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Group 1B Phospholipase A₂ in Metabolic and Inflammatory Disease Modulation

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Abstract

The group 1B phospholipase A₂ (PLA2G1B) is a secreted phospholipase that catalyzes the hydrolytic removal of the *sn*-2 fatty acyl moiety from phospholipids. This enzyme is synthesized most abundantly in the pancreas and is also expressed in the lung. The first part of this review article focuses on the role of pancreatic-derived PLA2G1B in mediating lipid absorption and discusses how the PLA2G1B-derived metabolic product contributes to cardiometabolic diseases, including obesity, hyperinsulinemia, hyperlipidemia, and atherosclerosis. The anti-helminth properties of PLA2G1B will also be discussed. The second part of this review will focus on PLA2G1B expressed in the lung, and *in vitro* data suggest that how this enzyme may modulate lung inflammation via both hydrolytic activity-dependent and -independent mechanisms. Finally, recent studies revealing a relationship between PLA2G1B and cancer will also be discussed.

Keywords

lipid absorption; lysophospholipids; obesity; diabetes; atherosclerosis; inflammation

1. Introduction

Phospholipase A₂ is a class of enzymes that catalyzes the hydrolytic removal of the *sn*-2 fatty acyl moiety from phospholipids, and includes enzymes secreted from cells as well as intracellular phospholipases. The first member identified in the secreted phospholipase family is the group 1B phospholipase A₂ (PLA2G1B). This enzyme is expressed abundantly in acinar cells of the pancreas and has also been reported to be present in islet β -cells of the pancreas [1,2]. Thus this enzyme is also referred to as the pancreatic phospholipase A₂ or SPLA2-1B. However, this enzyme is also found albeit in much lower levels in several other tissues including the lung, gastric mucosa, and spleen [3]. The PLA2G1B protein is encoded by a single-copy *PLA2G1B* gene located in chromosome 12 of the human genome and

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Conflict of interest

The author declares no conflict of interest.

chromosome 5 in the mouse genome. The *PLA2G1B* gene spans 4 exons interspersed by 3 introns and the exonic sequence is highly conserved with 70–80% sequence homology across all mammalian species [4]. Catalytic mechanism of substrate hydrolysis by PLA2G1B differs from other lipolytic enzymes in that the active site network of PLA2G1B contains 1 histidine, 2 tyrosine residues, and one aspartate acid while substrate hydrolysis by other lipolytic enzymes involves a catalytic triad of serine-histidine-aspartic acid. The codon for the active site histidine is located in exon 3, similar to the codons for the two tyrosine residues required by structural stability of the catalytic network, while the codon for the active site aspartic acid is located in exon 4 of the *PLA2G1B* gene [4, 5]. Enzymatic activity of PLA2G1B also requires calcium binding to a Y-X-G-X-G motif (where X represents any amino acids) that is also encoded by the second exon [4, 5]. Genetic variants of the *PLA2G1B* gene in humans are associated with central adiposity and colorectal neoplasia [6, 7]. Low expression levels of PLA2G1B also increases the risk of pancreatic cancer [8].

2. PLA2G1B in the digestive tract

2.1 Role of PLA2G1B in lipid nutrient absorption

The most prominent source of PLA2G1B is the acinar cells of the pancreas, where the inactive enzyme with a pro-peptide extension at the amino terminus is found within zymogen granules along with other digestive enzymes. Upon meal feeding, contents within the zymogen granules are released into pancreatic juice and transported to the intestinal lumen where the PLA2G1B can be proteolytic cleaved to remove the pro-peptide to form an active enzyme that mediates lipid nutrient digestion and absorption. Based on its enzymatic activity, it is likely that the major role of PLA2G1B is the digestion of dietary and biliary phospholipids in the digestive tract. It is of note that an average human diet contains 2 to 7 grams of phospholipids, and an additional 7 to 22 grams of phospholipids also enter the digestive tract from the bile each day [9]. These phospholipids provide an amphipathic monolayer to stabilize and transport hydrophobic lipid nutrients such as triacylglycerols and cholesteryl esters through the intestinal lumen of the digestive tract [10, 11]. However, phospholipid hydrolysis to remodel these lipid particles is required prior to lipid nutrient absorption into the intestinal mucosa [12, 13]. Evidence from *in vitro* cell culture experiments suggested that PLA2G1B in pancreatic extracts is responsible for phospholipid digestion and lipid absorption by enterocytes [12, 13]. Additional *in vivo* experiments with competitive phospholipase A₂ inhibitors also revealed the requirement of luminal phospholipid hydrolysis for efficient cholesterol absorption in the digestive tract [14, 15]. However, it is important to note that these phospholipase A₂ inhibitors may not be specific for PLA2G1B and may also inhibit other phospholipase enzymes. Indeed, our studies with *Pla2g1b* gene knockout mice showed no difference in fat and cholesterol absorption between *Pla2g1b*^{+/+} and *Pla2g1b*^{-/-} mice when the animals were fed a normal low fat chow. While delay in fat and cholesterol absorption was observed in *Pla2g1b*^{-/-} mice with chronic feeding of a high fat/high cholesterol diet [16], the total amount of fat and cholesterol absorbed by *Pla2g1b*^{-/-} was similar to that observed in high fat/high cholesterol-fed *Pla2g1b*^{+/+} mice [16]. These latter results suggested the existence of an alternative pathway for intestinal phospholipid digestion.

