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Review Article

Lipid metabolism-related proteins of relevant evolutionary and lymphoid interest (PRELI) domain containing family proteins in cancer

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Abstract: Metabolic reprogramming of tumor cells plays a critical role in the tumor microenvironment, including disorder of lipid metabolism. Recently, lipid metabolism has received increasing attention in cancer research. The proteins of relevant evolutionary and lymphoid interest (PRELI) domain containing family contains 6 proteins. Functionally, the PRELI-like family proteins were mainly involved in mitochondrial lipid transport and correlated with several types of diseases and malignant tumors. Here we review current knowledge of the functions, structures, biological functions and underlying mechanisms of the PRELI-like family proteins in cancer progression, which provide insights into the clinical translational application.

Keywords: Lipid metabolism, the PRELI-like family, tumor

Introduction

The proteins of relevant evolutionary and lymphoid interest (PRELI) domain containing family, which contains PRELI/MSF1 motif, is present in a wide variety of eukaryotic proteins [1]. The gene family contains six members, namely PRELID1 (PRELI domain containing 1), PRELID2, PRELID3A, PRELID3B, SCE1L1 and SCE1L5. The PRELI-like family proteins play an important role of embryonic and development lymphocyte differentiation. They have been proposed to involve many cellular functions including apoptosis, cellular lipid metabolism and cellular signaling. Therefore, the PRELI-like family proteins might be correlated with the occurrence and development of multiple malignant tumors. Recent studies have found that the PRELI-like family proteins regulated phospholipids transport in mitochondria, and regulated Mitochondrial ROS signaling as well as tumor progression and prognosis [2-4].

Lipid metabolism is one of the most important metabolic pathways in organism. It participates in signaling transduction, energy storage and release, and structural components of biofilms, which maintains internal and external environments homeostasis of cell. Lipid metabolic disorder can disrupt normal physiological function. Aberrant expressions of lipid metabolism-related genes lead to uncontrolled cell proliferation and tumor microenvironment remodeling. Therefore, the reprogramming of lipid metabolism may play an indispensable role in carcinogenesis, invasion and metastasis.

Here we summarize the recent progress of lipid metabolism-related PRELI family proteins. We also discuss the family members' effects on human diseases, especially the relationship between lipid metabolism disorders and cancer progression, which will highlight a novel tumor biomarker and potential molecular target for novel cancer therapy.

Structure characteristics of PRELI family

PRELI was first recognized as a stage-specific gene during mature B lymphocyte maturation and differentiation, and over 85% of PRELI amino acid sequence shared similar with the avian px19 [1, 5]. The PRELI domain containing proteins were ubiquitous and evolutionarily conserved from plants to mammals. The PRELI/MSF1 domain was characterized by a

mixed α/β globular fold associating six β strands and four α helices [6]. Among the 6 PRELI domain family proteins, PRELID1, PRELID2, PRELID3A (SLMO1) and PRELID3B (SLMO2) were proved to be homologous to Ups family in Saccharomyces cerevisiae. In addition, other PRELI-like family members, SEC14L1 and SEC14L5 (also named PRELID4A and PRELID4B) were similar to yeast SEC14, which also belonged to the SEC14 family (**Table 1**).

Structure characteristics of PRELID1

The PRELID1 gene was located on chromosome 5q35.3 and PRELID2 was localized to chromosome 5q32. Using differential mRNA display, PRELID1 was first cloned by isolating from the B lymphocyte-specific cDNA library. Like avian px19 protein, PRELID1 also contained sequence conservation with tandem repeats (A/TAEKAK) of the late embryogenesis abundant (LEA) motif [5]. Co-expression of PRELID1 with GTP-binding protein Rab24 was from a strong promoter [7]. MDM35 was a twin Cx9C protein family member and acted as an interaction partner of Ups [8]. PRELID1 was often combined with TRIAP1, which was a yeast homologue of MDM35 [9]. In human TRIAP1, the acetylation of N-terminus and extension of C-terminal helix (α2) contributed to the interaction between TRIAP1 and PRELID1 [9]. By contrast, PRELID2 lacked unique structure.

