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Harmful and protective roles of group V Phospholipase A₂: current perspectives and future directions

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Abstract

Group V Phospholipase A₂ (Pla2g5) is a member of the PLA₂ family of lipid-generating enzymes. It is expressed in immune and non-immune cell types and is inducible during several pathologic conditions serving context-specific functions. In this review, we recapitulate the protective and detrimental functions of Pla2g5 investigated through preclinical and translational approaches.

1. Identification and characterization

Group V Phospholipases A₂ (Pla2g5), identified by Chen and colleagues [1, 2] belongs to the group of secretory Ca²⁺-dependent Phospholipases A₂ (PLA₂). Its gene is located on mouse chromosome 4 (*Pla2g5*) and human chromosome 1 (*PLA2G5*) [3] in a cluster of genes containing 6 PLA₂s, *Pla2g2a*, *Pla2g2c*, *Pla2g5*, *Pla2g2d*, *Pla2g2e* and *Pla2g2f* [4–7]. PLA₂s hydrolyze membrane phospholipids to generate Lysophospholipids (LysoPL) and free fatty acids (FFAs). The FFA arachidonic acid (AA) can be further metabolized to generate eicosanoids, including prostaglandins and leukotrienes, or FFAs may signal through cognate receptors. To access membrane phospholipids, PLA₂s need to bind membrane components [8]. Pla2g5, Pla2g2a and Pla2g2d bind to heparan sulfate proteoglycans through a cluster of negatively charged residues [9, 10]. Pla2g5 and Pla2g10 bind to membrane phosphatidylcholine (PC) with high affinity [8]; a tryptophan residue in position 31 of the human PLA2G5 was critical for binding PC-rich plasma membranes [8, 11, 12]. Pla2g5 is the only enzyme that uses both mechanisms. To some extent, PLA₂s have substrate preferences [13]. While Pla2g5 and Pla2g10 may similarly bind PC, they have a preference for mono (or low) saturated FFAs or poly saturated FFAs (PUFA), respectively.

PLA₂s have tissue- and cell-specific expression [14]. Pla2g5 was found in immune cells including macrophage cell lines P338D1 [15, 16], bone-marrow derived mast cells [17, 18], T-cells [19], and human neutrophils [20, 21]. It was also expressed in human cardiomyocytes

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during infarction [22], human lung epithelial cells [23, 24] in addition to the renal tubular epithelium, gastric fibroblasts and male reproductive organs [14, 25].

2. Defining Pla2g5 ability to generate AA and eicosanoids

Pivotal studies elucidated the role of Pla2g5 in AA release and eicosanoid generation. Addition of exogenous PLA2G5 to human neutrophils induced AA release and leukotriene B4 (LTB4) generation by activating cytosolic PLA₂ (cPLA₂) α [21, 26], a PLA₂ absolutely required for AA release [27, 28]. The binding to membrane PC was necessary for AA release at the plasma membrane and internalization of PLA2G5 to which followed degradation in human neutrophils [21] or cysteinyl-leukotriene (CysLT) synthesis at the perinuclear membrane in HEK293 cells [29]. In human eosinophils internalization of PLA2G5, generated by epithelial cells [24], also led to CysLT release with a mechanism independent of cPLA₂ α [30]. As PLA2G5, PLA2G10 is expressed and secreted by epithelial cells [14, 31, 32]. Similarly to PLA2G5, PLA2G10 induced CysLT synthesis in eosinophils thorough transactivation but with a mechanism dependent on Lysophosphatidylcholine (LysoPC) generation, MAPK and cPLA₂ α activation [31].

Pla2g5 and Pla2g10 hydrolyze PC, the major phospholipid in the lung surfactant [33]. Interestingly, transgenic (Tg) overexpression of Pla2g5 or Pla2g10 had unanticipated consequences [34]. *Pla2g5-Tg* mice died within 8 hours from birth due to increased surfactant hydrolysis and lung damage, while CysLT levels in *Pla2g5-Tg* were similar to those of Wt mice. *Pla2g10-Tg* survived and had normal lungs, likely because Pla2g10 in the normal lung remained as an inactive proenzyme, whose activation may require proteolytic processing during inflammation. These reports established that although Pla2g5 may share cell expression and enzymatic properties with other conventional secreted PLA₂s, the identification of each function underscores the specific roles of Pla2g5.

