher levels of sPLA2-IIA mRNA than older adults without dementia (ND). Also observed in higher amounts in the AD hippocampal and inferior temporal gyrus (ITG) were The ITG study linked amyloid-containing plaques to most astrocytes positive for sPLA2-IIA.[45,46] In human astrocytes, oligomeric A1–42 and interleukin-1 (IL-1) increased sPLA2-IIA mRNA expression, showing that inflammatory cytokines can activate this gene. New therapy strategies to suppress sPLA2-IIA overexpression in AD brains are required to delay disease progression and reduce inflammation.[47] Exogenous sPLA2-IIA causes neuronal injury. FCMTE is caused by the A159T mutation in sPLA2GVI, an autosomal recessive epilepsy gene.[48] Two PAF-AH mutations reduce substrate affinity and thereby enhance PAF concentration, resulting in increased B cell survival and IgE levels. The PAF-AH enzyme R92H mutation in the eastern Chinese Han population has been associated with ischemic stroke.[48] Other sPLA2s and their roles in ALI are unknown. Like sPLA2-X, it can be activated by cleaving an inactive proenzyme. Pseudomonas aeruginosa-infected alveolar epithelial cells produce sPLA2-IB, a lipid exporter that enhances PC efflux via ABCTA1.[49,50] People who have ALI have more of the sPLA2-IB splice variant. This suggests that the splice variant is linked to the disease's cause.

Future Prospects and Conclusion

Biochemically, enzyme-oxidised lipids are PUFA or cholesterol derivatives that act as signalling mediators and hormones. Enzymes like LOXs, COXs, CYPs, and AKRs help make them. Enzyme research has revealed new lipid mediators and metabolic routes. Several enzymes and their byproducts require more study. In the future, lipidomics will likely improve, allowing researchers to better apply their results to medicine. Some of the sPLA2s that are important in human illnesses may be targetable with future study. It's safe to assume that higher expression, extracellular levels, and unique biologic activities of various isoforms in the lung compartment are associated with sPLA2 pathology. There is no effective treatment for the sPLA2 family of enzymes, despite their importance in Acute lung Injury(ALI). sPLA2 promotes inflammation in mammals by breaking down phospholipids and forming fatty acids, notably arachidonic acid. Inflammatory and thrombogenic molecules are formed from arachidonic acid. sPLA2 biology and their role in disease regulation are not well understood. There are certain specialised study topics that may benefit from further research. PLA2s' increased expression and sensitivity to pharmacological therapy suggest a role in ARDS diagnosis. But clinical studies must prove proof of concept. We believe that network biology can bring new insights into the monitoring mechanisms of ARDS growth and dissemination as well as new medication discoveries. BAL fluid from mechanically ventilated patients with or without ARDS contains exosomes with biochemical and physical characteristics. ARDS has neutrophil infiltration in the inflamed lung. Activated neutrophils cause oxidative stress, produce proteases, and form NETs, causing lung damage. Neutrophils, on the other hand, help heal damaged lung tissue.

Conflict of Interest

The authors are having no conflict of interest.

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Author Contributions

Conceptualization, Data curation, Writing – review & editing done by All Author Contribute equally in Manuscript.

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