Structure characteristics of PRELID3A and PRELID3B

The SLMO1 and SLMO2 genes were separately located on chromosome 18p11.21 and chromosome 20q13.32. SLMO was a mitochondrial protein in Drosophila which had yeast homolog UPS proteins (UPS1, UPS2, and Ups3) [10]. In yeast, UPS1 was a MSF1/PRELI family member and PRELID1, PRELID2, SLMO1 and SLMO2 were human homologues of it [2]. Like UPS1 and PRELID1, two additional homologous proteins (UPS2 and UPS3 in yeast; SLMO1 and SLMO2 in humans) were conserved in various organisms. Meanwhile, the structure of PRELID3A and PRELID3B were similar to that of PRELID1, which could be combined with TRIAP1 [3].

Structure characteristics of PRELID4A and PRELID4B

Partial homologies to yeast SEC14 and retinal-binding protein (RALBP) of the Japanese flying squid, PRELID4A and PRELID4B were also known as SEC14L1 (SEC14 Like Lipid Binding 1) and SEC14L5 (SEC14 Like Lipid Binding 5). They were located on human chromosome 17q25.2 and 16p13.3 [11]. Sec14-like proteins were highly conserved in eukaryotes with a huge number. Like other members of the SEC14 family, they were found to contain CRAL-TRIO domain and closely relate to yeast sec14p proteins [12]. In addition, they also had sequence homology to hTAP (tocopherol-associated protein) [13]. Among them, the GOLD (Golgi dynamics) domain has been proved to exist in the protein of PRELID4A [12]. Furthermore, SEC14 was similar to Vitamin E (a-tocopherol), combining a-tocopherol or biotinylated tocopherol into a hydrophobic pocket [13].

Biological processes, functions, and specificity of the PRELI-like family

Considering the findings that the yeast MSF1 gene could regulate sorting of mitochondrial proteins [14], the function of PRELI/MSF1 domain was hypothesized to be intimately related to cellular membranes. Several studies described that the PRELI-like family members acted as lipid transporters, and directly or indirectly involved in a lipid metabolism balance, especially phospholipids metabolism, which were located in cytoplasm or mitochondria. Besides the important roles in lipid transport and metabolism, individual PRELI-like family protein also have unique biological function in living organisms.

Mitochondrion intermembrane space complex

The PRELI-like proteins, like other mitochondrial proteins, required the outer Membrane (TOM) complex to cross the mitochondrial outer membrane. PRELID1, PRELID3A and PRELID3B and TRIAP1 (TP53-regulated inhibitor of apoptosis gene 1) could form mitochondrion intermembrane space complexes via the hydrophobic stripe of TRIAP [15, 16]. The TRIAP1/PRELI complex and its saccharomyces homologues MDM35/UPS had the same function in mitochondrial phospholipid metabolism [17]. The complex also included substrate proteins with a twin Cx(9)C motif that were located in the MIA pathway [15]. It was suggested that MDM35 protected UPS1 and UPS2 from the proteolysis of the i-AAA protease Yme1 and

Table 1. The general characteristics of PRELI-like family proteins

Name	Aliases	main domain	lipid transport type	Subcelluar location	Orthologs
PRELID1	PX19, PRELI	PRELI/MSF1	PA	mitochondrion	UPS1 (Saccharomycetes), prel (Drosophila melanogaster)
PRELID2		PRELI/MSF1	PA?	mitochondrion?	
PRELID3A	C18orf43, SLMO1	Slowmo/Ups, PRELI/MSF1	PA?	mitochondrion?	UPS2 (Saccharomycetes), Slmo1 (Mouse)
PRELID3B	C20orf45, SLMO2	Slowmo/Ups, PRELI/MSF1	PS	mitochondrion?	UPS3 (Saccharomycetes)
PRELID4A	SEC14L1	PRELI/MSF1, CRAL-TRIO, GOLD	PI and PC	Cytosol, Golgi apparatus	Retm (Drosophila melanogaster)
PRELID4B	SEC14L5	PRELI/MSF1, CRAL-TRIO, GOLD	PI?	Cytosol, Golgi apparatus	Retm (Drosophila melanogaster)

