Invited Mini Review

Emerging roles of PHLPP phosphatases in metabolism

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Over the last decades, research has focused on the role of pleckstrin homology (PH) domain leucine-rich repeat protein phosphatases (PHLPPs) in regulating cellular signaling via PI3K/Akt inhibition. The PKB/Akt signaling imbalances are associated with a variety of illnesses, including various types of cancer, inflammatory response, insulin resistance, and diabetes, demonstrating the relevance of PHLPPs in the prevention of diseases. Furthermore, identification of novel substrates of PHLPPs unveils their role as a critical mediator in various cellular processes. Recently, researchers have explored the increasing complexity of signaling networks involving PHLPPs whereby relevant information of PHLPPs in metabolic diseases was obtained. In this review, we discuss the current knowledge of PHLPPs on the well-known substrates and metabolic regulation, especially in liver, pancreatic beta cell, adipose tissue, and skeletal muscle in relation with the stated diseases. Understanding the context-dependent functions of PHLPPs can lead to a promising treatment strategy for several kinds of metabolic diseases. [BMB Reports 2021; 54(9): 451-457]

INTRODUCTION

The pleckstrin homology (PH) domain leucine-rich repeat protein phosphatase (PHLPP) was discovered in the suprachiasmatic nucleus (SCN) of the hypothalamus of a rat as a protein whose mRNA expression levels oscillated in a circadian rhythm-dependent fashion and was therefore named as SCN circadian oscillatory protein (SCOP) to represent its behavior (1). Several years later, the ability of SCOP to act as a serine/threonine kinase Akt-specific phosphatase was identified (2). Years after the discovery of Akt-specific phosphatase, more evidence has been accumulated that PHLPP family has different substrates which possess different biology in managing the activity and

stability of kinases with respect to cellular processes including cell growth, survival, or metabolism. This review provides an overview of PHLPPs by highlighting recent findings on their roles as novel regulators in cellular metabolism.

PHLPP: GENE AND PROTEIN ORGANIZATION

The PHLPP family of phosphatases composes of PHLPP1α (1205 amino acids), PHLPP1β (1717 amino acids, corresponding to SCOP), and PHLPP2 (1323 amino acids, also referred as PHLPPL). PHLPP1α and PHLPP1β are produced by two splice variants from the same gene located at chromosome 18q21.33, and have different sizes because of a 56 kDa N-terminal extension (3), while the PHLPP2 gene resides at the chromosomal location 16q22.3 (4).

The PHLPP family composes the same domain including N-terminal domain, PH domain, leucine-rich repeat (LRR) region, protein phosphatase 2C (PP2C) phosphatase domain, and C-terminal postsynaptic density protein PSD95, *Drosophila* disc large tumor suppressor DLG1, and zonula occludens-1 protein zo-1 (PDZ)-binding motif (Fig. 1) (2, 5). In addition, PHLPP1β and PHLPP2 comprises a Ras association domain (RA domain) preceding the PH domain, and PHLPP1 and PHLPP2 share 58% and 63% amino acid identify in the PP2C domain and PH domain, respectively (2). Despite the three isoforms namely PHLPP1α, PHLPP1β, and PHLPP2 have similar domain structures, they have a certain degree of substrate specificity. Additionally, although the PHLPP isoforms are ubiquitously expressed, their levels vary within different tissues and are broadly associated with its scaffolding proteins in the cytoplasm, nucleus, plasma membrane and mitochondria (6-10). The substrates of the PHLPP isoforms will be discussed briefly in the following section.