The first report of *Pla2g5*-null mice more than a decade ago focused on the contribution of endogenous Pla2g5 to eicosanoid generation in vitro and in vivo [35]. *Pla2g5*-null macrophages isolated from the peritoneal cavity and cultured for three hours had reduced prostaglandin E₂ (PGE₂) and CysLT generation following phagocytosis of zymosan, a yeast-derived particle [35]. Furthermore, *Pla2g5*-null mice had reduced vascular permeability and CysLT generation in vivo during zymosan-induced peritonitis. Phagocytosis, perhaps the primary function of macrophages, is a protective mechanism used by macrophages to fight infections and clear debris. Phagocytosis requires several steps: binding, uptake, and fusion. *Pla2g5*-null peritoneal macrophages cultured for two days had a marked reduction in phagocytosis of zymosan particles, complement- and IgG-opsonized sheep red blood cells [36]. Binding of zymosan was intact in resting *Pla2g5*-null peritoneal macrophages [37]. However, intracellular staining showed that Pla2g5 translocated to the phagosome and that the *Pla2g5*-null macrophages had a delay in the fusion of phagosomes containing zymosan with lysosomes. These data suggested that functions requiring intracellular fusion events, including the killing of pathogens and antigen presentation, could be regulated by Pla2g5 (see paragraphs on infectious diseases and asthma). In these latest reports [36, 37], CysLT generation in *Pla2g5*-null peritoneal macrophages following zymosan ingestion was comparable to Wild-type (Wt) peritoneal macrophages, likely due to differences in culture

conditions or to *Pla2g5*-null mice being fully backcrossed to the C57BL/6J strain (N10-N11). Furthermore, these data suggested that the function of Pla2g5 in macrophages during phagocytosis of zymosan could be independent of its enzymatic activity or mediated by lipids other than CysLTs. Perhaps, Pla2g5 induces CysLT production by other cells including mast cells, at least in certain conditions [38–40].

3. An integrated view of Pla2g5 functions through preclinical studies: more than eicosanoid generation

An additional level of complexity is dictated by the changes happening in the cells after activation in the context of diseases. Ex vivo and in vivo studies have been instrumental in elucidating the inducible nature of Pla2g5 and its apparent opposite functions due to its expression in several cell types including macrophages [41, 42], epithelial cells [43], and adipocytes [44]. The information obtained through preclinical studies and human studies have elucidated the functions of Pla2g5 in peculiar cell populations that develop and are activated during the specific immune response associated with each disease (Table 1). The data discussed here demonstrate the need for establishing cell- and context-specific strategies for targeting PLA2G5 expression and function in complex diseases including asthma, obesity, arthritis, cardiovascular and infectious diseases.

3.1 Asthma

Asthma is a complex disease driven by inflammation and characterized by permanent modifications of the lung, reduced compliance, and exacerbations. Although there are two major asthma phenotypes, one characterized by increased numbers of eosinophils and the other by the prevalence of neutrophils, it's clear that different mechanisms or endotypes may be involved [45]. Mouse models of allergic pulmonary inflammation mimic many features of human asthma and have helped to explore the contribution of PLA₂s to asthma pathogenesis. Particularly, eicosanoids generated by the cPLA₂α [28] had been implicated in the pathogenesis of asthma [46]. Using a model of Ovalbumin (OVA)-induced airway inflammation, which consists of a sensitization phase by intraperitoneal injection of OVA plus alum and a 3-day challenge phase with nebulized OVA, Munoz et al. reported that Pla2g5 was markedly induced in epithelial cells, airway smooth muscle cells and inflammatory cells infiltrating the lung [43]. Interestingly, administration of a blocking antibody against Pla2g5 at sensitization reduced airway narrowing and cell recruitment. When administered after challenge, the antibody decreased only airway resistance. However, a marked reduction in eosinophil numbers and airway resistance was reported in *Pla2g5*-null mice exposed to OVA compared to equally treated Wt mice [43], suggesting that Pla2g5 may act through multiple mechanisms. The effect of exogenous Pla2g5 on airway narrowing was independent of cPLA₂α activation [43], while a previous report showed that PLA2G5 released by epithelial cells increased CysLT production by human eosinophils and was associated with increased cell adhesion induced by LysoPC [47].