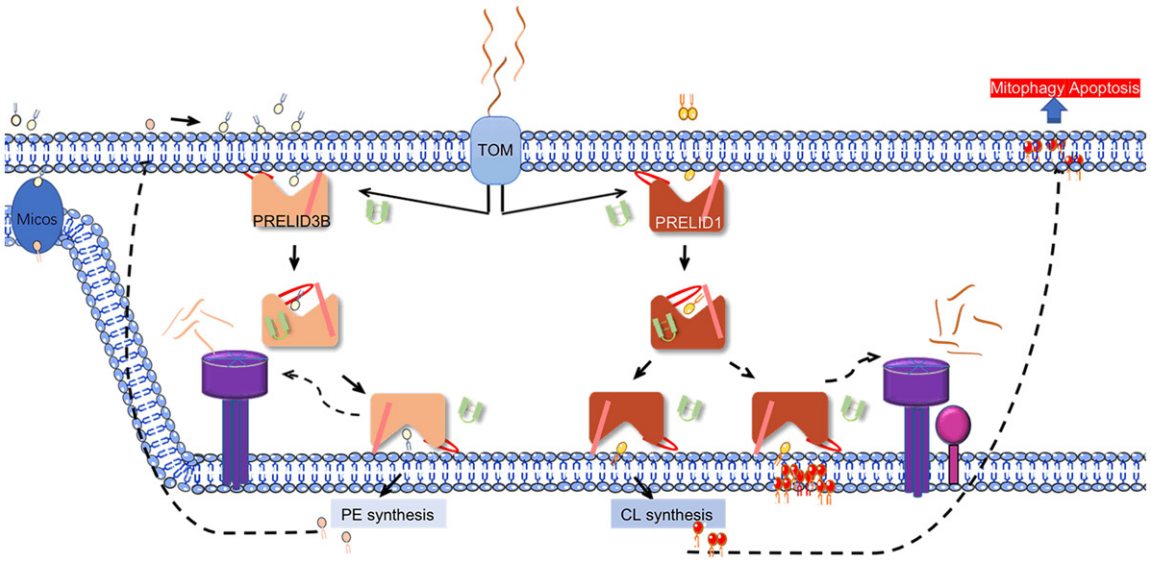

Figure 1. Lipid trafficking of PRELID1/PRELID3B in mitochondria. A dynamic model for lipid transfer protein PRELID1 (Hallow brown)/PELID3B (Coral) extracting PA (Yellow)/PS (Wheat) from MOM and delivering it to MIM. CL (Red) and PE (Bieque) are synthesized in the mitochondrial inner membrane. Importing of precursors into mitochondria is needed. RRELID1/PRELID3B enters the mitochondria through TOM and then combines with TRAIP1 (Green) to achieve stability. After separation of PRELID1/PRELID3B and TRAIP1, the PRELI-like proteins degraded by the i-AAA protease (Yme1: violet, Atp23: wine red). The small helix and motion Ω loop of PRELID1/PRELID3B participate in anchor and release of lipid. Moreover, mitochondrial MICOS complex also associates with the synthesis of PE. PE can be transported to the ER and further turned to PC or specially, turn to PS in liver. Accumulation of CL could inhibit release of PA by negative feedback. In addition, Mitochondrial oxidative stress induces release of CL, and thus causes mitochondrial-dependent apoptosis.

