Review Article

ROLE OF PHOSPHOLIPASE A2 RECEPTOR AND NEUTROPHILS IN HUMAN CELL BIOLOGY

Abstract

Sn-2 glycerophospholipid is hydrolyzed to lysophospholipids and free fatty acids by a new family of plant enzymes known as secreted phospholipases (sPLA2s). Few sPLA2s exist in plants. Research into plant sPLA2s' molecular, biochemical, and catalytic properties Phylogenetic, evolutionary, and three-dimensional structures are also taken into account in the comparison. Plants, animals, and various types of SLP2s are all compared to Glycine max. Phospholipases A2 (sPLA2s) secreted by cells are enzymes that bind to membrane and soluble receptors. They also operate as signalling molecules. SPLa2 enzyme roles are well known, but their ligand actions are still a mystery to researchers. sPLA2-binding proteins have evolved significantly in the decade since the last review was conducted. The use of more accurate analytical techniques has led to the discovery of new sPLA2-BPs. SPLa2 proteins are promiscuous in nature, and we explain why this is advantageous to evolution. Pla2-BPs appear to be involved in cell transport, signalling, and control over Pla2 activity. sPLA2s appear to be ideal therapeutic targets because of their wide range of functions in the human body. We show that sPLA2s can be used to develop new diagnostic and therapeutic strategies by interacting with other proteins.

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

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. 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]. Every year since the early 1990s, some 1700 new publications have been added to the database, with no signs of slowing down. They named PLA2 enzyme activity after its structural and functional features [3,4]. This approach identified two active enzyme classes: secreted PLA2 (sPLA2) and cytoplasmic PLA2 (cPLA2). PAF acetyl-hydrolase (platelet activating factor acetylhydrolase). Humans express sPLA2 enzymes from groups IB, IIA, IID, IIE, and IIF. The remaining sPLA2 enzymes are in groups X and XIIA. hGIIA) phospholipase A2 (hGIIA) has been studied extensively in recent decades, as illustrated in Fig 1.

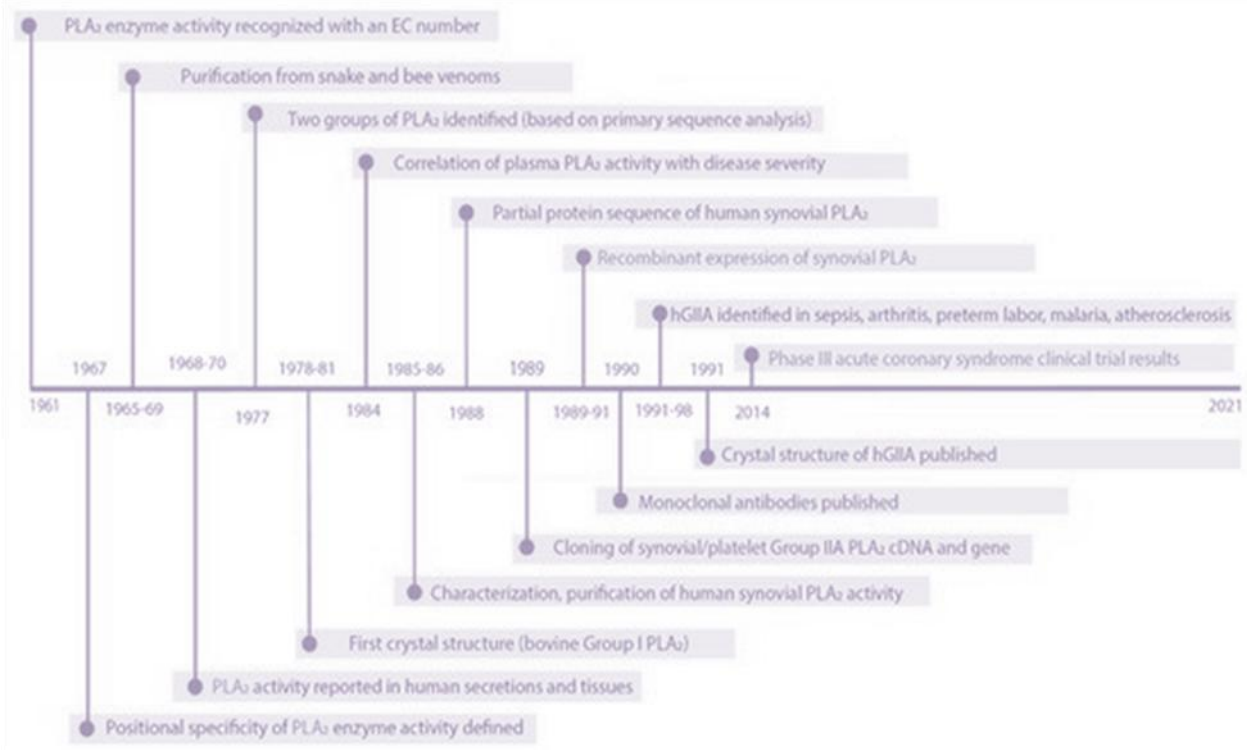

Fig. 1: Timeline of major discoveries in hGIIA drug development

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.