Using a model of pulmonary inflammation induced by the house dust mite (HDM) *Dermatophagoides farinae* and based on the notion that Pla2g5 regulates intracellular trafficking events in macrophages [37], in a subsequent study we proved that intracellular

Pla2g5 in dendritic cells was required for antigen uptake, processing and T-cell activation, critical features of allergic sensitization [48] (Figure 1). The adaptive immune response to HDM was also impaired in the absence of Pla2g5, as restimulation with HDM of lymphocytes obtained from parabronchial lymph nodes resulted in significantly reduced production of IL-4, IL-5, and IL-13. Serum IgE were almost absent in HDM exposed *Pla2g5*-null mice [48]. Similar findings were obtained using an OVA model where the authors also showed that the function of Pla2g5 in inducing airway remodeling extended to a chronic model [49]. Mouse models based on clinical relevant allergens have significantly improved our understanding of the innate immune response to allergens involved in the pathogenesis of asthma. Transfers of Wt dendritic cells into HDM-exposed *Pla2g5*-null mice partially restored Th2 cytokine production by restimulated lymph node cells. However, they did not restore HDM-induced pulmonary inflammation (cell infiltration and goblet cell metaplasia) [48], suggesting that at least another lung resident cell expressing Pla2g5 was necessary for the development of pulmonary inflammation. Pla2g5 is expressed by lung epithelial cells and macrophages [34, 41, 43], among other cells. Bone marrow transplant experiment suggested that Pla2g5 was required in hematopoietic-derived cells to develop HDM-induced pulmonary inflammation [41]. Macrophages developing in Type 2 immune responses, including asthma, polarize toward a group of macrophages broadly referred as M2 macrophages [50, 51]. Hence, Wt lung macrophages isolated from mice exposed to HDM were activated toward an M2 phenotype characterized by the expression of the Resistin-like molecule- α (Relm- α), Arginase-1 (Arg-1) and YM1, all of which were reduced in lung macrophages isolated from equally treated *Pla2g5*-null mice. Lung macrophages required Pla2g5 for M2 activation, and to produce CCL22, a chemokine that recruits T-cells into the lung [41]. Furthermore, Pla2g5 was induced by IL-4, the prototypical Type 2 cytokine, in mouse bone marrow (BM)-macrophages and human macrophages derived from blood monocytes [41]. IL-13 also induced *Pla2g5* expression but at lower levels compared to IL-4 in both mouse BM-macrophages [41, 44] and human monocyte-derived macrophages [41]. However, activation of BM-macrophages in vitro by IL-4 was not sufficient to elicit critical features of macrophages developing in the lungs of mice exposed to HDM. Indeed, only when BM-macrophages were activated in vitro with a cocktail of type 2 cytokines (GM-CSF, IL-33, and IL-4), they produced CCL22, which was significantly reduced in the absence of Pla2g5 [41] (Table 1). These data emphasize how the activation state of the macrophages can influence the role of Pla2g5 and vice versa.

Human monocyte-derived macrophages cultured in M-CSF and polarized by IL-4 for 24h produced low amounts of CCL22 and Transglutaminase 2 (TGM2), a marker of human M2 macrophages developing in asthmatic patients [51]. However, culture of monocyte-derived macrophages in GM-CSF for 13 days and polarization with IL-4 for 24h sharply increased *CCL22*, *TGM2*, and *PLA2G5* expression [52]. Compared to monocyte-derived macrophages treated with *vector*-siRNA, monocyte-derived macrophages treated with *PLA2G5*-siRNA had reduced PGE₂ production and reduced transglutaminase activity, which was up-regulated by exogenous PLA2G5 or PGE₂ [52]. Furthermore, PLA2G5 and TGM₂ translocated during IL-4 activation and colocalized on the plasma membrane, suggesting possible crosstalk in human macrophages. In specimens obtained from patients with eosinophilic sinusitis and nasal polypsis, a chronic Type 2 disease which is frequently

associated with asthma, PLA2G5 was highly expressed in macrophages co-expressing TGM2. These data suggest that the function of PLA2G5 in M2 macrophages could extend to human Type 2 diseases [52].