Atp23 in the intermembrane space [17]. TRIAP1 also initiated PRELID folding to maintain a phospholipid-bound cavity. The small helix of PRELID1, which acted as a lid and motion of PRELI-like proteins Ω loop, participated in anchor and release of lipid [18]. After diffusion to the mitochondrial inner-membrane protein (MIM), the complex then separated and lipids were delivered [9]. The MDM35/UPS complex transports phosphatidylinositol (the precursor forms of cardiolipin) or phosphatidylserine (the precursor forms of phosphatidylethanolamine) from the outer mitochondrial membrane to inner mitochondrial membrane [17]. TRIAP1/PRELI complex could serve as an intramitochondrial lipid transfer complex and play a role in promoting Cardiolipin (CL) and Phosphatidylethanolamine (PE) accumulation (**Figure 1**). CL was an essential mitochondrial-specific phospholipid and coordinates death-inducing protein functions in the process of apoptosis [19]. TRIAP1 and PRELI involved transport of the PA from the outer to inner mitochondrial membrane [19]. At high concentration of CL, Ups1 might tightly integrate with MIM so as to form a negative feedback [2]. In addition, deletion of Ups1/PRELI inhibited cells apoptosis by impacting the production of CL and further facilitating the release of cytochrome c.

Similarly, through incubating Ups2-Mdm35 with liposomes, Phosphatidylserine (PS) was found to be transferred to acceptor liposomes selectivity [15]. Therefore, as a mitochondrion lipid transport protein, Ups2-Mdm35 influenced expression level of PE [3]. Apart from above, MICOS coordinated mitochondrial PE synthesis independently in vivo. In MICOS-deficient cells, the Ups2-Mdm35 limited the transfer of the PS, reduced the accumulation of mitochondria PE, and thus protected the formation of mitochondrial respiration and crest [3] (**Figure 1**). In addition, overexpression of Ups2 diminished CL levels to affect cell growth [17]. Ups3 had a redundant function with Ups2 [15]. Knocking out or knocking down PRELID3B results in reduced mitochondrial PE levels. After restoring PRELID3B expression but not transfer-inactive mutation PRELID3B (T57K) in HeLa cells, mitochondrial PE levels were rescued [20]. These results show that TRIAP1/PRELI complex acting as a mitochondrial lipid trans-

porter to preserve mitochondrial structure and function.

Embryogenesis and lymphocyte differentiation

Yeast LEA-like domain binding to a dynamin-like GTPase Optic Atrophy-1 (OPA1) protein has been demonstrated to protect against cell death induced by oxidative stress [15, 16]. With a N-terminal mitochondrial targeting signal, the LEA proteins acted as a biochemical hub that explained the link between bioenergetics and cell responses to stress and death signaling [1, 21]. PRELI homologous protein were expressed highly in the blood island and liver of avian embryonic, and also ubiquitous in Drosophila melanogaster embryonic, especially in the central nervous system [22-24]. PRELID2 was also ubiquitously, continuously expressed and unmethylated during mid-later-gestation mouse embryogenesis [25].

PRELID1 could be used to maintain Mitochondria energy metabolism. High PRELID1 expression in human fetal liver indicated their important roles in germinal center B lymphocytes, which protected B lymphocytes differentiation and maturation during lymphocyte selection pressure [5]. Overexpression of PRELID1 increased the ROS production in primary Th cells and inhibited Th cell differentiation through down-regulating STAT6 [26]. By a yeast two-hybrid screen, SEC14L1 was found that bound to RIG-I after virus infection, to regulate innate antiviral response negatively [27]. Therefore, the PRELI-like proteins were involved in embryogenesis and lymphocyte differentiation.