One potential candidate to compensate for the absence of PLA2G1B in mediating phospholipid digestion and lipid absorption by *Pla2g1b*^{-/-} mice is the Group X-secreted phospholipase A₂ (PLA2G10) that expresses in enterocytes throughout the cephalocaudal axis of the intestine [17]. Another candidate is the intestinal phospholipase B (PLB) expressed in the distal intestine (ileum) that hydrolyzes both *sn*-1 and *sn*-2 fatty acyl groups from phospholipids to yield glycerylphosphorylcholine [18, 19]. The increased expression of PLB in intestine of rats with pancreatic insufficiency is consistent with the possibility of its involvement in this process [20]. One important difference between PLA2G1B and these enterocyte-expressed phospholipases is that PLA2G1B secreted by the pancreas is found mainly in the proximal intestine (duodenum and jejunum) where most of the triacylglycerol-derived fatty acids and cholesterol derived from the diet are absorbed into the enterocytes for chylomicron synthesis and secretion into the plasma circulation (Fig. 1). Hence, the delayed lipid absorption observed in *Pla2g1b*^{-/-} mice indicates that in the absence of PLA2G1B, PLA2G10 expressed in proximal intestine is not sufficient to catalyze complete phospholipid digestion and lipid absorption in the proximal intestine, and requires PLA2G10 and PLB activities in the distal intestine for complete nutrient digestion and absorption. It is important to note that phospholipid digestion at the proximal intestine by PLA2G1B and PLA2G10 is expected to yield lysophospholipids, primarily lysophosphatidylcholine (LPC), and fatty acids whereas phospholipid digestion at the distal intestine is predicted to generate glycerylphosphorylcholine and fatty acids owing to the presence of PLB that is capable of hydrolyzing both *sn*-1 and *sn*-2 fatty acyl groups from phospholipids and lysophospholipids (Fig. 1). Thus, less lysophospholipids are produced in the absence of PLA2G1B [21, 22].

2.2. Products of PLA2G1B promotes diet-induced cardiometabolic diseases

Despite the ability of intestinal PLA2G10 and PLB to compensate for the lack of PLA2G1B in catalyzing luminal phospholipid hydrolysis and lipid nutrient absorption, the *Pla2g1b*^{-/-} mice were found to be resistant to high-fat high-carbohydrate diet-induced obesity and displayed increased glucose tolerance and insulin sensitivity when compared to wild type mice under similar dietary conditions [16]. The *Pla2g1b*^{-/-} mice also utilizes fat as nutrient source more efficiently than the *Pla2g1b*^{+/+} mice due to elevated expression and activities of peroxisome proliferator-activated receptor genes [22]. When bred to LDL receptor-null background, *Pla2g1b* inactivation was shown to be protective against diet-induced hyperlipidemia and atherosclerosis [23, 24]. These metabolic differences between fat-fed *Pla2g1b*^{+/+} and *Pla2g1b*^{-/-} mice cannot be attributed to the difference in lipid absorption under these conditions because similar amount of fat was absorbed between these 2 groups of animals. Additionally, the fat-fed *Pla2g1b*^{-/-} mice absorbed more fat than chow-fed *Pla2g1b*^{+/+} mice yet their weight gains were similar [16]. Thus, PLA2G1B has a direct contributory role in diet-induced cardiometabolic diseases in a mechanism that is independent of fat absorption.

As noted above, a major difference between PLA2G1B, PLA2G10, and PLB activities is the generation of lysophospholipids as a result of PLA2G1B-catalyzed phospholipid hydrolysis at the proximal intestinal lumen [21, 22]. The contributory role of lysophospholipids absorbed through the intestine toward promoting cardiometabolic diseases in wild type mice was illustrated by the restoration of postprandial glucose intolerance in *Pla2g1b*^{-/-} mice

after intraperitoneal injection of lysophospholipids [21]. The influence of lysophospholipids toward cardiometabolic disease manifestation is also illustrated by studies showing that the *Pla2G10*^{-/-} mice also display reduced adiposity and improved muscular insulin sensitivity [17]. However, whether the reduced adiposity in *PLA2G10*^{-/-} mice is a direct result of impaired phospholipid hydrolysis in the gastrointestinal tract or due to the reduced phospholipase enzyme activity in other tissues remains to be resolved. Regardless, the contributory role of lysophospholipids toward cardiometabolic disease is clear and is due at least in part to its induction of mitochondrial permeability and inhibition of hepatic fatty acid β -oxidation [25].

