



Phosphatases of regenerating liver are key regulators of metabolism in cancer cells – role of Serine/Glycine metabolism

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Purpose of review

Phosphatases of regenerating liver (PRL) are dual-specificity phosphatases and comprise three members, PRL-1, -2 and -3. Despite the importance of PRLs as oncoproteins, there is no consensus function for this family of phosphatases. In the current review paper, we summarize recent findings on the role of PRLs in metabolic regulation.

Recent findings

Reprogramming of cellular metabolism is a cancer hallmark. Glucose is the major source of energy in cells. Glucose metabolism occurs through the glycolysis and can continue through the pathways such as serine synthesis pathway or the tricarboxylic acid cycle (TCA). Magnesium (Mg^{2+}), the second most abundant cation in cells, plays an essential role in energy production by acting as a cofactor for most enzymes involved in glycolysis and in TCA. Recent findings have shown that the PRL family has a role in metabolic reprogramming mediated by (1) Mg^{2+} homeostasis, (2) shifting the energy source preference to glucose consumption and fueling serine/glycine pathway and (3) regulating PI3 kinase/Mammalian target of rapamycin complex. Both the phosphatase and nonphosphatase activity of PRLs appear to be important for its oncogenic role.

Summary

The PRL family contributes to the metabolic plasticity of cancer cells and, thereby, allows cancer cells to meet the high metabolic demands required for cell proliferation.

Keywords

magnesium, metabolism, phosphatase of regenerating liver, pseudo-phosphatase, PTP4A, Serine/Glycine metabolism

INTRODUCTION

Phosphatases of regenerating liver (PRL) are dual-specificity phosphatases and there is evidence for upregulation of this group of phosphatases in various human cancers. In the current review paper, we summarize recent findings on the role of PRLs in cancer metabolism.

CANCER METABOLISM

Metabolic reprogramming is a hallmark of cancer. Cancer cells maintain their survival and proliferation under stress conditions through their metabolism. This reprogramming allows the cells to produce essential energy and building blocks required for proliferation. Glucose is one of the major carbon sources for biosynthesis of building blocks for macromolecules and adenosine triphosphate (ATP). Glucose is mainly converted into pyruvate, which under normal conditions fuels the mitochondrial

tricarboxylic acid cycle (TCA) and oxidative phosphorylation, a series of chemical reactions that generate energy in the form of ATP. Unlike normal cells, cancer cells preferentially switch from mitochondrial oxidative phosphorylation to glycolysis even

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KEY POINTS

- Phosphatases of regenerating liver (PRLs) are oncoproteins that enable cancer cells to meet the requirement for rapid cell proliferation by providing metabolic plasticity.
- PRLs' role in metabolic reprogramming is mediated by (1) Mg^{2+} homeostasis, (2) shifting the energy source preference to glucose consumption and fueling serine/glycine pathway, and (3) regulating PI3 kinase/mTORC.
- Both the phosphatase and nonphosphatase activity of PRLs appear to be important for its oncogenic role.

under normoxia, a phenomenon known as the Warburg effect. The Warburg effect is a metabolic signature of 70–80% of human cancers. Through glycolysis, large amounts of lactate are produced from pyruvate by lactate dehydrogenase (LDH) [1–4]. Recent studies have demonstrated that lactate is not just a metabolic byproduct but has diverse roles such as suppressing immune responses, activating oncogenic signaling, and cell-to-cell communication in the tumor microenvironment [5,6]. Instead of being fueled through glycolysis and TCA, glucose can also be used in the serine synthesis pathway. Serine biosynthesis is an important side branch of glycolysis and represents a critical turning point for glucose conversion. Serine derived from endogenous synthesis or from exogenous uptake can be converted to glycine and provide methyl groups for one-carbon metabolism. One-carbon metabolism provides intermediate metabolites that can be used as precursors for the synthesis of macromolecules such as proteins and nucleic acids [7,8].

The magnesium cation (Mg^{2+}) is the second most abundant cation in cells and plays an essential role in cellular energy production by interacting with numerous intracellular molecules such as phospholipids, proteins, and nucleic acids. For example, ATP, the main source of energy in the cells, must be bound to Mg^{2+} to be biologically active. Moreover, most enzymes involved in glycolysis, the TCA cycle, and the respiratory chain are dependent on Mg^{2+} ions. Therefore, Mg^{2+} plays a prominent role in regulating metabolism, glucose homeostasis and cell growth. Cellular Mg^{2+} levels are strictly regulated by a coordinated balance between Mg^{2+} influx and efflux [9,10¹¹,11,12¹³].