Intracellular transport system

PRELID4A and PRELID4B is a pair of paralog genes. They were first speculated to participate in intracellular transport system because of their homolog proteins-yeast SEC14 and Japanese flying squid RALBP [11]. The fold of Sec14p consisted twelve α-helices, six β-chains and eight 310-helices, which could hold up to one phospholipid molecule [28]. In addition to lipid binding sites, there was a tripod-shaped motif, which played a vital role in targeting Golgi membrane [28]. As a member of lipid-binding transfer proteins family, the yeast phosphatidylinositol-transfer protein (Sec14) could accommodate phosphatidylinositol within the C-terminal domains by forming a large hydrophobic pocket, involving in the exchange of phosphatidylinositol and phosphatidylcholine between membrane bilayers and the process of Golgi complex vesicle budding [29, 30].

Additionally, SEC14L1 presented to be co-located with VAChT or CHT1 depending on the GOLD domain [31]. Overexpression of prelid4A decreased choline uptake by changing lipid composition in endosomes and vesicles and CHT1 trafficking [31].

Although several studies have reported that the PRELI-like family proteins are involved in lipid transport, the biological functions and underlying mechanisms of them in lipid metabolism are less clear.

Lipid metabolism and cancer

Lipids, including triglycerides, glycerolipids, sterols and sphingolipids, play important roles within all living organisms. The organism degrades triglycerides (TGs), releases fatty acids and oxidizes fatty acids to provide energy. Glycerolipids, sterols and sphingolipids participate in the formation of biofilms. Besides, lipids are also involved in metabolism as second messengers and hormones. The excess lipids in the cell are mainly stored as droplets.

To sustain a high cellular proliferative capacity and metabolic rate, tumor cells develop metabolic reprogramming to fulfills their need of nutrients and energies [32]. Besides “Warburg effect”-the most famous of metabolic changes in cancer cell, disorder of lipid metabolism is a novel hallmark of cancer [6, 33]. Cancer cells achieve high metabolic activity through activating their endogenous synthesis or increasing the uptake of exogenous (or dietary) sources [34]. Moreover, cancer cells may uniquely rely on fatty acids de novo synthesis to provide more lipids for generating and maintaining cell membrane and energy supply of cancer cells [6, 35].

On one hand, when the cancer cells were cultured in a medium lacking lipoprotein, they would occur growth inhibition or even death [36]. Therefore, replenishment of these lipoproteins would reverse this phenomenon [36]. On the other hand, more and more epidemiological data showed that there was a positive correlation between cancer and dyslipidemia, such as multiple and invasive tumors and cardiovascular disease, obesity, type 2 diabetes

and hyperinsulinemia [37]. Obesity impacted cancer phenotype, disease signaling pathways, and drug sensitivity. Lipid metabolism might be also related to the insensitivity of chemotherapy treatment [38].

Phospholipids (PLs) are important components of cell membranes and second messengers in cellular signal transduction pathways. Analysis of 179 phospholipid species in malignant and matched non-malignant lung tissue of 162 Non-small cell lung cancer patients identified 91 differential phospholipids [39]. Similarly, the same phenomenon happened in Colorectal cancer cells, Hepatocellular Carcinoma Cells, et al. [40, 41]. Ferlin family proteins were reported that they could be interacted with phospholipids and involved in multiple membrane processes [42]. Targeting myoferlin was a novel measure to exert the anti-tumor efficiency in breast cancer which had an effect on membrane biological behavior [43]. In addition, some studies have revealed that the levels of DSPC (such as phosphatidylcholine) could be regulated to affect growth factor signaling pathways in tumor cells [44]. Certain phospholipids were also found to induce cancer multidrug resistance by altering membrane phospholipids composition of plasma membrane and triggering multiple signaling cascades [45]. In short, changes in the phospholipid composition were closely associated with tumor initiation and progression.

Taken together, these studies provided compelling evidences of a mechanistic link between changes of lipid metabolism and malignant tumors.