The contributory role of PLA2G1B toward diet-induced cardiometabolic diseases suggests that PLA2G1B inhibition may be a viable strategy to lower the risk of atherosclerosis, obesity, diabetes, and fatty liver diseases. In a proof of concept study, we showed that the inclusion of the secreted phospholipase A2 inhibitor methyl indoxam in the high-fat high-carbohydrate meal was effective in suppressing diet-induced weight gain and hyperglycemia [26]. Although methyl indoxam is capable of inhibiting the activities of a wide spectrum of different secreted phospholipase A₂ [27], this inhibitor is sparingly absorbed through the digestive tract. Thus, the ability of oral methyl indoxam to suppress diet-induced metabolic disorders indicates that PLA2G1B and PLA2G10 inhibition in the lumen of the digestive tract is responsible for the metabolic improvement. Additional studies testing the effectiveness of methyl indoxam, or other PLA2G1B-specific inhibitors, in improving hyperglycemia, hyperlipidemia, and cardiometabolic diseases after their onset are clearly warranted.

2.3. PLA2G1B expression in epithelial cells of the intestine

Recent studies have found that PLA2G1B is also expressed in epithelial cells of the intestine, albeit at much lower levels than in pancreas, where it appears to play a key role in anti-helminth immunity. In studies comparing *Pla2g1b*^{+/+} and *Pla2g1b*^{-/-} mice in response to intestinal helminth infection, Entwistle et al. found that whereas wild type C57BL/6 mice were susceptible to primary infection, but developed resistance to a second infection challenge after anthelmintic treatment, mice lacking PLA2G1B failed to be protected against a second infection [28]. The role of PLA2G1B in intestinal immunity is not related to type 2 immune response as no difference was observed between *Pla2g1b*^{+/+} and *Pla2g1b*^{-/-} mice in Th2 cell commitment and differentiation and in regulatory T cells. Alternative activation of macrophages, which are essential for helminth immunity, B cell frequency, and serum antibody levels were also similar between *Pla2g1b*^{+/+} and *Pla2g1b*^{-/-} mice. The mechanism underlying the anthelmintic effects of PLA2G1B is due to its killing of tissue-embedded larvae and requires its phospholipid hydrolytic activity (Fig. 2). Lipidomic analysis of PLA2G1B-treated larvae revealed substantial reduction of phospholipid abundance, in particularly the reduction of phosphatidylethanolamine species that are required for numerous cell functions including membrane fusion, cytokinesis, cell division, and maintenance of membrane curvature [29]. However, while PLA2G1B is required for killing of the helminth larvae, it is not sufficient and type 2 immunity-mediated expulsion is necessary for the complete clearance of the infection [28]. Thus, PLA2G1B activity synergizes with immune cells to confer anti-helminth immunity.

The anti-helminth properties of PLA2G1B may pose significant challenge to the use of PLA2G1B inhibitors for cardiometabolic disease intervention. Nevertheless, it is interesting to note that selective helminth infection has been proposed as an alternative therapy for intestinal diseases such as inflammatory bowel disease and celiac disease [30, 31]. The mechanism underlying the beneficial properties of helminth infection is due at least in part to the modulation of the gut microbiota [30, 31]. The gut microbiome composition also plays an important role in metabolic regulation with significant impact on cardiometabolic disease manifestation [32–34]. In fact, a recent study reported that helminth infection improved insulin sensitivity in high fat diet-fed mice via modulation of gut microbiota and fatty acid metabolism [35]. These potential metabolic benefits of selective helminth infection are reminiscent of the benefits of PLA2G1B inhibition. Whether Pla2g1b activity and/or its hydrolytic products also modulate gut microbiome composition remains to be determined.