PHLPP SUBSTRATES AND SIGNALING NETWORK

Akt
PHLPP was identified in a rational research for a phosphatase that dephosphorylated Akt (2). Three Akt isoforms in mammals, Akt1, Akt2, and Akt3, require phosphorylation at the hydrophobic motif (Ser473) and activation loop (Thr308) to acquire full catalytic activity, which further characterize the downstream substrates of Akt (11). PHLPPs specifically regulate dephospho-
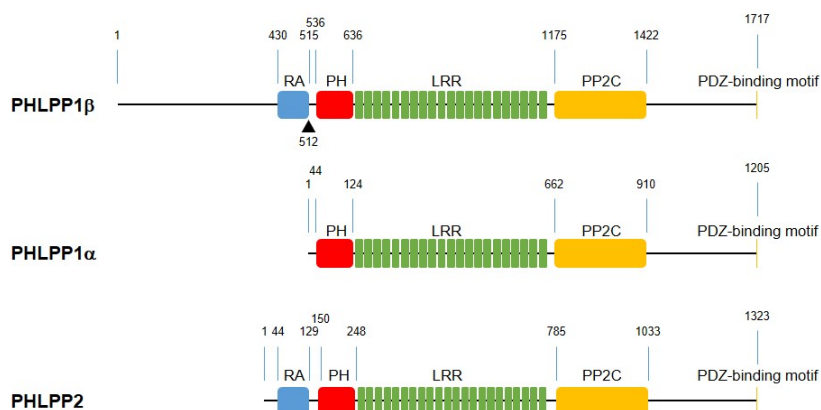
Fig. 1. Domain architecture of PHLPP isoforms. PHLPP family retains the Ras association domain (RA), pleckstrin homology (PH) domain, leucine rich repeat region (LRR), PP2C domain and PDZ binding motif. Black arrow head denotes the splice site for PHLPP1β.

rylation on the hydrophobic motif of Akt in cells, resulting in decreased activity of Akt (2). Interestingly, isoforms of PHLPPs have substrate specificity in regulating three Akt isoforms. Genetic depletion study elucidated that PHLPP1 regulated the Akt2 and Akt3 phosphorylation, while PHLPP2 affected the Akt1 and Akt2 phosphorylation (4). Specificity of PHLPPs in regulation of Akt isoforms could rewire the differential regulation of specific Akt substrates. For example, the PHLPP1-Akt2 pathway acts on both HDM2 and glycogen synthase 3α (GSK3α) to prevent p53 degradation, whereas the PHLPP2-Akt1 plays the activity of p27 to inhibit cell cycle progression (3, 4). Both isoforms dephosphorylate Akt2, modulating the GSK3β and tuberous sclerosis complex 2 (TSC2) phosphorylation to restrain cell survival (4). As the Akt signaling contributes to the expanding repertoire of metabolic regulation, especially in the insulin-responsive tissues, we will further discuss its tissue-specific function in disease contexts in the following section.

PKC

Further study demonstrated that both PHLPP1 and PHLPP2 modulate dephosphorylation of the hydrophobic motif site Ser660 on PKC βII (3, 12), which is one of the stable and priming phosphorylation occurring during initial translation, maintaining the protein in a stable, autoinhibited state (13). PKC is unique among the PHLPP1 hydrophobic motif substrates as that phosphate stabilizes the kinase, while dephosphorylation of other substrates, such as Akt and S6K1, attenuates catalytic activities without affecting their stability (2, 14). Thus, total PKC expression levels are negatively correlated with PHLPP1 expression, showing that PKC in tumor is phosphorylated and dephosphorylated PKC is degraded (15). Whereas PKC is reframed as having a tumor suppressive function (16, 17), development of novel approaches to block the dampening of PKC by PHLPP1 may open a new therapeutic strategy for cancer progression.

Mst1

Both PHLPP1 and PHLPP2 manifest their tumor-suppressing roles to induce apoptosis irrespective of the well-known targets of PHLPPs. A member of the STE kinase family, mammalian sterile 20-like kinase 1 (Mst1), is dephosphorylated on the Thr387 inhibitory site, which in turn activates Mst1 and its downstream targets p38 and JNK to impose apoptosis. Similar to Thr387 that is found to be phosphorylated by Akt, the PHLPP-Akt-Mst1 axis constitutes an inhibitory triangle that regulates apoptosis and proliferation, probably in a cell type-dependent fashion (18).

S6K1

Ribosomal protein S6 Kinase 1 (S6K1) is a closely related cousin of Akt and PKC in the AGC kinase family. The S6K1 activation is governed by signaling inputs from growth factor, nutrient, and energy balance directed by downstream of mechanistic target of rapamycin (mTOR), a phosphoinositide 3-kinase-like serine/threonine protein kinases (19, 20). S6K1 activation positively directs protein translation by phosphorylating several downstream components, which is required for protein translation initiation, as S6K1 acts as one of the major substrates of mTOR (21). The study suggested that PHLPP-mediated S6K1 dephosphorylation is independent of its ability to induce Akt dephosphorylation. PHLPP negatively contributes to regulation of both protein translation and cell growth via managing the S6K1 activity directly (14).