Lipid biosynthesis pathway in cancer cells

Metabolic disorders are induced by cancer mutations of proteins in Lipid biosynthesis pathway or altering related gene epigenetic mechanisms [46]. Lipid metabolism regulators would be inhibited or activated by regulation of signaling pathways involved in tumorigenesis. Sterol regulatory element binding proteins (SREBPs) and PPARγ were two key regulators of adipogenesis promotion. SREBP1, the core protein of lipid metabolism, were significantly up-regulated in human cancer [47]. SREBP1 was regulated by the mTOR signaling to enhance lipogenesis in nasopharyngeal carcinoma and liver cancer [48, 49]. The Wnt/β-catenin signaling pathway down-regulated PPAR production in preadipocytes by activating TCF/LEF, which thereby inhibited fat formation and colorectal cancer cell growth [50]. In addition, other signaling pathways involved in Lipid biosynthesis pathway also play a regulatory role for cancer cells metabolic reprogramming.

Expressions of metabolic enzymes had also evolved with oncogenesis. For instance, mutation of the IDH1 leaded to the accumulation of the oncometabolite 2-hydroxyglutarate (2-HG), which contributed to change oxoglutarate-dependent dioxygenases activity and control the methylation state of histone in glioblastomas [51]. ATP-citrate lyase (ACLY) was an enzyme which linked glucose to de novo FA synthesis of lipid metabolism, epigenetically potentiated oxidative phosphorylation to promote melanoma growth [52]. Clinically, the overall survival of patients with high ACLY expression was significantly worse than their low expression in lung cancer [53]. These results have illustrated that the regulation of metabolic enzymes were stably associated with tumor microenvironment.

Lipid transporters in cancer celsl

Distribution of lipid molecules across the membrane bilayer are normally asymmetrically, particularly in the plasma membrane and mitochondrial membranes. Lipids are made by membrane-embedded synthases. Lipid transport systems transfer lipid precursors to specific site for lipid synthesis. Newly synthesized lipids are then secreted by membrane vesicles or lipid transfer proteins. The lipid composition of cellular membranes modulated by lipid transport system is associated to protein sorting and membrane dynamics in the endocytic pathway. Lipid transport proteins also regulated the lipid second messengers [54].

It has been proved that lipid transfer proteins were closely associated with cancer progression and outcomes. NIR2, a phosphatidylinositol (PI)-transfer proteins (PITPs), coupled PA to phosphoinositide signaling through binding PA and transferring PI [55]. The overexpression of NIR2 enhanced EMT in breast cancer cells, while depletion of Nir2 had the opposite effect [56]. In animal models and immunohistochemical analysis of breast cancer tissue samples, high Nir2 levels correlated with advanced tumor stage and poor prognosis [56]. CERT,

Table 2. The PRELI-like family involvement in biology process and clinical prognosis in different cancers

Cancer type	Target gene	Biological process	Cancer therapy and prognosis	References
Breast tumor	PRELID1	promote proliferation		[4]
	PRELID4A		lymphovascular invasion status	[66, 67]
Hepatoma	PRELID1	inhibit apoptosis		[62]
Nasopharyngeal carcinoma	PRELID2		radiotherapy resistance	[63]
Prostate cancer	PRELID4A	promote proliferation	high tumor grade, advanced stage and early recurrence	[68]

which could transfer ceramide from the ER to the Golgi, promoted triple-negative breast cancer (TNBC) progression [57]. Besides, depletion of CERT was helpful for colorectal cancer cells death [58]. The mitochondrial protein mitofusin 2 specifically binds to PS and facilitates PS transfer to mitochondria [59]. Hepatic MFN2 deficiency drives defective PS metastasis and impaired PE synthesis, which leads to endoplasmic reticulum stress and other Membrane-dependent cellular function disorders [60, 61]. Recombinant mitochondrial phospholipid causes liver disease and even liver cancer [61].

The negative feedback regulation mechanism of lipid synthesis fails in tumor cells. Lipid metabolic reprogramming provides material and energy for the rapid proliferation of tumor cells. Generally, lipid metabolism involved in the occurrence and development of cancer remains to be elucidated. In distinctive types of cancer cells, lipid metabolism disorders induce different appearances and effects, their unknown mechanism needs to be more explored. Because of the important role of lipid metabolism in biogenesis, it is crucial for us to find new and effective targets for tumor biotherapy.