3. PLA2G1B in the lung

3.1. Products of PLA2G1B in the lung promote inflammation

The second highest PLA2G1B-expressing tissue is the lung [4]. Lung expression of PLA2G1B is induced after birth, reaching a level that is 10 times higher than during the gestation period and this level persists throughout the adult life [36]. However, the physiological role of PLA2G1B in lung biology is not clear. *In vitro* data showed that PLA2G1B can hydrolyze surfactant phospholipids, but the hydrolysis can be inhibited by surfactant protein [37]. Another *in vitro* study revealed that addition of PLA2G1B to culture medium of mast cells increases prostaglandin D2 production, which in turn elevates inflammatory cytokine production by Th2 cells [38]. The confirmation of these *in vitro* observations *in vivo* would suggest that, in contrast to the digestive tract where PLA2G1B activity is not associated with type 2 immune response, its activity in the lung has the potential to activate Th2 cells, albeit via an indirect mechanism. The addition of PLA2G1B has also been shown to induce lung parenchymal strip contraction *ex vivo* [39]. The PLA2G1B-induced contractile response is unrelated to mast cell activation and prostaglandin production, thus implying a potential PLA2G1B effect on endothelial and/or smooth muscle cells [39]. These *in vitro* observations also need to be confirmed *in vivo* by comparing bronchial constriction and asthmatic response between *Pla2g1b^{+/+}* and *Pla2g1b^{-/-}* mice prior to assigning these functions for PLA2G1B in the lung.

It is important to note that several secreted phospholipase A₂ including PLA2G10 are also expressed in lung tissue [36]. In fact, *in vivo* studies with *Pla2g10^{-/-}* mice showed a significant reduction of ovalbumin-induced airway inflammation and asthma [40]. These results indicate that PLA2G10 is the main enzyme in the lung for phospholipid hydrolysis and PLA2G1B does not compensate for the lack of PLA2G10 in stimulating Th2 inflammatory response in the lung. Whether PLA2G1B inactivation has similar effect and/or act in conjunction with PLA2G10 for asthma protection, similar to their roles in the digestive tract, remains to be determined. Additional experiments with *Pla2g1b^{-/-}* mice are worthwhile to resolve this issue.

3.2. Phospholipase A₂ and phospholipase A₂ receptor-1 in the lung

Despite the uncertainties regarding the physiological role of PLA2G1B in the lung, particularly its potential role in lung inflammation, the level and activity of both PLA2G1B and PLA2G10 were found to be elevated in the lung with ovalbumin-induced inflammation [38]. This inflammation-induced accumulation of the phospholipases was exaggerated in the absence of phospholipase A₂ receptor-1 (PLA2R1) in parallel with a more robust inflammation [38]. The elevated lung inflammation associated with PLA2R1 deficiency is reported to be due to impaired clearance of PLA2G1B and PLA2G10 by endocytosis and lysosomal degradation in airway smooth muscle cells [38]. Interestingly, this study reported several-fold higher PLA2G1B activity compared to PLA2G10 activity in the bronchoalveolar lavage fluid of ovalbumin-treated mice with or without PLA2R1 inactivation [38]. This observation suggests that PLA2G1B may in fact participate in lung inflammation. As noted above, this possibility requires additional investigation. Nevertheless, it is noteworthy that while Tamaru et al. did not find evidence to suggest that PLA2G1B-mediated eicosanoid production is mediated through its binding to the phospholipase A₂ receptor [38], thus implying that PLA2G1B hydrolysis of phospholipids to liberate arachidonic acid is the key, several *in vitro* studies have shown that PLA2G1B binding to its cognate receptor may trigger pro-inflammatory response through signal transduction mechanisms. For example, Triggiani and colleagues reported that phospholipase A₂ binding to PLA2R1 is sufficient and phospholipase A₂ enzyme activity is not necessary to initiate and amplify inflammatory reactions in inflammatory and allergic diseases [41]. Granata and coworkers also showed that PLA2G1B can elicit pro-inflammatory cytokine release from human lung macrophages in a process that requires its binding to PLA2R1 but is independent of its enzyme activity [42]. Additional *in vitro* cell culture studies revealed that PLA2G1B binding to PLA2R1 promotes inflammatory response through indirectly mechanisms, including the activation of stress kinases to induce cytoplasmic phospholipase A₂ and cyclooxygenase-2 expression as well as activation of sphingomyelinase to generate pro-inflammatory bioactive lipid metabolites [43]. Taken together, results from these *in vitro* studies raise the possibility that PLA2G1B in the lung may have hydrolytic activity-dependent and -independent functions in inflammatory response (Fig. 2). Nevertheless, it is important to note that there are other phospholipase A₂ enzymes synthesized and secreted by lung cells that are capable of phospholipid hydrolysis and PLA2R1 binding, including PLA2G10 and PLA2G2D [44]. Whether PLA2G1B has unique functional properties that are not shared by these other secreted phospholipase A₂ enzymes is not clear at this time. Additional studies with *Pla2g1b*^{-/-} mice that focus on lung functions and inflammatory response may shed light on this issue.