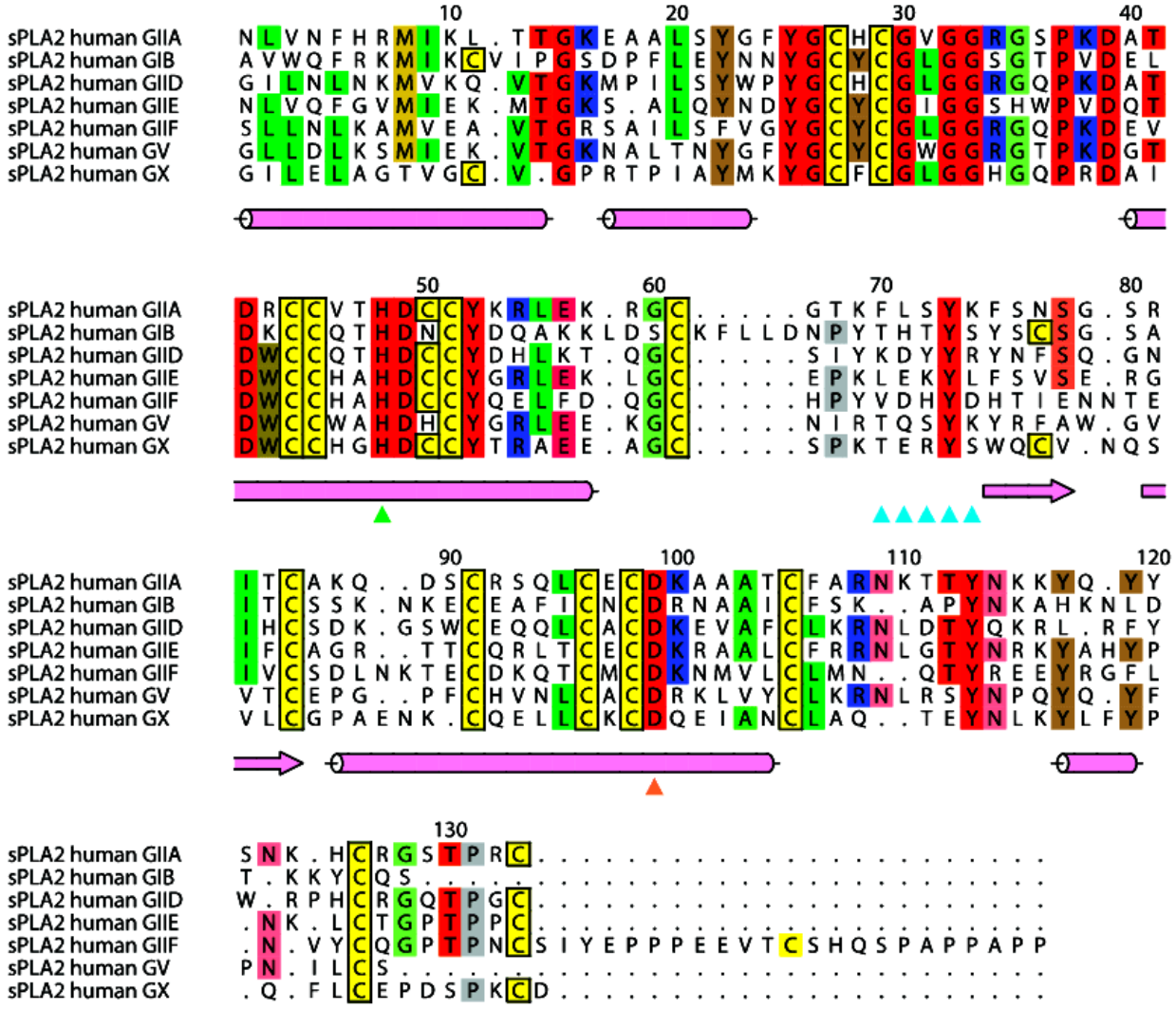

Fig: 2 Comparison of seven secreted phospholipases A2, The active site, calcium binding, and disulfide bond have substantial sequence conservation. Complete conservation among these proteins is displayed in red, except that all Cys are marked in yellow. Disulfide bonding Cys are boxed. Other amino acids with four or more identities are highlighted and coloured by amino acid type. There are other crucial sites in the sequence shown with triangles: catalytic HIS (green), catalytic ASP (orange), calcium binding loop (blue) (cyan). Using ALINE to create this fig

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 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.