The PRELI-like family and tumor

As regulators of lipid metabolism and signaling pathways, the PRELI-like family proteins have been reported to be correlated with several types of diseases and malignant tumors (**Table 2**).

PRELID1 and tumor

TRIAP1/PRELI complexes supplied phosphatidic acid (PA) for cardiolipin (a mitochondria-specific glycerophospholipid) synthesis in the mitochondrial intermembrane space. Deletion of PRELID1 would release cytochrome c from mitochondria, and thus promote apoptosis during conditions of cell stress. By comparing human primary breast tumor specimens and matched normal tissue, Kim BY, et al. have found that there was an alternative polyadenylation (APA) event in the PRELID1 mRNA, affecting its stability and translational efficiency. In the cellular response to stress (nutrient deprivation), knockdown of TRIAP1 or PRELID1 consistently inhibited breast cancer cell growth. In ER^+ breast cancers, the expression of PRELID1 maintained efficient mitochondrial respiration. Besides, knockdown of PRELID1 in ER^- breast cancer cells increased mitochondrial ROS production. ROS mediated activation of HIF and NFκB, which driving breast cancer cells proliferation. Moreover, alternative polyadenylation and expression of PRELID1 were significantly correlated with outcomes in 14 of the cancers contained in TCGA [4]. In addition, knockdown of PRELID1 caused up-regulation of caspase-3 expression and down-regulation of SOD-1 level in Hep2014G2 cells, which then induced mitochondrial apoptosis or senescence during Oxidative stress [62]. Therefore, PRELID1 could inhibit apoptosis in hepatoma cells in vitro through regulating expression of SOD-1 and caspase-3 genes, and stabilizing mitochondrial membrane potential.

Together, PRELID1 influenced mitochondrial ROS signaling level and increased cellular buffer stress. PRELID1 was also involved in the inhibition of mitochondrial apoptosis and cell injury induced by oxidative stress. These results might explain that PRELID1 contribute to regulation of cancer progression.

PRELID2 and tumor

RNA-Seq analysis of three paired NPC patients with pre-radiotherapy and post-radiotherapy of peripheral blood mononuclear cells, PRELID2 was suggested as one of 45 genes associated with HNSCC radiotherapy response. This revealed possible relationships between PRELID2 and radiotherapy resistance [63].

PRELID3B and tumor

As a solid tumor, Pancreatic ductal adenocarcinoma cells (PDACs) are under a hypoxia tumor microenvironment [64]. Reduction in mitochondrial PE levels following knockdown or knockout of PRELID3B. The levels of mitochondrial PE have been suggested to be decreased in hypoxic or nutrient-deficient cells. Further study observed that its reduction may activate proteolysis using YME1L, leading to a remodeling of mitochondrial proteome [20]. Thus PDACs survival is supported by limiting mitochondrial lipid metabolism including a reducing effect of PRELID3B [20].

PRELID4A and tumor

Human SEC14L1 localized to a discrete region of 17q25 which was a suppressor region that mutated frequently in breast and ovarian cancer patients. Moreover, the CRAL/TRIO domain of SEC14L1 was also found in cellular retinaldehyde-binding protein (CRALBP), and retinoids have previously been shown to inhibit breast cancer cell proliferation. Altering expression of PRELID4A was related to carcinogenesis and prognosis of breast cancer [65]. By analyzing genomic data of invasive breast cancer patients, alterative expression of PRELID4A mRNA was found to be linked with lymphovascular invasion status, which indicated that PRELID-4A might serve as an independent prognostic indicator for breast cancer patients [66]. PRELID4A was associated with poor clinical features in patients with prostate cancer, including high tumor grade, advanced stage and early recurrence [67]. Up-regulation of prelid4A was particularly relevant to Ets-related gene fusion–positive subtypes of prostate cancers [68]. These results proved that PRELID4A promote tumor cell proliferation by reducing oxidative stress, regulating lipid metabolism and maintaining genome stability.