4. PLA2G1B in cancer

A recent meta-analysis of 9 pancreatic cancer datasets in the Oncomine database revealed the association between reduced PLA2G1B expression and pancreatic cancer [8]. Interestingly, the human *PLA2G1B* gene variant that is associated with reduced central adiposity, *rs5637*, is also associated with reduced risk of colorectal cancer [7]. Since the reduced central adiposity associated with this *PLA2G1B* variant resembles the obesity protection phenotype of the *Pla2g1b*^{-/-} mice, these results suggest that the *rs5637* variant

form of *PLA2G1B* may lower protein expression or encodes a dysfunctional protein with reduced enzyme activity. How does low PLA2G1B expression promotes pancreatic cancer while low PLA2G1B activity may potentially reduce the risk of colorectal cancer have not been established. Lipidomic analysis of plasma lysophospholipid levels in colorectal cancer patients suggested that the relationship may be unrelated to lysophospholipid generation in the intestinal lumen as high plasma levels of a selective lysophospholipid are associated with lower risk of colorectal cancer [45] whereas reduced lysophospholipid levels are detected in colorectal cancer patients [46, 47]. It is possible that PLA2G1B promotes colorectal cancer progression through its interaction with PLA2R1 and the subsequent transactivation of cytoplasmic phospholipase A₂ and the generation of bioactive lipid metabolites, as discussed above for its role in the lung, to favor the proliferation of tumor cells. In this regard, high expression of the *PLA2G1B* gene has been associated with increased susceptibility to pulmonary adenomas in mice and humans [48, 49]. Additional studies to explore the mechanism underlying the relationship between PLA2G1B expression and activity with tumor progression will shed light on whether this is a gene target for oncotherapy.

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Abbreviations used:

PLA2G1B	group 1B phospholipase A ₂
PLB	phospholipase B

References

- [1]. Stemby B, Nilsson A, Melin T, Borgstrom B, Pancreatic lipolytic enzymes in human duodenal contents. Radioimmunoassay compared with enzyme activity, *Scand. J. Gastroenterol* 26 (1991) 859–866. [PubMed: 1771390]
- [2]. Ramanadham S, Ma Z, Arita H, Zhang S, Turk J, Type IB secretory phospholipase A₂ is contained in insulin secretory granules of pancreatic islet beta-cells and is co-secreted with insulin from glucose stimulated islets, *Biochim. Biophys. Acta* 1390 (1998) 301–312. [PubMed: 9487151]
- [3]. Homan R, Jain MK, Biology, pathology, and interfacial enzymology of pancreatic phospholipase A₂ in: Mansbach CMI, Tso P, Kuksis A (Eds.) *Intestinal Lipid Metabolism*, Kluwer Academic/Plenum Publishers, New York, 2001, pp. 81–104.
- [4]. Richmond BL, Hui DY, Molecular structure and tissue-specific expression of the mouse pancreatic phospholipase A₂ gene, *Gene* 244 (2000) 65–72. [PubMed: 10689188]
- [5]. Scott DL, White SP, Otwinowski Z, Yuan W, Gelb MH, Sigler PB, Interfacial Catalysis: The Mechanism of Phospholipase A₂, *Science* 250 (1990) 1541–1546. [PubMed: 2274785]
- [6]. Wilson SG, Adam G, Langdown M, Reneland R, Braun A, Andrew T, Surdulescu GL, Norberg M, Dudbridge F, Reed PW, Sambrook PN, Kleyn PW, Spector TD, Linkage and potential association of obesity-related phenotypes with two genes on chromosome 12q24 in a female dizygous twin cohort, *Eur. J. Hum. Genet* 14 (2006) 340–348. [PubMed: 16391564]
- [7]. Abbenhardt C, Poole EM, Kulmacz RJ, Xiao L, Curtin K, Galbraith RL, Duggan D, Hsu L, Makar KW, Caan BJ, Koepf L, Owen RW, Scherer D, Carlson CS, Potter JD, Slattery ML, Ulrich CM, Phospholipase A2G1B polymorphisms and risk of colorectal neoplasia, *Int. J. Mol. Epidemiol. Genet* 4 (2013) 140–149. [PubMed: 24046806]
- [8]. Goonesekere NCW, Andersen W, Smith A, Wang X, Identification of genes highly downregulated in pancreatic cancer through a meta-analysis of microarray datasets: implications for discovery of