RAF1

Hyperactivation of the RAS-RAF signaling in various cancer types is associated with metastasis and poor survival of patients. Both PHLPPs dephosphorylate RAF1 at Ser338, which is downstream of EGFR and Ras (22), inhibiting its kinase activity *in vitro*. The knockdown of PHLPP1 or PHLPP2 increases the invasiveness of colorectal cancer (CRC) cells by inducing duration of RAF-MEK-ERK signaling, epithelial-mesenchymal transition (EMT), which expands properties of tumor progression (23).

Myc

Myc is an oncogenic driver of many types of cancer, including human prostate cancer (PC) and classic genetically engineered mice (GEMs) of the disease (24, 25). Recent study showed that

PHLPP2 induces direct dephosphorylation on the Thr58 site of Myc, leading to an increased in its stability (26). Interestingly, the recurrent mutation on T58A was found in patient with Burkitt's lymphoma to cause increased transformation both *in vitro* and *in vivo* (27, 28). The T58A mutant is constitutively dephosphorylated, which constantly mimic PHLPP2 activity. Therefore, PHLPP2 can be an unexpected, druggable target on PC and its progression driven by myc.

HSL

Hormone-sensitive lipase (HSL) is a critical enzyme in mobilizing fatty acids from stored triacylglycerols (TAGs) (29). Its activity is regulated by phosphorylation of at least four serine. In rat HSL, the Ser563, Ser569 and Ser660 were phosphorylated by protein kinase A (PKA). It is reported that Ser659 and Ser660 are the activity regulating sites *in vitro*. However, the precise molecular events of PKA-mediated activation and dephosphorylation were not yet to be determined. Recent study showed that PHLPP2 directly dephosphorylates HSL on Ser563 and Ser660, which leads to a decreased HSL activity and alters its localization in cytoplasm or at the peripheries of the lipid droplets (30). The PHLPP2-HSL axis is further associated with systemic lipid and glucose homeostasis as well as hepatic lipid accumulation as discussed in the following section.

PHLPPs: IMPLICATIONS IN METABOLIC DISEASES

Since PHLPPs are a negative regulator of key processes and signaling pathways, they have critical roles in several pathologies. The most well-known examples of their roles are in cancer progression, as PHLPPs have been identified as tumor suppressors in many types of cancers (31-34). Since maintaining balanced levels of PHLPP expression is critical for preventing cancer progression, the loss of PHLPP increases cell proliferation, migration, metastasis, and cell motility by activating Akt phosphorylation in the diverse cancer cells, such as pancreatic cancer, colon cancer, prostate cancer, leukemia and glioblastoma, breast cancer and melanoma (8, 26, 35-37). On the other hand, an overexpression of PHLPP leads to inhibition of tumor formation and increases apoptotic cell death decreasing Akt phosphorylation on Ser473 in pancreatic, lung, colon and breast cancer cells (5). Apart from the progression of cancer, growing evidences revealed promising functions of PHLPPs in metabolic diseases, as dysregulation of Akt pathway is related with obesity, insulin resistance, and type 2 diabetes. In addition, identification of novel substrates is associated with cellular metabolic disturbances, emphasizing the significance of PHLPPs in the progression of metabolic diseases, highlighting recent findings on their functions in metabolic regulation.

PHLPPs and regulation of hepatic lipids

With the increased prevalence of obesity and its metabolic consequences, nonalcoholic fatty liver disease (NAFLD), defined by excess liver fat, is becoming the most common chronic liver disease (38-40). Although the molecular mechanisms underlying hepatic lipid homeostasis in NAFLD are not clearly defined, an increase in *de novo* lipogenesis (DNL), a process to synthesize new fatty acids from acetyl coenzyme A (acetyl-CoA), could contribute to the development of NAFLD (41, 42). Obesity-associated insulin resistance and compensatory hyperinsulinemia increases DNL, exacerbating hepatic lipid accumulation in NAFLD (43). Identification of molecular regulator of DNL associated with insulin resistance and hyperinsulinemia is expanding to develop novel therapeutics to improve public health problems including obesity-induced type 2 diabetes and NAFLD. One of the promising targets of DNL is the mTOR that comprises of the catalytic core of two distinct protein complexes namely mTOR complex 1 (mTORC1) and 2 (mTORC2) (44-46). Previous studies suggested that mTORC1-independent Raptor (free Raptor) stabilizes PHLPP2, but not PHLPP1, to reduce signaling through Akt (47, 48). In aged or obese mice, hepatic PHLPP2 levels were lower with decreased free Raptor levels, resulting to prolonged Akt signaling. This allows increased Akt-mediated DNL, that exacerbates NAFLD. These data explain how insulin-mediated Akt action is permissive for increased DNL in obesity-induced insulin resistance.

