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Metabolic regulation by secreted phospholipase A$_2$

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Abstract

Within the phospholipase A$_2$ (PLA$_2$) superfamily that hydrolyzes phospholipids to yield fatty acids and lysophospholipids, the secreted PLA$_2$ (sPLA$_2$) enzymes comprise the largest family that contains 11 isoforms in mammals. Individual sPLA$_2$s exhibit unique distributions and specific enzymatic properties, suggesting their distinct biological roles. While sPLA$_2$s have long been implicated in inflammation and atherosclerosis, it has become evident that they are involved in diverse biological events through lipid mediator-dependent or mediator-independent processes in a given microenvironment. In recent years, new biological aspects of sPLA$_2$s have been revealed using their transgenic and knockout mouse models in combination with mass spectrometric lipidomics to unveil their target substrates and products in vivo. In this review, we summarize our current knowledge of the roles of sPLA$_2$s in metabolic disorders including obesity, hepatic steatosis, diabetes, insulin resistance, and adipose tissue inflammation.

Keywords: Fatty acid, Lipoprotein, Obesity, Phospholipid, Phospholipase A$_2$

Background

Phospholipase A$_2$ (PLA$_2$) is a group of enzymes that hydrolyze phospholipids to yield fatty acids and lysophospholipids (Fig. 1). In general, this reaction is best known as the initial, rate-limiting step of arachidonate metabolism leading to the production of bioactive lipid mediators including prostaglandins and leukotrienes. The mammalian genome encodes more than 30 PLA$_2$s or related enzymes, among which the secreted phospholipase A$_2$ (sPLA$_2$) family consists of low molecular mass and Ca^{2+}-requiring enzymes with a conserved His-Asp catalytic dyad and includes 11 isoforms (IB, IIA, IIC, IID, IIE, IIF, III, V, X, XIIA, and XIIB) [1–5]. Beyond cytosolic PLA$_2$ (cPLA$_2$α; group IVA PLA$_2$) whose regulatory roles in arachidonate metabolism have been well documented [6], the biological roles of sPLA$_2$s remained a mystery for more than two decades. Recent studies using mice that have been gene manipulated for sPLA$_2$s have begun to reveal their distinct and unique roles in various biological events [7–14]. The current understanding of the in vivo functions of sPLA$_2$s has been summarized in several reviews [1–5].