- novel tumor-suppressor genes and therapeutic targets, *J. Cancer Res. Clin. Oncol* 144 (2018) 309–320. [PubMed: 29288362]
- [9]. Carey MC, Small DM, Bliss CM, Lipid digestion and absorption, *Ann. Rev. Physiol* 45 (1983) 651–677. [PubMed: 6342528]
- [10]. Tso P, Kendrick H, Balint JA, Simmonds WJ, Role of biliary phosphatidylcholine in the absorption and transport of dietary triolein in the rat, *Gastroenterology* 80 (1981) 60–65. [PubMed: 6893826]
- [11]. Tso P, Simmonds WJ, Importance of luminal lecithin in intestinal absorption and transport of lipid in the rat, *Aust. J. Exp. Biol. Med. Sci* 55 (1977) 355–357. [PubMed: 911285]
- [12]. Homan R, Hamelehle KL, Phospholipase A₂ relieves phosphatidylcholine inhibition of micellar cholesterol absorption and transport by human intestinal cell line Caco-2, *J. Lipid Res* 39 (1998) 1197–1209. [PubMed: 9643351]
- [13]. Mackay K, Starr JR, Lawn RM, Ellsworth JL, Phosphatidylcholine hydrolysis is required for pancreatic cholesterol esterase- and phospholipase A₂-facilitated cholesterol uptake into intestinal Caco-2 cells, *J. Biol. Chem* 272 (1997) 13380–13389. [PubMed: 9148961]
- [14]. Homan R, Krause BR, Established and emerging strategies for inhibition of cholesterol absorption, *Curr. Pharm. Design* 3 (1997) 29–44.
- [15]. Richmond BL, Boileau AC, Zheng S, Huggins KW, Granholm NA, Tso P, Hui DY, Compensatory phospholipid digestion is required for cholesterol absorption in pancreatic phospholipase A₂ deficient mice, *Gastroenterology* 120 (2001) 1193–1202. [PubMed: 11266383]
- [16]. Huggins KW, Boileau AC, Hui DY, Protection against diet-induced obesity and obesity-related insulin resistance in Group 1B PLA₂-deficient mice, *Am. J. Physiol* 283 (2002) E994–E1001.
- [17]. Sato H, Isogai Y, Masuda S, Taketomi Y, Miki Y, Kamei D, Hara S, Kobayashi T, Ishikawa Y, Ishii T, Ikeda K, Taguchi R, Ishimoto Y, Suzuki N, Yokota Y, Hanasaki K, Suzuki-Yamamoto T, Yamamoto K, Murakami M, Physiological roles of group X-secreted phospholipase A₂ in reproduction, gastrointestinal phospholipid digestion, and neuronal function, *J. Biol. Chem* 286 (2011) 11632–11648. [PubMed: 21266581]
- [18]. Gassama-Diagne A, Rogalle P, Fauvel J, Willson M, Klæbe A, Chap H, Substrate specificity of phospholipase B from guinea pig intestine. A glycerol ester lipase with broad specificity, *J. Biol. Chem* 267 (1992) 13418–13424. [PubMed: 1618844]
- [19]. Delagebeaudeuf C, Gassama-Diagne A, Nauze M, Ragab A, Li RY, Capdevielle J, Ferrara P, Fauvel J, Chap H, Biochemical characterization and cloning of guinea pig intestinal phospholipase B, *Ann. N. Y. Acad. Sci* 859 (1998) 192–193. [PubMed: 9928384]
- [20]. Tchoua U, Ito M, Okamoto M, Tojo H, Increased intestinal phospholipase A₂ activity catalyzed by phospholipase B/lipase in WBN/Kob rats with pancreatic insufficiency, *Biochim. Biophys. Acta* 1487 (2000) 255–267. [PubMed: 11018477]
- [21]. Labonté ED, Kirby RJ, Schildmeyer NM, Cannon AM, Huggins KW, Hui DY, Group 1B phospholipase A₂-mediated lysophospholipid absorption directly contributes to postprandial hyperglycemia, *Diabetes* 55 (2006) 935–941. [PubMed: 16567514]
- [22]. Labonté ED, Pfluger PT, Cash JG, Kuhel DG, Roja JC, Magness DP, Jandacek RJ, Tschop MH, Hui DY, Postprandial lysophospholipid suppresses hepatic fatty acid oxidation: the molecular link between group 1B phospholipase A₂ and diet-induced obesity, *FASEB J* 24 (2010) 2516–2524. [PubMed: 20215528]
- [23]. Hollie NI, Hui DY, Group 1B phospholipase A₂ deficiency protects against diet-induced hyperlipidemia in mice, *J. Lipid Res* 52 (2011) 2005–2011. [PubMed: 21908646]
- [24]. Hollie NI, Konanah ES, Goodin C, Hui DY, Group 1B phospholipase A₂ inactivation suppresses atherosclerosis and metabolic diseases in LDL receptor-deficient mice, *Atherosclerosis* 234 (2014) 377–380. [PubMed: 24747111]
- [25]. Hollie NI, Cash JG, Matlib MA, Wortman M, Basford JE, Abplanalp W, Hui DY, Micromolar changes in lysophosphatidylcholine concentration cause minor effects on mitochondrial permeability but major alterations in function, *Biochim. Biophys. Acta* 1841 (2014) 888–895. [PubMed: 24315825]