Alternaria alternata (*Alternaria*) is a major fungal allergen. Exposure to *Alternaria* spores induces development of asthma and asthma exacerbations [53, 54]. In mouse models, *Alternaria* triggers IL-33 release from epithelial cells and activation of Group 2 innate lymphoid cells (ILC2s), a type of innate cells responsive to IL-33 and central to the development of asthma [55, 56]. *Pla2g5*-null mice exposed to *Alternaria* had a significantly reduced number of activated lung ILC2s, expressing ST2, CD25, IL-5 and IL-13 and eosinophils [42]. Furthermore, intranasal administration of *Alternaria* induced IL-33 protein and mRNA expression in Wt lung macrophages which were both reduced in *Pla2g5*-null lung macrophages. In BM-macrophages IL-4 again was not sufficient to induce IL-33 in vitro, but a cocktail of Th2 cytokines including IL-4, GM-CSF and IL-33 [41] induced IL-33 protein and mRNA expression in Wt BM-macrophages, which were significantly reduced in equally activated *Pla2g5*-null BM-macrophages. Furthermore, mass spectrometry analysis revealed that *Pla2g5*-null BM-macrophages and macrophages isolated from the lungs of *Alternaria*-exposed *Pla2g5*-null mice had reduced production of oleic acid (OA), linoleic acid (LA), and arachidonic acid (AA) (OA > LA > AA). Transfers of Wt BM-Macrophages into *Pla2g5*-null mice significantly increased eosinophil numbers and ILC2 numbers, confirming that Pla2g5 in macrophages was required for ILC2 activation. However, when administered intranasally, LA and OA in the presence of IL-33 but not alone significantly potentiated ILC2 activation and increased lung eosinophils numbers, while in *Pla2g5*-null mice LA was ineffective [42]. LA binds the free fatty acid receptor (FFAR)-1 and FFAR4 [42]; in this study we reported for the first time that FFAR1 is expressed in Wt ILC2s and its expression is significantly reduced on *Pla2g5*-null ILC2s, which likely accounts for the reduced activation of *Pla2g5*-null ILC2s by LA in vivo and ex vivo. These findings highlight for the first time a critical innate pathway involving Pla2g5, macrophages, IL-33, FFA production and ILC2 activation (Figure 1).

In summary, endogenous Pla2g5 contributes to allergic asthma through at least 3 mechanisms: antigen presentation by dendritic cells [48, 49]; macrophage activation and production of the chemokine CCL22 for T cell recruitment into the lung [41], and macrophage production of IL-33 and FFAs for ILC2 activation [42] (Figure 1). The generation of mice lacking Pla2g5 in selected cell types will further elucidate the functions of Pla2g5-expressing cells in asthma and other diseases.

Transfers of Wt BM-macrophages into *Pla2g5*-null mice exposed to *Alternaria* increased eosinophil numbers and ILC2 numbers; however, these values did not reach the extent of Wt mice receiving *Alternaria* alone or *Alternaria* and Wt BM-Macrophages [42]. One possible explanation was that *Pla2g5*-null macrophages still present in *Pla2g5*-null mice prevented the full development of the allergic inflammatory response. Indeed, transfers of *Pla2g5*-null macrophages in Wt mice exposed to *Alternaria* significantly reduced the numbers of lung eosinophils and ILC2s [42]. These data suggest that cell therapy using *Pla2g5*-null macrophages represent potentially a new therapeutic approach at least in selected patients with asthma.