Historically, sPLA$_2$s have long been implicated in inflammation and atherosclerosis. This idea stems from the observations that sPLA$_2$-IIA, a prototypic "inflammatory sPLA$_2$," is induced during inflammation [15] and that hydrolysis of low-density lipoprotein (LDL) by sPLA$_2$s gives rise to pro-atherogenic LDL, which promotes macrophage foam cell formation in vitro [16, 17]. Indeed, subsequent genetic and pharmacological approaches support the pro-inflammatory or atherosclerotic roles of sPLA$_2$s [10–14]. However, the regulatory roles of sPLA$_2$s in metabolic disorders including obesity and insulin resistance have not yet been fully elucidated. Recently, it has become clear that several sPLA$_2$s are expressed in the adipose tissue or gastrointestinal (GI) tract and have variable influences on systemic metabolic states [18–20]. Here, we will make an overview of the novel biological roles of sPLA$_2$s and the lipid pathways underlying metabolic regulation, as revealed by sophisticated knockout and lipidomics techniques.
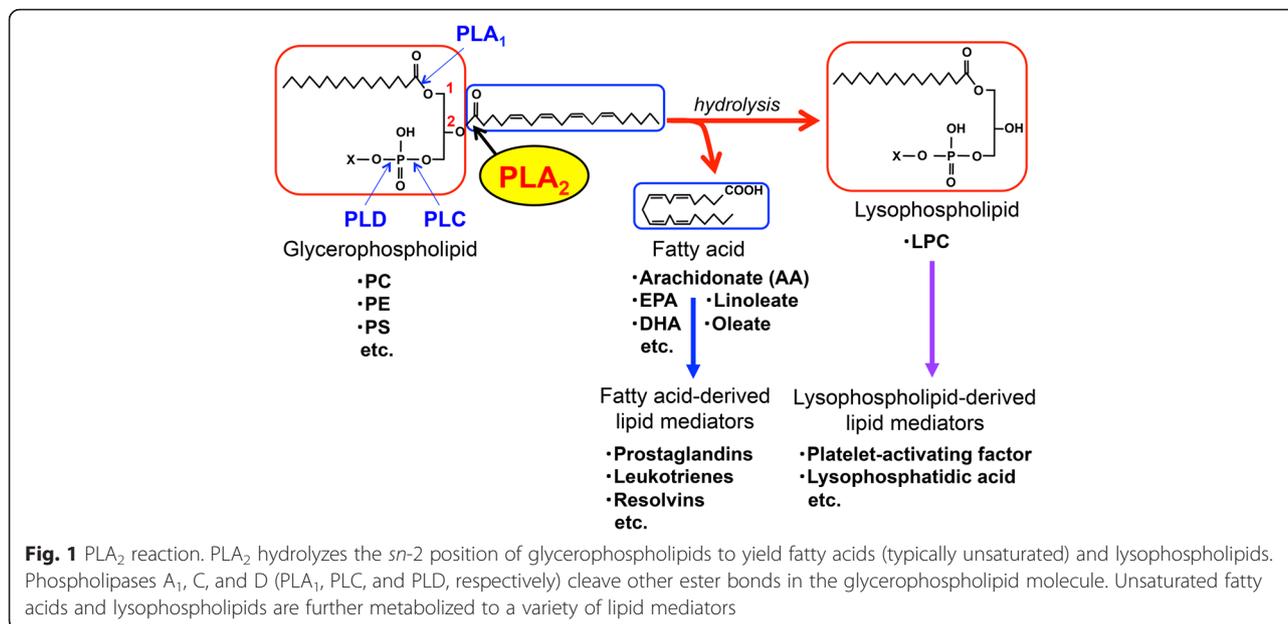
sPLA$_2$-V, a "metabolic sPLA$_2$"

Metabolic syndrome is increasing at an explosive rate worldwide due to a pandemic of obesity associated with diabetes, insulin resistance, non-alcoholic fatty liver disease, and hyperlipidemia [21]. The mechanisms connecting obesity to insulin resistance include an elevated level

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Sato *et al. Inflammation and Regeneration* (2016) 36:7

Page 2 of 7

Fig. 1 PLA$_2$ reaction. PLA$_2$ hydrolyzes the *sn*-2 position of glycerophospholipids to yield fatty acids (typically unsaturated) and lysophospholipids. Phospholipases A$_1$, C, and D (PLA$_1$, PLC, and PLD, respectively) cleave other ester bonds in the glycerophospholipid molecule. Unsaturated fatty acids and lysophospholipids are further metabolized to a variety of lipid mediators

of circulating lipids, ectopic lipid deposition leading to lipotoxicity, and chronic inflammation in metabolically active tissues [22]. Obesity arises through the dysregulations of intracellular lipid metabolism or extracellular lipid partitioning among tissues, and the perturbation of intracellular/extracellular lipases variably and often profoundly affect obesity and insulin resistance [23–26]. For instance, lipoprotein lipase is an obesity susceptibility factor showing an inverse relationship between its activity and obesity-related traits in humans [23]. The imbalanced accumulation of LDL in favor of high-density lipoprotein (HDL) is a critical risk factor not only for atherosclerosis but also for insulin intolerance [27]. As lipoprotein particles are shielded by phospholipids, aberrant lipoprotein phospholipid metabolism could also influence lipid partitioning and thereby obesity.