A recent study suggested more defined mechanisms underlying PHLPP2 degradation in obesity-induced fatty liver. PHLPP2 is rapidly phosphorylated by glucagon/PKA signaling to trigger PHLPP2 degradation. However, its phosphorylation is necessary but not sufficient to induced its degradation. The authors further suggested that obesity-mediated increased potassium channel tetramerization domain containing 17 (KCTD17) in hepatocytes is critical to link PHLPP2 phosphorylation with proteasomal degradation, which elevated Akt signaling and hepatic lipid accumulation (49). Therefore, normalized PHLPP2 levels in the context of NAFLD could provide therapeutic benefits.

PHLPPs, regulation of insulin resistance and pancreatic beta cell dysfunction

Pancreatic beta cell failure, which is characterized by the impaired insulin action or the intrinsic susceptibility of the beta cell to functional exhaustion, is critical to develop insulin resistance and type 2 diabetes (50). While the impaired insulin action in peripheral tissues remains constant as diabetes progresses, beta cell function worsens continuously with disease progression, resulting from the persisting exposure to damaging factors, such as high glucose concentrations (glucotoxicity), increased levels of circulating free fatty acid (lipotoxicity), and chronic inflammation (51-53), which therefore necessitates further studies in beta cell failure. Since Akt contributes to the regulation of beta cell homeostasis (54), modulation of Akt should be actively sought to restore a healthy beta cell. The observations showed that the altered pancreatic beta cell homeostasis upon the chronic high glucose exposure is accompanied by an increased PHLPP1 and PHLPP2 expression both at mRNA and protein levels with a consequent reduction of the phosphorylation levels of Akt. Further knockdown of PHLPPs

is able to curtail a pro-survival profile in INS-1 cells chronically exposed to high glucose concentrations as well as increased Akt phosphorylation and mTOR activation (55). These findings trigger the need for further studies in order to identify pharmacological PHLPPs modulators, raising the possibility of new treatments for beta cell dysfunction.

PHLPPs, insulin resistance, and lipolysis on adipose tissue

Obesity and type 2 diabetes are closely associated with increased adiposity, and insulin resistance is a fundamental characteristic of both diseases (56). As stated above, PHLPPs' substrates specificity on Akt isoforms raised the intriguing possibility of tissue-specific functions of PHLPP family in the context of insulin-responsive or nonresponsive tissues. A report highlighted that the protein levels of PHLPP1 are greatly induced in adipose tissue of morbidly obese participants as compared to non-obese participants and are negatively associated to Ser473 phosphorylation of Akt (57). Interestingly, increased level of PHLPP1 is positively associated with body mass index (BMI), fasting insulin levels and homeostatic model assessment for insulin resistance (HOMA-IR). However, it is observed that PHLPP1 is not further induced in obese participants with impaired fasting glucose or type 2 diabetes (57), showing that enhanced PHLPP1 levels may be related with a state of insulin resistance and compensatory hyperinsulinemia, but not with hyperglycemia.

The function of adipose PHLPP2 in normal or obese states is not well documented. A recent discovery sheds light on a unique role of PHLPP2 in obese adipocytes. The authors revealed that adipocyte PHLPP2 levels are higher in obese mice than in lean animals (30). Interestingly, a decrease in adipocyte PHLPP2 increases adipose lipolysis due to prolonged hormone-sensitive lipase (HSL) phosphorylation, which allows to improve glucose homeostasis, increase peroxisome proliferator-activated receptor alpha (PPARα)-dependent adiponectin secretion, and hepatic fatty acid oxidation to alleviate obesity-induced fatty liver. These findings suggested that blocking excess PHLPP2 in adipocyte may be a therapeutic strategy to improve obesity-induced metabolic comorbidities.