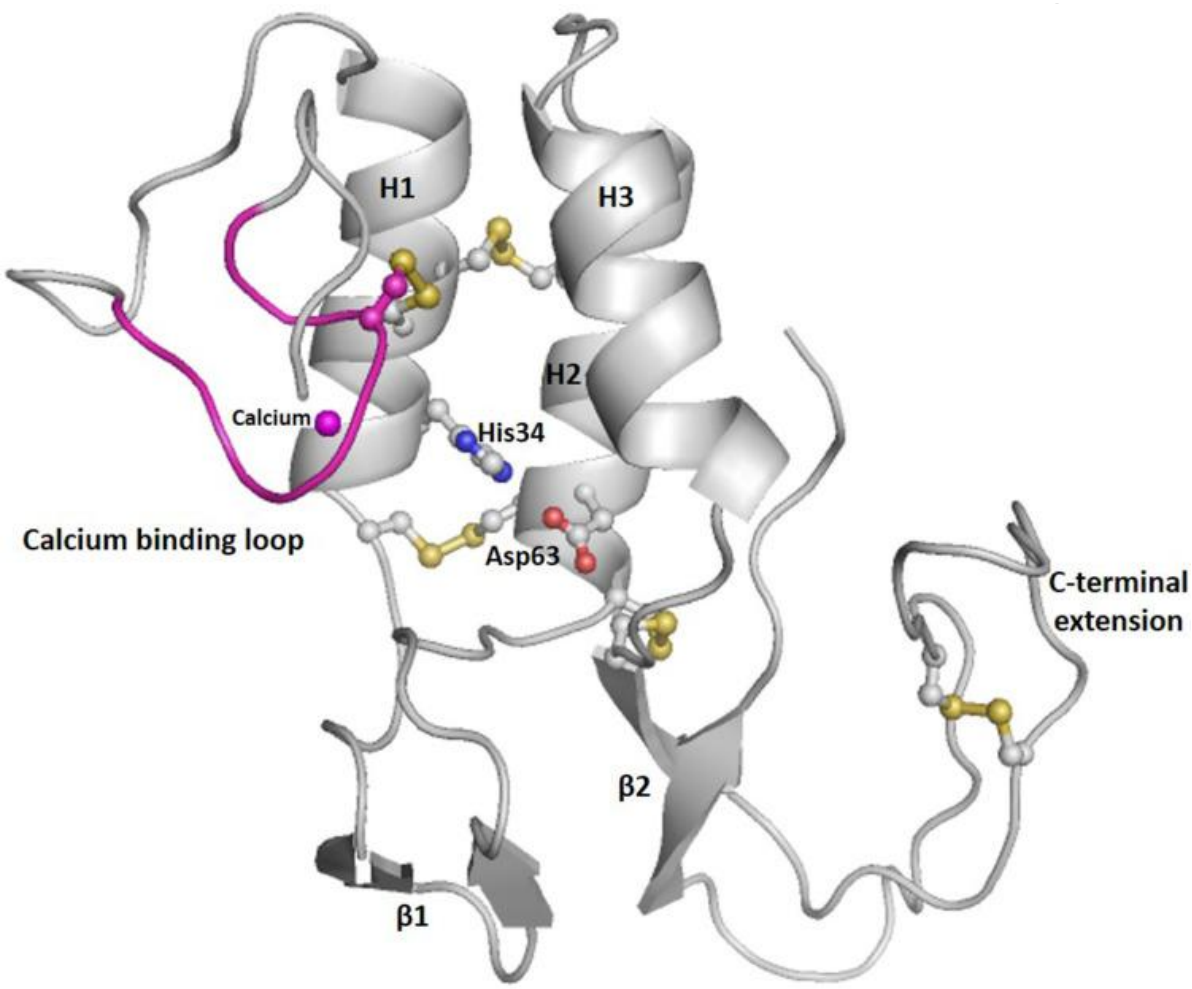

Fig 3: Overall structure of human group III PLA_2, a prototype human $_sPLA_2$. Ribbon diagram The calcium binding loop (pink) containing the calcium ion (sphere in magenta) is part of the structure. The active site contains residues of histidine 34 and aspartic acid 63, and the C-terminal extension is maintained by five disulfide bonds (yellow). Homology modelling was used to create the structure, which was viewed on Pymol Software.