Among the sPLA$_2$ isoforms, sPLA$_2$-V potently hydrolyzes phospholipids in lipoproteins (LDL > HDL) in vitro [17]. However, studies using *Pla2g5*$^{-/-}$ mice have failed to demonstrate the participation of sPLA$_2$-V in LDL metabolism in atherosclerosis models [11, 28]. Except for studies using sPLA$_2$-overexpressing transgenic mice [17, 29, 30], no reports have firmly established whether endogenous sPLA$_2$s affect lipoprotein metabolism in vivo. In a microarray search for unique lipase-related genes whose expressions are associated with obesity, we recently found that sPLA$_2$-V (and sPLA$_2$-IIE; see below) is robustly induced in adipocytes of obese mice [18]. This sPLA$_2$-V induction is dependent on adipogenesis plus endoplasmic reticulum (ER) stress. Because of this property plus the fact that sPLA$_2$-V is constitutively expressed at relatively high levels in several metabolic tissues such as the heart and skeletal muscle, we refer to sPLA$_2$-V as a "metabolic sPLA$_2$."

Notably, when fed a high-fat diet (HFD), *Pla2g5*$^{-/-}$ mice display hyperlipidemia with higher plasma levels of LDL, increased obesity and hepatic steatosis, and lower insulin sensitivity [18]. Furthermore, the adipose tissues in *Pla2g5*$^{-/-}$ mice show a greater infiltration of M1 macrophages and a higher expression of pro-inflammatory cytokines. Thus, sPLA$_2$-V plays anti-obesity and anti-inflammatory roles in the context of metabolic disorders. Lipidomics have revealed that sPLA$_2$-V secreted from hypertrophic adipocytes preferentially hydrolyzes phosphatidylcholine (PC) in fat-overladen LDL to release unsaturated fatty acids (e.g., oleate and linoleate) in vivo [18]. As such, the increased LDL lipid levels in *Pla2g5*$^{-/-}$ mice could impact on adipocyte hypertrophy and the fatty liver. Furthermore, in accordance with the alterations in LDL phospholipids, the levels of free oleate and linoleate are lower in the adipose tissue of HFD-fed *Pla2g5*$^{-/-}$ mice than in that of WT mice. These unsaturated fatty acids released by sPLA$_2$-V dampen the M1 macrophage polarization by saturated fatty acids (e.g., palmitate) likely through the attenuation of ER stress. This mechanism fits with the view that sPLA$_2$-V has an apparent, even if not strict, substrate preference for PC bearing a fatty acid with a low degree of unsaturation.

It remains obscure whether the sPLA$_2$-V action would depend on the production of ω6 arachidonic acid-derived eicosanoids (e.g., prostaglandins and leukotrienes) or ω3 polyunsaturated fatty acid (e.g., eicosapentaenoic acid and docosahexaenoic acid)-derived pro-resolving lipid mediators (e.g., resolvins and protectins), since the adipose tissue levels of these fatty acid metabolites were not affected by *Pla2g5* deficiency. Rather, sPLA$_2$-V contributes to

Sato *et al. Inflammation and Regeneration* (2016) 36:7

Page 3 of 7

controlling the quality of the lipids, i.e., the balance between saturated (detrimental) and unsaturated (beneficial) fatty acids, in adipose tissue microenvironments, providing a novel insight into the sPLA$_2$ action beyond lipid mediators. Together, these results reveal a functional link between lipoprotein metabolism and anti-inflammation for this particular sPLA$_2$ and provide a rationale for the long-standing issue of the physiological importance of lipoprotein hydrolysis by this extracellular enzyme family (Fig. 2).