Pla2g10 also has a prominent role in asthma [57-59]. It was found in the bronchoalveolar lavage (BAL), in the airway epithelial cells and alveolar macrophages obtained from asthmatic patients [32, 58]. In addition, Pla2g10 levels were significantly elevated upon allergen inhalation in both murine and human airways [32, 59]. *Pla2g10*-null mice challenged with OVA had reduced lung inflammation and reduced eicosanoids release in BAL [59]. PLA2G10 highly expressed by lung epithelial cells, was released during inflammation acting on eosinophils to generate LysoPC and induce CysLTs generation in a cPLA₂ α dependent fashion [31]. Furthermore, Pla2g10 induced AA release by epithelial cells but not PGE₂.

The role of Pla2g10 in asthma has been recently further investigated using the HDM murine model of airway hyperresponsiveness (AHR) [60]. Pla2g10 deletion protected mice from HDM-elicited AHR and resulted in reduced eosinophil and T cell infiltration in the lungs. While only IL-13 was reduced in in vitro restimulated *Pla2g10*-null lymphocytes, *Pla2g10*-null mice also showed reduced mucus formation and reduced M2 macrophage recruitment. Compared to HDM-exposed Wt mice, in *Pla2g10*-null mice exposed to HDM IL-33 prenylzymatic properties with other conventional secreted PLA[isp]₂s, theotein released in the BAL but not IL-33 mRNA in lung tissue was reduced and was associated with reduced ILC2 activation and mast cell production of IL-13 [60]. Furthermore, compared to HDM-exposed Wt mice, HDM-exposed *Pla2g10*-null mice had reduced CysLT in BAL as reported in the murine OVA model of AHR [32, 59, 60].

All together in vivo studies on the roles of Pla2g5 and Pla2g10 in asthma suggest that these enzymes synergistically contribute to asthma pathogenesis; however, their relative functions could be prevalent in selected cells and therefore in certain patients or asthma endotypes.

3.2 Cardiovascular diseases

Hydrolysis of phospholipids in low-density lipoproteins (LDL) and macrophage foam cell formation are some of the early events in the development of the atherosclerotic plaque. Pla2g5 promoted atherogenic functions in vitro [61, 62] and could be detected in mouse and human atherosclerotic lesions [62]. In LDL-receptor (*LDLR*)-null mice, overexpression of Pla2g5 resulted in an increased area of the atherosclerotic lesion, while Pla2g5 deficiency in bone marrow reduced the atherosclerotic lesion area in the aortic arch and thoracic aorta [63]. In vitro studies showed that these modifications were likely due to the capacity of Pla2g5 to modify LDL and induce foam cell formation [61] through Syndecan 4 (a proteoglycan receptor) uptake [64]. Additionally, hydrolysis of LDL and HDL by PLA2G5 could generate pro-atherogenic products acting on smooth muscle cells [65]. Accordingly, a recent report showed that hydrolysis of phospholipids in LDL is accomplished by several PLA₂s, PLA2G10, PLA2G3, PLA2G2F, PLA2G2A, and PLA2G5. PLA2G5 targeted PC species containing 18:1 (OA) and 18:2 (LA), PLA2G10 preferred 20:4 (AA), and PLA2G3 was active on most PC species [66]. However, Pla2g5 was dispensable in developing atherosclerotic lesion in *Apolipoprotein E* (*ApoE*)-null mice, likely due to the different nature of circulating LDL [67]. In absence of Pla2g5, *ApoE*-null mice showed reduced aortal aneurysm but increased perivascular fibrosis and macrophage accumulation [68]. It is possible that this dual effect of Pla2g5 on LDL or perivascular fibrosis reflects the

expression of Pla2g5 in different cell types or different activation of cells involved in the pathogenesis or resolution phase of cardiovascular diseases.