- [26]. Hui DY, Cope MJ, Labonte ED, Chang H-T, Shao J, Goka E, Abousalham A, Charnot D, Buysse J, The Phospholipase A₂ inhibitor methyl indoxam suppresses diet-induced obesity and glucose intolerance in mice, *Br. J. Pharmacol* 157 (2009) 1263–1269. [PubMed: 19563529]
- [27]. Singer AG, Ghomashchi F, Le Calvez C, Bollinger J, Bezzine S, Rouault M, Sadilek M, Nguyen E, Lazdunski M, Lambeau G, Gelb MH, Interfacial Kinetic and Binding Properties of the Complete Set of Human and Mouse Groups I, II, V, X, and XII Secreted Phospholipases A₂, *J. Biol. Chem* 277 (2002) 48535–48549. [PubMed: 12359733]
- [28]. Entwistle LJ, Pelly VS, Coomes SM, Kannan Y, Perez-Lloret J, Czieso S, Silva dos Santos M, MacRae JI, Collinson L, Sesay A, Nikolov N, Metidji A, Helmby H, Hui DY, Wilson MS, Epithelial-cell-derived phospholipase A₂ group 1b is an endogenous anthelmintic, *Cell Host Microbe*, 22 (2017) 484–493. [PubMed: 29024642]
- [29]. Wellner N, Diep TA, Janfelt C, Hansen HS, N-acylation of phosphatidylethanolamine and its biological functions in mammals, *Biochim. Biophys. Acta* 1831 (2013) 652–662. [PubMed: 23000428]
- [30]. Sipahi AM, Baptista DM, Helminths as an alternative therapy for intestinal diseases, *World J. Gastroenterol* 23 (2017) 6009–6015. [PubMed: 28970717]
- [31]. Zuo T, Kamm MA, Colombel JF, Ng SC, Urbanization and the gut microbiota in health and inflammatory bowel disease, *Nat. Rev. Gastroenterol. Hepatol* 15 (2018) 440–452. [PubMed: 29670252]
- [32]. Burcelin R, Gut microbiota and immune crosstalk in metabolic disease, *Mol. Metab* 5 (2016) 771–781. [PubMed: 27617200]
- [33]. Hartstra AV, Bouter KEC, Backhed F, Nieuwdorp M, Insights into the role of the microbiome in obesity and type 2 diabetes, *Diabetes Care* 38 (2015) 159–165. [PubMed: 25538312]
- [34]. Kootte RS, Vrieze A, Holleman F, Dallinga-Thie GM, Zoetendal EG, de Vos WM, Groen AK, Hoekstra JBL, Stroes ES, Nieuwdorp M, The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus, *Diabetes Obes. Metab* 14 (2012) 112–120. [PubMed: 21812894]
- [35]. Pace F, Carvalho BM, Zanotto TM, Santos A, Guadagnini D, Silva KLC, Mendes MCS, Rocha g.Z., Alegretti SM, Santos GA, Catharino RR, Paroni R, Folli F, Saad MJA, Helminth infection in mice improves insulin sensitivity via modulation of gut microbiota and fatty acid metabolism, *Pharmacol. Res* 132 (2018) 33–46. [PubMed: 29653264]
- [36]. Xia W, Xie L, Cao a., Cheng S, Wan H, Liu H, Genes involved in leukotriene synthesis pathway are dynamically regulated during lung development in Rhesus monkeys, *Prostaglandins. Leukotr. Essent. Fatty Acids* 122 (2017) 1–6.
- [37]. Hite RD, Grier BL, Waite BM, Veldhuizen RA, Possmayer F, Yao LJ, Seeds MC, Surfactant protein B inhibits secretory phospholipase A₂ hydrolysis of surfactant phospholipids, *Am. J. Physiol* 302 (2012) L257–L265.
- [38]. Tamaru S, Mishina H, Watanabe Y, Watanabe K, Fujioka D, Takahashi S, Suzuki K, Nakamura T, Obata JE, Kawabata K, Yokota Y, Murakami M, Hanasaki K, Kugiyama K, Deficiency of phospholipase A₂ receptor exacerbates ovalbumin-induced lung inflammation, *J. Immunol* 191 (2013) 1021–1028. [PubMed: 23817419]
- [39]. Kanemasa T, Arimura A, Kishino J, Ohtani M, Arita H, Contraction of guinea pig lung parenchyma by pancreatic type phospholipase A₂ via its specific site, *FEBS Lett* 303 (1992) 217–220. [PubMed: 1607021]
- [40]. Henderson WR, Chi EY, Bollinger JG, Tien Y.-t., Ye X, Castelli L, Rubtsov YP, Singer AG, Chiang GKS, Nevalainen TJ, Rudensky AY, Gelb MH, Importance of group X-secreted phospholipase A₂ in allergen-induced airway inflammation and remodeling in a mouse asthma model, *J. Exp. Med* 204 (2007) 865–877. [PubMed: 17403936]
- [41]. Triggiani M, Granata F, Giannattasio G, Marone G, Secretory phospholipase A₂ in inflammatory and allergic diseases: not just enzymes, *J. Allergy Clin. Immunol* 116 (2005) 1000–1006. [PubMed: 16275367]
- [42]. Granata F, Petraroli A, Biolard E, Bezzine S, Bollinger JG, Del Vecchio L, Gelb MH, Lambeau G, Marone G, Triggiani M, Activation of cytokine production by secreted phospholipase A₂ in