Another intriguing feature of sPLA$_2$-V is that it is a "Th2/M2-prone sPLA$_2$," allowing a shift in the immune balance toward the Th2/M2 status. Apart from the crucial role of adipocyte- rather than macrophage-derived sPLA$_2$-V in obesity, the *Pla2g5* expression in macrophages is markedly induced by the M2-skewing Th2 cytokines IL-4 and IL-13 and the *Pla2g5* ablation decreases the Th2-mediated immune responses [18, 31]. In vitro, exogenous sPLA$_2$-V is capable of facilitating the M2 polarization of macrophages probably through augmenting the prostaglandin E$_2$ production [18]. Furthermore, in human macrophages, sPLA$_2$-V induced by IL-4 promotes phagocytosis through the production of lysophosphatidylethanolamine [32]. Given the increased incidence of metabolic disorders resulting from the genetic ablation of Th2 or M2 inducers (e.g., *Il4*, *Il13*, *Il33*, *Stat6*, or *Pparg*) [33], the decreased whole-body Th2/M2 status resulting from *Pla2g5* deficiency may also contribute to the exacerbation of obesity-associated inflammation. This notion also accords with the observations that *Pla2g5*$^{-/-}$ mice are protected from asthma (Th2 dependent) [31], while suffering from more severe fungal infection (Th1 dependent) or arthritis (Th17 dependent) [10, 34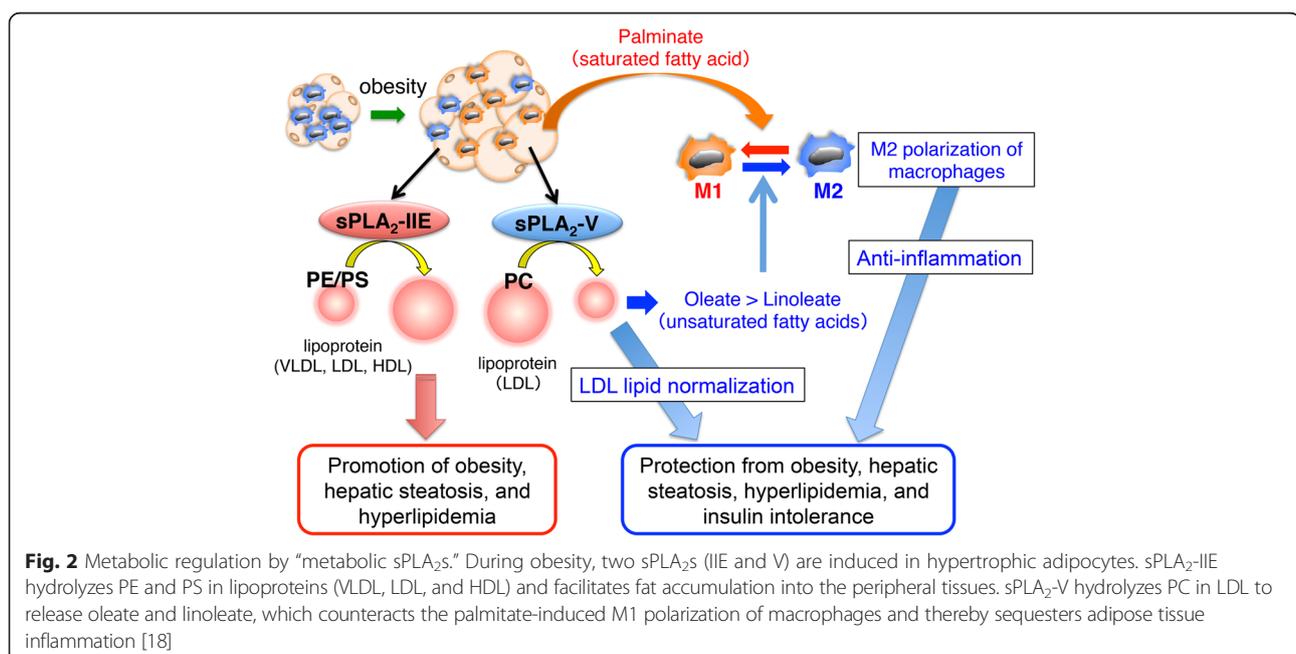], where the Th2 immunity counteracts the Th1/Th17-based inflammations. Thus, the fact that sPLA$_2$-V acts as a Th2/M2-prone sPLA$_2$ can account for the pro- versus anti-inflammatory actions of this enzyme in distinct immunopathological settings (Fig. 3).