Accumulated evidences showed an association of PHLPP2 with insulin resistance and glucose intolerance (57-61). However, mechanisms underlying increased adipose PHLPP2 expression in patients associated with obesity or diabetes are far less understood. A recent report suggested that hepatic miR-130a-3p targets PHLPP2 to retard dephosphorylation of Akt to change self-stability, which in turn reduced PHLPP2 to activate Akt signaling in adipose cells (62). These data supported new molecular mechanisms by which the crosstalk between liver and adipose tissues improve glucose metabolism, further providing therapeutic options for insulin resistance.

PHLPPs and insulin action on skeletal muscle

Skeletal muscle is also a sub-optimal response of peripheral tissues in insulin resistance to the insulin action (63). Several studies speculated the relevance of PHLPPs during patho-

genesis of insulin resistant in skeletal muscle. A study showed that PHLPP1 levels were greater in primary myoblasts derived from 9 obese type 2 diabetes patients than in cells taken from lean healthy participants (64). Furthermore, it has confirmed by showing higher PHLPP1 level in skeletal muscle biopsies from 12 obese insulin-resistant individuals (57). Although it is evident that elevated levels of PHLPPs, probably PHLPP1, might be associated with hampering insulin resistance in skeletal muscle, the mechanisms underlying increased PHLPP1 in insulin-resistant skeletal muscle are not clear. Over-nutrition provokes low-grade chronic inflammation, dyslipidemia, and dysbiosis incrementally affecting in endoplasmic reticulum (ER) stress, a physiologically changed condition of the ER (65). A study showed that ER stress enhanced the PHLPP1 expression as well as its ERK1/2-mediated phosphorylation. Additionally, the study identified that PHLPP1 is associated with and dephosphorylated AMPK, a key mediator in insulin-independent glucose utilization (66), supporting that PHLPP1 as a novel therapeutic option for the management of ER stress-mediated insulin resistance and type 2 diabetes.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Years after the discovery of Akt-specific phosphatases, there was growing evidence demonstrating that PHLPPs have several
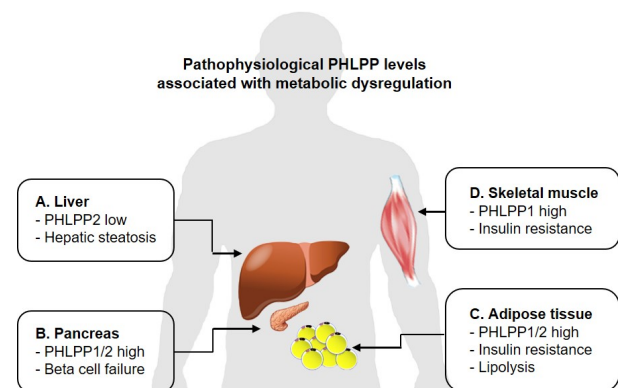
Fig. 2. The roles of PHLPPs in the regulation of tissue metabolism in pathophysiological state. (A) PHLPP2 suppresses *de novo* lipogenesis in the liver via interfering with prolonged Akt activation. Aging or obesity reduces the level of PHLPP2, resulting in the sustenance of the Akt signaling and hepatic steatosis. (B) In the pancreas, both PHLPP1 and PHLPP2 regulate pancreatic beta cell survival and proliferation. Insulin resistance drives pancreatic beta cell failure partially by upregulation of both PHLPP1 and PHLPP2 in response to high glucose exposure, which favors progression toward type 2 diabetes. (C) In adipose tissue, PHLPP1 or PHLPP2 controls insulin action and lipolysis. Obesity promotes PHLPP2 levels, which dephosphorylates HSL and causes glucose and lipid dysregulation. (D) In skeletal muscle, PHLPP1 plays crucial role in regulating insulin action. High circulating nutrient or ER stress potentiates increased PHLPP1 expression, contributing to insulin resistance.

substrates and the majority are engaged in the control of cellular growth and survival (67). Recent accumulated evidences suggested PHLPPs as critical players in the regulation of metabolism, which unveiled their different expressions and novel substrates in a tissue-specific or disease-specific manner. Studies concerning PHLPPs in metabolic diseases are being studied to identify their substrates and upstream regulators. It would be greatly impressive to ascertain various new targets and mechanisms underlying functions in different pathophysiologies in the tissue-specific or disease-specific context. For now, it is clear that PHLPPs perform multifaceted and complex functions in metabolic diseases (Fig. 2). Collectively, our understanding of PHLPP regulation in normal and pathophysiological conditions will uncouple the development of desirable therapeutic options to ameliorate specific metabolic diseases in which PHLPPs are involved.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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