The elevated expression of PLA2G5 in the heart suggests that it may have a function in cardiac homeostasis [14]. Following different types of cardiac stress, including myocardial infarction and hypertension, the heterogeneous populations of cardiac cells including cardiomyocytes, fibroblasts, smooth muscle cells, endothelial cells, and immune cells, contribute to remodeling processes. In an ischemia/reperfusion model, the absence of PLA2G5 resulted in reduced size of the myocardial injury [22]. The effects of Pla2g5 in cardiomyocytes involved activation of cPLA₂α through p38, a mitogen-activated protein kinase (MAPK) [69] as similarly reported in mast cells [39], a macrophage-like cell line [70], mesangial cells [71] and neutrophils [26]. PLA2G5 was also found in human aortic valves localized in cells expressing CD68 and alpha-smooth muscles [72]. By immunofluorescence, its expression and that of PLA2G2E, correlated with the expression of the pro-osteogenic molecules, bone morphogenetic protein (BMP)-2, Osteopontin and Alkaline Phosphatase (ALP) [72]. The role of PLA2G5 in valve calcifications was confirmed by knocking down *PLA2G5* or *PLA2G2E* in valve interstitial cells which significantly reduced the expression of pro-osteogenic molecules. Furthermore, a study in humans showed that at least one PLA2G5 polymorphism, likely involving PLA2G5 expression, was associated with premature coronary artery disease [73].

Although these reports do not definitively support the use of PLA2G5 inhibitors as therapeutics for cardiovascular diseases, they warrant further investigation both through mouse models, ideally using a Pla2g5 conditional knock-out, and human studies.

3.3 Infectious diseases

The defect in phagocytosis of the yeast-derived particles zymosan by *Pla2g5*-null macrophages [36] prompted us to investigate the function of Pla2g5 in infectious diseases in vivo. Mice lacking Pla2g5 were injected intravenously with the fungus *Candida albicans*. *Pla2g5*-null mice showed increased fungal burden and mortality compared to Wt mice [37]. In vitro phagolysosome fusion, necessary for pathogen killing, was reduced in peritoneal macrophages lacking Pla2g5, due to a defect in intracellular trafficking of phagosomes containing *Candida albicans*. *Pla2g5*-null peritoneal macrophages also had a delay in the killing of *Candida albicans* likely responsible for the increased fungal burden in vivo. Therefore, Pla2g5 protected from *Candida albicans* infections in vivo and regulated several steps of the phagocytic cascade in vitro: uptake, fusion, and killing of *Candida albicans* [36, 37] (Table 1). Interestingly, some of these findings were reproduced in human monocyte-derived macrophages treated with *PLA2G5*-siRNA, which showed reduced phagocytosis of zymosan particles due to reduced Lysophosphatidylethanolamine (LysoPE) generation [74].

Among hematopoietic cells, PLA2G5 is expressed by human neutrophils, stored in azurophil granules as PLA2G10 [20]. However, following activation with formyl-Met-Leu-Phe (fMLP) or priming with pro-inflammatory cytokines [20, 75], only PLA2G5 is released extracellularly where it likely performs bactericidal functions. Pla2g5 has been involved in the inflammatory response to Gram-negative bacteria in vivo. In an LPS-induced acute lung

injury model, Pla2g5 was expressed in epithelial cells and lung parenchyma 24h after LPS intratracheal administration. The absence of Pla2g5 reduced neutrophil recruitment into the lung [76]. Furthermore, in a model of LPS-induced cell migration, Pla2g5 was required for early leukocyte recruitment into the mouse air pouch, through ICAM and VCAM upregulation [77]. Consistently, infection of lungs with *E. coli* resulted in reduced leukocyte recruitment in BAL and reduced ICAM-1 and PECAM-1 expression in *Pla2g5*-null mice. Pla2g5 was required on structural cells and hematopoietic-derived cells to clear *E. coli* infection respectively from BAL and lung parenchyma. Eicosanoids levels were similar in BAL of *E. coli*-treated *Pla2g5*-null mice compared to equally treated Wt mice, while in lung parenchyma PGD₂ and PGF₂α were reduced. These data suggest that in the absence of Pla2g5 the decreased inflammatory response to bacteria was responsible for the reduced bacterial clearance and therefore worsening infection [78]. These studies point to the possible use of PLA2G5 as a therapeutic agent against infectious diseases, although its role in the development of type 2 inflammatory responses should be considered.