Notably, in humans, *Pla2g5* gene polymorphisms correlate with the LDL levels in subjects with type 2 diabetes or obesity [35, 36]. The in vitro sPLA$_2$-V susceptibility of LDL from patients with type 2 diabetes is greater than that of LDL from healthy controls [37]. Moreover, the *Pla2g5* expression in the human visceral adipose tissue inversely correlates with LDL plasma levels [18]. These results imply a human relevance for the metabolic role of sPLA$_2$-V.

sPLA$_2$-IIE, another "metabolic sPLA$_2$"

We also found that sPLA$_2$-IIE, which remained a functionally orphan sPLA$_2$ for more than a decade, acts as another "metabolic" sPLA$_2$ that is induced in hypertrophic adipocytes [18]. An adipogenic stimulus is sufficient for induction of sPLA$_2$-IIE in adipocytes. *Pla2g2e*$^{-/-}$ mice are modestly protected from diet-induced obesity, hepatic steatosis, and hyperlipidemia. In contrast to sPLA$_2$-V, which hydrolyzes PC in LDL to selectively release oleate and linoleate (see above), sPLA$_2$-IIE preferentially hydrolyzes minor lipoprotein phospholipids, phosphatidylserine (PS), and phosphatidylethanolamine (PE), with no apparent fatty acid selectivity. As such, sPLA$_2$-IIE alters the lipid composition of lipoproteins, thereby moderately affecting the lipid accumulation in the adipose tissue and liver.

Although the molecular mechanism that links lipoprotein PS/PE hydrolysis with obesity still remains unclear, this study revealed for the first time the importance of
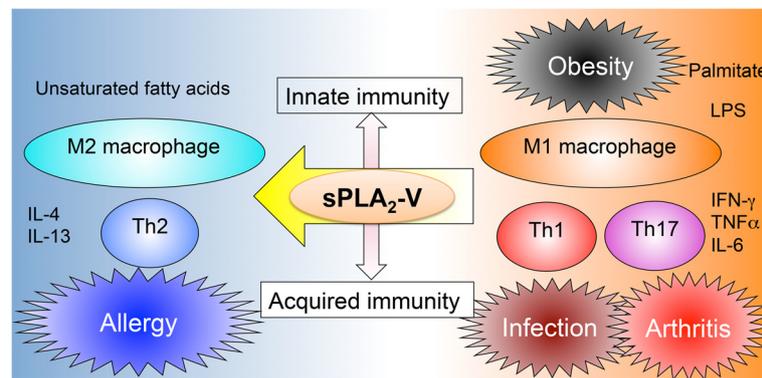

Fig. 2 Metabolic regulation by "metabolic sPLA$_2$s." During obesity, two sPLA$_2$s (IIE and V) are induced in hypertrophic adipocytes. sPLA$_2$-IIE hydrolyzes PE and PS in lipoproteins (VLDL, LDL, and HDL) and facilitates fat accumulation into the peripheral tissues. sPLA$_2$-V hydrolyzes PC in LDL to release oleate and linoleate, which counteracts the palmitate-induced M1 polarization of macrophages and thereby sequesters adipose tissue inflammation [18]

Sato *et al. Inflammation and Regeneration* (2016) 36:7

Page 4 of 7

Fig. 3 Immune balance regulation by sPLA$_2$-V. sPLA$_2$-V is induced in the M2 macrophages and Th2 cells by IL-4 or IL-13 and promotes Th2/M2-dominant immunity such as asthma [31, 32]. Conversely, sPLA$_2$-V plays protective roles in Th1- or Th17-type immune responses including obesity, infection, and arthritis [10, 18, 34]

these minor lipoprotein phospholipids in metabolic regulation. As the increase of the negative charges in lipoproteins by oxidative modification renders the particles smaller, the increase of the anionic phospholipids (e.g., PS) in lipoproteins by the absence of sPLA$_2$-IIE may also afford a similar effect. Alternatively, lysophosphatidylethanolamine or lysophosphatidylserine produced by sPLA$_2$-IIE might have some metabolic effects, a possibility that awaits future studies. Collectively, these results underscore the physiological relevance of lipoprotein hydrolysis by distinct sPLA$_2$s and highlight the importance of "metabolic sPLA$_2$s" as the integrated regulators of metabolic responses (Fig. 2).