Three helices in SPLA2 are locally preserved. The backbone of the substrate-binding pocket is supported by two lengthy anti-parallel helices welded together by twin disulfide bridges. Half-cysteines generated from this substructure are detected in disulfide bridges in sPLA2s. The anti-

parallel helices' conserved side chains help to coordinate Ca2+ and form the deeper outlines of the hydrophobic channel, resulting in a catalytic network composed of histidine, aspartic acid, and tyrosine that keeps the active site's geometry stable. Ca2+ coordinates with these side chains. A disulfide bridge (Cys61–Cys91) is present in the region, but there is little three-dimensional homology among sPLA2s. This improvement in activity can be as much as 16-fold when the porcine pancreas zwitterionic sPLA2 residues 62–66 are deleted.

It doesn't matter which sPLA2 structure you have; all of them have a fully developed wing GI/II or GIII. The -wing of some enzymes may have other pharmacological effects, such as preventing blood clots, depending on the structure of the enzyme.

The Function of sPLA2-IIA in ALI

Recently, elevated plasma sPLA2-IIA levels were linked to COVID-19 disease severity. Despite preclinical evidence that the small drug LY315920Na/S-5920 selectively inhibits sPLA2-IIA, clinical studies with the same inhibitor failed to protect patients with sepsis and organ failure. The sPLA2-IIA has been shown to be bactericidal and anti-infective, which may explain the poor results. Despite its importance as a lung damage marker, SPLA2-IIA inhibition may impair the host's ability to fight infection, aggravating ALI. Despite extensive research on sPLA2-IIA, it is obvious that more research is required to distinguish between its pro- and anti-inflammatory activities in ALI control. We wondered if sPLA2-IIA mRNA was present in the BAL fluid of early ARDS patients linked with exosomal type EVs, since EVs are well-established carriers for long-range mRNA transfer across tissues and cell types. qRT-PCR was used to assess PLA2G2A sPLA2-IIA m-RNA levels in EVs from early, late, and non-ARDS patients.

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. 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. 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. 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.