3.4 Arthritis

Another example of a worsening condition in the absence of Pla2g5 was shown by the K/bxN arthritis model [79]. PLA2G5, and to a greater extent PLA2G2A, were highly expressed in the joints of patients with rheumatoid arthritis [79]. Balb/cJ-*Pla2g5*-null mice [36], generated from embryonic stem cells from 129 strain which also lack Pla2g2a due to a frameshift mutation [80], had increased clinical features of serum-induced arthritis. Mechanistically, reduced phagocytosis of immune complexes (ICs) by *Pla2g5*-null macrophages caused increased IC deposition in the joints and worsening arthritis. Addition of exogenous Pla2g5 increased IC phagocytosis by mouse peritoneal macrophages and CD14+ human synovial macrophages in vitro. Furthermore, because CysLTs ameliorated disease in vivo and IC phagocytosis in vitro, the effect Pla2g5 in improving arthritis was attributable to increased CysLTs production and phagocytosis. This study suggested that in circumstances where phagocytosis by macrophages resolves detrimental conditions as in arthritis (Table 1), PLA2G5 could be used as therapeutic. Compared to Wt mice *Pla2g2a*-null mice had instead reduced clinical signs of arthritis using the same arthritis model [79], highlighting the opposite functions of Pla2g5 and Pla2g2a in this model.

Another study investigated the role of PLA2G5 in synovial fibroblasts obtained from a small group of patients with rheumatoid arthritis. In this report, PLA2G5 increased cartilage degradation and proinflammatory effects of endothelial protein C receptor (EPCR) activation [81].

Altogether these reports point once again to the cell-specific effect of Pla2g5 during pathological condition and the need of dissecting its cell-specific function with more sophisticated tools.

3.5 Metabolic syndrome

When fed a high fat diet (HFD) rich in OA, *Pla2g5*-null mice had increased body weight associated with increased plasma phospholipids and insulin resistance [44]. Pla2g5 was markedly induced in mouse white adipocytes following HFD feeding and human mesenteric

white adipose tissue [44]. Low-density lipoproteins (LDL) from *Pla2g5*-null mice feeding HFD had significantly higher cholesterol and phospholipids (mainly PC containing OA and LA) compared to LDL from equally fed Wt mice [44]. Remarkably, the expression of PLA2G5 in human white adipose tissue inversely correlated with levels of plasma LDL. WAT macrophages from HFD-fed *Pla2g5*-null mice had reduced expression of CD206, one of the molecules expressed by mouse M2 macrophages, and increased ratio M1/M2 macrophages. The addition of exogenous Pla2g5 to BM-derived macrophages polarized them toward a protective Type 2 phenotype [44]. However, the M2 polarization of BM-macrophages by IL-4 or IL-13, as monitored by Arg-1 expression, was not affected by Pla2g5 deficiency, suggesting that macrophage-derived Pla2g5 was insufficient to drive M2 polarization in this ex vivo experimental setting. These data are in line with other reports showing that IL-4 alone is not sufficient to elicit the role of endogenous Pla2g5 in M2 polarization of BM-macrophages [41, 42]. Interestingly in the model of HFD-induced obesity, transfers of Wt BM or *Pla2g5*-null BM into *Pla2g5*-null irradiated mice had similar HFD-induced obesity, insulin resistance, and hyperlipidemia, suggesting that the protective role of Pla2g5 in obesity was due to its expression in structural cells, namely adipocytes. Mechanistically, OA and to a lesser extent LA released from hyperlipidemic LDL by adipocyte-derived Pla2g5, attenuated (or counteracted) palmitate-induced M1 macrophage polarization in adipose tissue, resulting in protective effects in obesity and associated inflammation. Consistently, increased glucose-stimulated insulin secretion (GSIS) was reported in non-obese *Pla2g5*-null mice [82]. Interestingly, *Pla2g2e*-null mice had reduced HFD-induced obesity, and reduced phospholipids and cholesterol in plasma lipoproteins [44]. These findings highlight once more the opposite roles of Pla2g5 vs. other conventional PLA₂s, Pla2g2e in the pathogenesis of obesity [44] and Pla2g2a in arthritis [79].