On the other hand, another study has recently reported that $Pla2g2e^{-/-}$ mice accumulate more epididymal fat as they age [38]. During adipogenesis, the genetic deletion or siRNA knockdown of sPLA$_2$-IIE increases the triglyceride in adipocytes, while its overexpression or exogenous addition facilitates lipolysis. Although the reason for the discrepancy between the two studies is unclear, it might have arisen from different experimental conditions (HFD versus chow diets or female versus male mice) in different animal facilities.

sPLA$_2$-IB, a "digestive sPLA$_2$"
Systemic lipid metabolism is often affected by the digestion and absorption of dietary lipids in the GI tract. sPLA$_2$-IB is synthesized by pancreatic acinar cells, and after secretion as a zymogen into pancreatic juice, an *N*-terminal propeptide of the inactive zymogen is cleaved by trypsin to yield an active enzyme in the duodenum. The hydrolysis of PC by sPLA$_2$-IB is greatly accelerated in the presence of a low concentration of detergent such as deoxycholate [39]. This property appears to be physiologically important since the digestion of dietary phospholipids by sPLA$_2$-IB occurs in the presence of bile acid in the GI tract.

$Pla2g1b^{-/-}$ mice show resistance to obesity, lower plasma insulin and leptin levels, and improved glucose tolerance when fed a high-fat/carbohydrate diet [40]. These phenotypes of $Pla2g1b^{-/-}$ mice are most likely due to a marked reduction in the hydrolysis of dietary and biliary PC and thereby in the production and absorption of lysophosphatidylcholine (LPC) in the GI tract. The increased intestinal absorption of LPC promotes postprandial hyperglycemia by inhibiting the glucose uptake by the liver and muscle, and accordingly, the absence of sPLA$_2$-IB reduces the postprandial LPC levels, leading to improved insulin sensitivity and hepatic fatty acid oxidation [41, 42]. It is noteworthy that $Pla2g1b^{-/-}$ mice on a $Ldlr^{-/-}$ background are protected from body weight gain and atherosclerosis in response to a hypercaloric diet [43] and that the oral administration of the sPLA$_2$ inhibitor methyl indoxam along with a diabetogenic diet effectively suppresses diet-induced obesity and diabetes in mice likely through the prevention of the intestinal digestion of dietary and biliary PC by sPLA$_2$-IB [44]. In further support of these observations, pancreatic acinar cell-specific $Pla2g1b$-transgenic mice develop more severe obesity and insulin resistance [45]. These results suggest that the inhibition of sPLA$_2$-IB, a "digestive sPLA$_2$," may be an effective oral therapeutic option for the treatment of diet-induced obesity and diabetes.

Complex and enigmatic roles of sPLA$_2$-X in metabolism
Lastly, we briefly summarize the possible metabolic roles of sPLA$_2$-X, although details remain uncertain because of the fact that conflicting results have been obtained. Like sPLA$_2$-IB, sPLA$_2$-X also has an *N*-terminal propeptide, and its proteolytic removal leads to the full activation of the enzyme. A series of studies have provided some insights into the functional link of sPLA$_2$-X-released polyunsaturated fatty acids to lipid-sensing nuclear receptor signaling. Macrophages from $Pla2g10^{-/-}$ mice show an increased

Sato *et al. Inflammation and Regeneration* (2016) 36:7

Page 5 of 7

expression of the cholesterol efflux transporters ABCA1 and ABCG1, and this effect appears to be dependent on the suppression of the liver X receptor (LXR) by sPLA$_2$-X-released polyunsaturated fatty acids [46]. Moreover, the increased cholesterol content of the lipid rafts in $Pla2g10^{-/-}$ macrophages leads to significant reduction of endotoxin-induced inflammation [47]. The sPLA$_2$-X-dependent suppression of LXR can also occur in the adipose tissue, where $Pla2g10$ deficiency facilitates adipogenesis and obesity [48], and in the adrenal glands, where its deficiency promotes corticosteroidogenesis through the activation of steroidogenic acute regulatory protein [49]. In the latter case, pro-sPLA$_2$-X is proteolytically processed to a mature, active form by the protein convertases furin and PCSK6, which are induced by the adrenocorticotropic hormone, in adrenal cells [50]. However, as far as we have been able to examine, the $Pla2g10$ expression in mouse macrophages and the adipose tissue is very low, arguing against the above observations. Rather, we prefer the idea that sPLA$_2$-X might be expressed in a limited subset of these cells or supplied from proximal or distal cells in a paracrine manner.