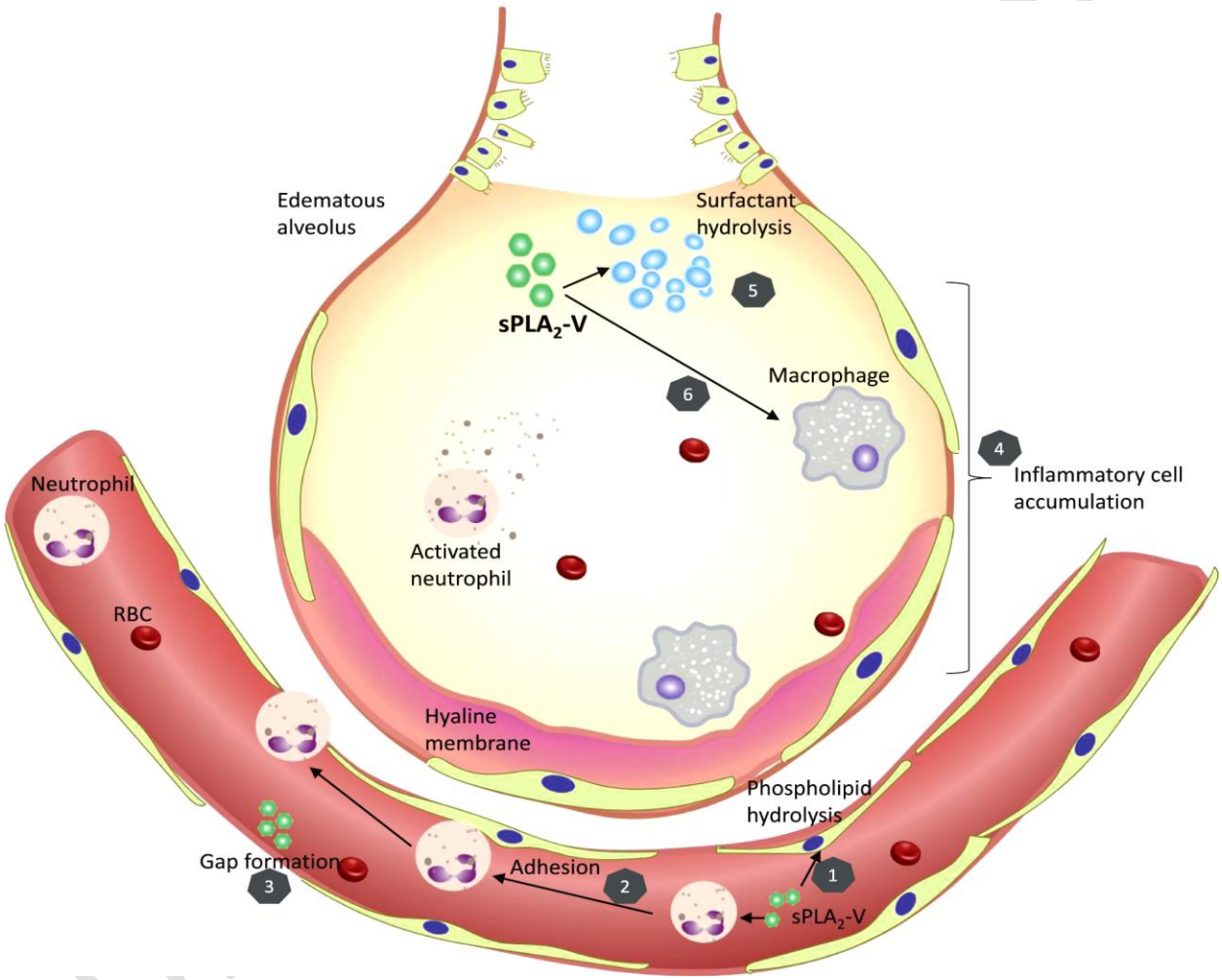

Fig. 4: sPLA2-V plays a role in acute lung injury. Lung endothelial cells produce sPLA2-V (green hexagons), which directly hydrolyzes phospholipids to generate inflammation. Activated neutrophils stick to the EC of the lungs, then move to the interstitium and alveolar space, causing inflammation. sPLA2-V directly affects the ECs of the lung, causing gaps and increased blood flow. During acute lung injury, an increase in sPLA2-V causes surfactant hydrolysis, alveolar damage, hyaline membrane formation, edoema fluid

buildup, and inflammatory cell recruitment (ALI). sPLA2-V may also affect lung macrophage function, such as phagocytosis, using Biorender Software for fig.

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

COPD patients have less surfactant and a different surfactant composition, which may reduce the surface tension of their lungs. In COPD patients, we found reduced amounts of total surfactant lipid and specific lipid species. In BAL samples, increases in PC 30:0 and PC 32:0, as well as total cholesterol, were linked to reduced lung function. Secondary smoking exposure mirrors lipid changes reported in COPD patients, paving the way for further pathophysiology studies. This result supports previous findings that smoking reduces BAL PL content. Unstable bronchitis, a common COPD symptom, was improved in a small clinical trial with surfactant replacement. Also, the role of surfactant lipids in COPD and the mechanism of improvement are unknown. COPD and emphysema can influence alveolar T2C and lipid metabolism, resulting in lowered T2C or premature senescence. An imbalance in proteolysis–antiproteolysis is one of the processes implicated in T2C damage produced by smoking. In T2C-derived human A549 cells, cigarette smoke produced apoptosis, reduced cell growth, and induced EMT (EMT). Smoking impacted T2C degradation and surfactant secretion and composition in many animal models. In other words, systemic pro-inflammatory stimuli increase the production of the sPLA2 GIID protein in different tissues, including the lung. A loop with the missense mutation G80S forms the interfacial binding surface (IBS). Because the mutant enzyme is open, it has a larger interfacial binding surface area, resulting in stronger binding to the M-type receptor. In other words, when G80S is mutated in human sPLA2 GIID, the cytokines responsible for weight loss rise.

Other Diseases Caused by $sPLA_2$ Mutations

This gene encodes a phospholipase A2 enzyme, which catalyses fatty acid release from phospholipids. 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. 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. 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. Exogenous sPLA2-IIA causes neuronal injury. FCMTE is caused by the A159T mutation in sPLA2GVI, an autosomal recessive epilepsy gene. 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. 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. 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 ALI. 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. Exosomes contain sPLA2-IIA mRNA, which has been reported to be more common in patients with early ARDS than in late ARDS or no ARDS. The sPLA2 protein is only found in EVs in the early stages of the disease, suggesting it can be employed as a diagnostic marker. Because of its co-localization on exosomal-like EVs in early ARDS, this study emphasises the role of sPLA2-IIA in spreading the immediate and long-term inflammatory response.sPLA2-IIA, a biological response modulator, is a very important part of the pathophysiology of ARDS because it can affect cells in other parts of the body as well as the extracellular lung environment right here at home.

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