human lung macrophages expressing the M type receptor, *J. Immunol* 174 (2005) 464–474. [PubMed: 15611272]

- [43]. Mandal AK, Zhang Z, Chou JY, and Mukhejee AB, Pancreatic phospholipase A₂ via its receptor regulates expression of key enzymes of phospholipid and sphingolipid metabolism, *FASEB J* 15 (2001) 1834–1836. [PubMed: 11481246]
- [44]. Hanasaki K, Arita H, Phospholipase A₂ receptor: a regulator of biological functions of secretory phospholipase A₂, *Prostaglandins Other Lipid Mediat* 68–69 (2002) 71–82.
- [45]. Kuhn T, Floegel A, Sookthai D, Johnson TE, Rolle-Kampczyk U, Otto W, Von Bergen M, Boeing H, Kaaks R, High plasma levels of lysophosphatidylcholine 18:0 are related to a lower risk of common cancers in a prospective metabolomics study, *BMC Med. Genet* 14 (2016) 13.
- [46]. Zhao Z, Xiao Y, Elson P, Tan HS, Plummer SJ, Berk M, Aung PP, Lavery IC, Achkar JP, Li L, Casey G, Xu Y, Plasma lysophosphatidylcholine levels: potential biomarkers for colorectal cancer, *J. Clin. Oncol* 25 (2007) 2696–2701. [PubMed: 17602074]
- [47]. Shen S, Yang L, Li L, Bai Y, Cai C, Liu H, A plasma lipidomics strategy reveals perturbed lipid metabolic pathways and potential lipid biomarkers of human colorectal cancer, *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci* 1068–1069 (2017) 41–48.
- [48]. Stearns TM, Cario CL, Savage HS, Sundberg JP, Paigen B, Berndt A, Early gene expression differences in inbred mouse strains with susceptibility to pulmonary adenomas, *Exp. Mol. Pathol* 93 (2012) 455–461. [PubMed: 23026400]
- [49]. Liu Y, Ni R, Zhang H, Miao L, Wang J, Jia W, Wang Y, Identification of feature genes for smoking-related lung adenocarcinoma based on gene expression profile data, *Onco. Targets Ther* 9 (2016) 7397–7407. [PubMed: 27994470]

Figure 1.

Schematic diagram depicting differences between PLA2G1B and PLB activities in the digestive tract. Lipolytic enzymes secreted by the pancreas, including pancreatic triacylglycerol lipase (PTL), carboxyl ester lipase (CEL) and PLA2G1B catalyze the hydrolysis of lipid droplets in intestine lumen near the duodenum and jejunum region, liberating free fatty acid (FFA), cholesterol (CH), and lysophospholipids such as lysophosphatidylcholine (LPC) for absorption into the intestine. The FFA and CH are used for triacylglycerol and cholesterol ester synthesis and packaged into chylomicrons (chylo's) for secretion into the plasma. The phospholipase B (PLB) catalyzes similar process in the ileum area but generates glycerylphosphoryl choline (GPC) instead of lysophospholipids.

Figure 2.

Schematic diagram comparing intestinal helminth infection in *Pla2g1b*^{+/+} and *Pla2g1b*^{-/-} mice. After ingestion of the worm, the larvae penetrates the intestinal epithelium into the mucosa. In *Pla2g1b*^{+/+} mice, PLA2G1B hydrolyzes the larval phospholipids to enable trapping of the larvae by Th2 cells and killing of the helminth. In *Pla2g1b*^{-/-} mice, Th2 killing of helminth is ineffective due to lack of larval phospholipid hydrolysis. The larvae can germinate to adult worm and reinfection of the gut epithelium.