On the other hand, we have shown that sPLA$_2$-X is expressed abundantly in GI-lining cells and participates in phospholipid digestion [19]. Accordingly, $Pla2g10^{-/-}$ mice display a reduced age-associated adiposity and improved insulin sensitivity in the skeletal muscle, likely through a mechanism reminiscent of that in $Pla2g1b^{-/-}$ mice. Thus, the two "digestive sPLA$_2$s" (IB and X) may spatiotemporally control the hydrolysis of dietary and biliary phospholipids and thereby the absorption of their hydrolytic products, depending on the quantity and quality of the dietary and biliary fat input. As in the case of $Pla2g2e^{-/-}$ mice (see above), the opposite phenotypes of $Pla2g10^{-/-}$ mice observed in different studies might have been due to differences in the experimental models or housing conditions employed, and further studies will be necessary to clarify more definitively the roles and mechanistic actions of sPLA$_2$-X in metabolism.

It has been recently reported that the glucose-stimulated insulin secretion by islet β cells is augmented in $Pla2g10^{-/-}$ mice, underscoring a novel metabolic role of sPLA$_2$-X [51]. Mechanistically, sPLA$_2$-X negatively regulates insulin secretion by augmenting the cyclooxygenase-2-dependent prostaglandin E$_2$ production. In this scenario, targeting sPLA$_2$-X may be an effective therapeutic option for enhancing β cell function in the treatment of diabetes.

Conclusions

It is now obvious that at least four sPLA$_2$s are involved in metabolic regulation through distinct mechanisms, as summarized below. sPLA$_2$-V is induced in hypertrophic adipocytes by obesity-associated ER stress and hydrolyzes PC in hyperlipidemic LDL to facilitate the skewing of macrophages from M1 to M2 subsets, thereby conferring protection from adipose tissue inflammation, insulin resistance, obesity, hepatic steatosis, and hyperlipidemia. The saturated fatty acids supplied abundantly from adipocytes trigger the M1 polarization of macrophages, which is counterregulated by the sPLA$_2$-V-driven unsaturated fatty acids from LDL. sPLA$_2$-IIE is induced in adipocytes in accordance with adipogenesis and hydrolyzes PE and PS in lipoproteins, eventually promoting fat storage in the adipose tissue and liver. sPLA$_2$-IB, a pancreatic sPLA$_2$ that is secreted into the GI lumen, hydrolyzes dietary and biliary phospholipids to promote lipid digestion and absorption, which is associated with obesity and hepatic insulin resistance. sPLA$_2$-X variably affects metabolism possibly through the production of polyunsaturated fatty acids that modify the LXR signaling in the adipose tissue, through the digestion of the dietary and biliary phospholipids in the gut, or through the generation of prostaglandin E$_2$ that suppresses insulin secretion in the pancreatic islet. In addition, sPLA$_2$-IIA is abundantly expressed in the human and rat adipose tissues in obesity and the pharmacological inhibition of this isoform attenuates the adipose tissue inflammation in rats [18, 52]. It remains possible that other sPLA$_2$ isoforms may also participate in metabolic regulation, and this issue is now under investigation. Together, these studies have brought about a paradigm shift toward a better understanding of the biological roles of this extracellular lipolytic enzyme family as coordinators of metabolism.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
HS, YT, and MM wrote this review. All authors read and approved the final manuscript.

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Sato *et al. Inflammation and Regeneration* (2016) 36:7

Page 6 of 7

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Sato *et al. Inflammation and Regeneration* (2016) 36:7

Page 7 of 7

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