Phospholipids are important biological components of tumor cells, PEs and/or CLs biosynthesis pathway may affect different biological processes in cancer cells. Regulating the LACTB-PISD-LPE/PE signaling axis, for example, can realize changes in mitochondrial lipid metabolism and thus inhibit the differentiation of breast cancer cells [69]. Phosphatidylethanolamine is required for hepatoblasts differentiation, synthesis mechanism of PE is a new direction for hepatocellular carcinoma with targeted therapy [70]. However, there are relatively few studies in relevance between the PRELI-like family proteins and cancer (**Table 2**). It remains to be seen whether some family proteins have function in tumor microenvironment and tumor progression. What's more, the mechanisms of the PRELI-like family proteins regulating cancer progression and associating with poor prognosis in different types of cancer need to be further studied.

Conclusion and perspectives

Evidence is emerging that the PRELI-like family proteins play vital roles in cancer progression. However, we are just beginning to understand the functions and underlying molecular mechanisms of the PRELI-like family proteins in human cancers. Lipid metabolism-related genes regulate the transport of lipid and thus provide lipid synthesis with precursors or affect lipid localization and quantity. However, there are numerous questions to be answered. For instance, how could the PRELI-like family genes choose their ligands and decide their modes of the motion and localization? What determines activation or deactivation states of the lipid transporters? What we understand about spatiotemporal regulation of lipid metabolism was not enough to completely and clearly investigate the lipid transporters' biological functions. Besides as lipid transporters, the PRELI-like family proteins also participate in the control of mature B lymphocyte differentiation and selection, T-helper cell differentiation. It is also likely that they relate to tuberculosis, multidrug resistance in parasites, for instance, the PRELI-like was found associated with P. falciparum parasites drug resistance [71]. Meanwhile, Sec14p influenced virulence of the pathogenicity of fungi such as Cryptococcus neoformans [72]. However, its biological functions have not yet been fully elucidated.

The development and progression of cancer depend on metabolic reprogramming. In cancer cells, Metabolic changes are mediated by intrinsic factors such as cells and tissues and external influencing factors include tumor microenvironment and patient status [73]. It is unknown whether the relationship between lipid metabolic disorder and tumor progression, which is related to heterogeneity of tumor type or individuality. How dodifferent types of lipid metabolism have a collaborative effect on regulating the proliferation, invasion and

metastasis of cancer cells? Though the PRELI-like family proteins were reported to associate with occurrence, development and prognosis of tumors, current knowledge of the PRELI-like family proteins is mainly restricted to basic structure and function, while it has been scarce to explore in-depth mechanisms of the relationship between the PRELI-like family proteins and tumorigenesis.

Apparently, it is imperative to fully understanding of the roles of the PRELI-like family proteins and lipid metabolism-related proteins in cancer, and identifying novel metabolic markers and molecular targets for individualized treatment of cancer. The Emerging precise genomic view of tumors also provides means to reach a solution.

Disclosure of conflict of interest

None.

Abbreviations

ACLY, ATP-citrate lyase; CL, Cardiolipin; FA, Fatty acids; hTAP, tocopherol-associated protein; LEA motif, the late embryogenesis abundant motif; MICOS, mitochondrial contact site and crista organizing system; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PRELI domain family, the proteins of relevant evolutionary and lymphoid interes domain family; PS, phosphatidylserine; Sec14, the yeast phosphatidylinositol-transfer protein; the GOLD domain, Golgi dynamics domain; MIM, the mitochondrial inner-membrane protein; TOM, translocase of the outer mitochondrial membrane; TRIAP1, TP53-regulated inhibitor of apoptosis gene 1.

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