4. Conclusions

Pla2g5 is an enzyme that can generate an array of lipids including FFAs, particularly OA>LA>AA, and LysoPL. These lipids can act at cognate receptors or be further metabolized as AA in leukotrienes and prostaglandins, therefore potentially targeting multiple cells and multiple pathways within each cell. However, the ability of each cell type to express Pla2g5, produce lipid or respond to them depends also on the activation state of the cell, as proven for macrophages activating ILC2s during allergic pulmonary inflammation. Systemic administration of PLA2G5 inhibitors could ameliorate certain diseases including asthma but would exacerbate obesity, infections, and arthritis. However, in asthmatic patients, local administration of cells lacking PLA2G5 could prevent further activation of proinflammatory macrophages and release of dangerous lipid mediators. Personalized cell therapy could be a valuable option at least for selected patients with asthma or other diseases in which modulation of PLA2G5 expression and function must be locally targeted to particular cell types.

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Abbreviations:

Pla2g5	Group V Phospholipase A ₂
PGE2	prostaglandin E ₂
CysLTs	cysteinyl-leukotriene
Wt	Wild-type
OVA	Ovalbumin
HDM	house dust mite/ <i>Dermatophagoides farinae</i>
Relm-α	Resistin-like molecule-α
Arg-1	Arginase-1
Alternaria	Alternaria alternata
AHR	airway hyperresponsiveness
PC	phosphatidylcholine
LDL	low density lipoproteins
BMP	bone morphogenetic protein
ALP	Alkaline Phosphatase
LysoPC	Lysophosphatidylcholine
AA	arachidonic acid

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Figure 1.

Illustration of Pla2g5 expression and function during allergen-induced pulmonary inflammation.

Dendritic cells (DCs) expressing Pla2g5 uptake and process allergens for presentation to T-cells in lymph nodes (LN). Activated T-cells are recruited to the lung by Pla2g5-expressing macrophages producing CCL22.

Epithelial cells release IL-33, which activates ILC2s and macrophages. Activated macrophages expressing Pla2g5 produce IL-33 and the FFAs, LA and OA, which further activate ILC2s to produce IL-5 for eosinophil recruitment and activation.

Table 1

Role of Pla2g5 determined by cell expression and its specific disease function

Pathogenic /detrimental functions						
	Mouse cells	Function	Ref	Human cells	Function	Ref
Asthma	BM-Dendritic cells	Antigen presentation	18,19			
	-Lung Macrophages -BM-M2 macrophages (GM-CSF, IL-4, IL-33)	M2 activation CCL22 generation T- cell recruitment	10	Monocyte-derived macrophages (IL-4)	M2 activation PGE ₂ generation TGM2 activation	10, 22
	-Lung Macrophages -BM-M2 macrophages (GM-CSF, IL-4, IL-33)	IL-33 generation LA and OA generation ILC2 activation	11			
Cardiovascular diseases	Cardiomyocytes	Myocardial injury	41, 42	Alpha smooth muscles Valve Macrophages	Aortic valve calcification	47
	Atherosclerotic plaque	Hydrolysis of LDL Macrophage foam cell	32, 33, 34	Atherosclerotic plaque	Hydrolysis of LDL	32
Resolving/protective functions						
Infectious diseases	Peritoneal Macrophages	Phagocytosis of zymosan Phagocytosis and killing of <i>Candida albicans</i>	8,9	Monocyte-derived macrophages (IL-4)	M2 activation LysoPE generation Phagocytosis of zymosan	49
	Structural cells and hematopoietic-derived cells, neutrophils	Neutrophil recruitment Clearance of Gram negative bacteria	52, 53, 54	Neutrophils	Bactericidal function	50, 51
Metabolic syndrome	Adipocytes Adipose macrophages	LDL hydrolysis OA and LA generation M2 activation, GSIS	13	White adipose tissue	LDL Hydrolysis	13
	Pancreatic beta-cells	GSIS in vivo	57			
Arthritis	Peritoneal macrophages	Phagocytosis of immunocomplexes	55	CD14+ synovial and blood cells	Exogenous Pla2g5 IC Phagocytosis	55