Transport of Mg^{2+} across cell membranes is controlled by a series of different transporter molecules. In recent years, mammalian genes encoding proteins directly involved in the transport of Mg^{2+} have been discovered. Cyclin and CBS Domain

Divalent Metal Cation Transport Mediator (CNNM) is a family of such Mg^{2+} transporter proteins with four members, CNNM1–CNNM4. CNNM family proteins are evolutionarily highly conserved, suggesting a crucial biological function [9]. Structurally, they have a transmembrane domain followed by two cystathionine- β -synthase (CBS) domains in the cytoplasmic region. They maintain intracellular Mg^{2+} levels within the normal range. Moreover, they play an important role in Mg^{2+} (re)absorption in the intestine and kidneys by mediating the directional transport of Mg^{2+} across epithelial tissue from the tubular lumen [13]. CNNM proteins themselves selectively bind Mg^{2+} -ATP via their CBS-pair domain and they are important for regulating metabolism and preventing overproduction of reactive oxygen species (ROS) by controlling Mg^{2+} levels [10¹¹].

Dysfunction of CNNM family proteins can lead to abnormalities in intracellular Mg^{2+} homeostasis and is linked to many diseases such as cancer, hypomagnesemia and the Jalili syndrome [9,10¹¹,13,14].

PRLs are dual-specificity phosphatases and have three members, PRL-1, -2 and -3 (encoded by *PTP4A1*, -2 and -3) [15]. The three PRLs in humans show high amino acid identity, ranging from 75% to 86%. They are small proteins of 20 kDa and can be anchored to the plasma membrane in cells by a farnesyl group linked to a prenylation motif at the C-terminus. PRL-1 was discovered by Mohn *et al.* as one of the genes that were highly up-regulated in the regenerating rat liver after partial hepatectomy. The PRL-family got more attention in 2001, when Saha *et al.* found PRL-3 as one of the most consistently overexpressed genes in metastatic colon cancer lesions and negligible expression in normal colon. Since then, a large number of studies have established the importance of the PRLs in oncogenesis [10¹¹,13,15,16]. In contrast to PRL-1 and PRL-2, which are ubiquitously expressed in various tissues, the expression of PRL-3 is restricted to a few specific organs and cancer cells, which makes it an attractive target for treatment [15]. In this review paper, we give a brief discussion of the most recent findings on the role of PRLs in cancer cell metabolism.

ROLE OF PHOSPHATASES OF REGENERATING LIVER IN CANCER METABOLISM

Several studies have revealed that proteins in the PRL family regulate Mg^{2+} homeostasis. PRLs bind directly to a conserved aspartic acid in the CBS domain of CNNMs that acts as a pseudo-substrate and inserts into the PRL catalytic pocket. This subsequently leads to sustained intracellular Mg^{2+} levels, thereby promoting cellular proliferation and

tumor progression. All four CNNM proteins in humans bind with similar affinity to all the three PRLs [10²²,14]. Various studies have confirmed that PRL level is dynamically regulated in response to Mg²⁺ level in the cells [10²²,13,17]. A mechanism suggested by Hardy *et al.* is that AMP-activated protein kinase (AMPK) senses low ATP- Mg²⁺ level upon Mg²⁺ depletion. AMPK then leads to activation of mammalian target of rapamycin (mTOR) Complex 2 (mTORC2) which further induces PRL-2 expression by a posttranscriptionally regulated mechanism [12²²].

In line with the role of PRLs in Mg²⁺ homeostasis through CNNMs, other studies introduced PRLs as important metabolic mediators in cancer cells. Knockdown of PRL-2 leads to reduced uptake of glutamine and glucose, decrease in intracellular ATP levels and lactate production, suggesting a lower glycolytic flux in knockdown cells. Cells isolated from PRL-2^{-/-} animals showed decreased mitochondrial respiration and ATP turnover. This is also consistent with the reduced body weight of PRL-2^{-/-} mice, suggesting that their cellular metabolism is impaired [12²²]. Later, by using Seahorse XF analyzer technology and metabolic profiling of the cells, our group found that PRL-3 potently induced both oxidative phosphorylation and aerobic glycolysis. Proteomic profiling of the cells overexpressing PRL-3, showed upregulation of glucose and amino acid transporters, enzymes catalyzing glycolysis, and the serine/glycine pathway. The glucose transporter GLUT1, and the glycolysis genes Hexokinase 2 (HK2) and Lactate dehydrogenase A were among the genes upregulated by PRL-3, genes which previously were shown by Xu *et al.* to correlate with PRL-3 [18]. Surprisingly, none of the most known regulators of metabolism such as HIF-1 α , C-MYC and AMPK were involved in the PRL-3-driven Warburg effect.

As mentioned, conversion of glucose to serine and further to glycine is an important part of cancer cell metabolism and supports cancer progression by providing methyl units for one-carbon metabolism [7]. Fueling of the one-carbon metabolism cycle is done through two parallel reactions, located in cytosol and in mitochondria, respectively. Interestingly, PRL-3 mostly regulated the mitochondrial isoforms of these enzymes, which are the isoforms known to be predominantly active in cancer cells [19²²].

Glycine decarboxylase (GLDC), one of the mitochondrial enzymes involved in the glycine cleavage system, was identified as one of the genes most upregulated by PRL-3. In addition to fueling the one-carbon metabolism cycle, GLDC is reported to be involved in glycolysis in cancer [20]. Knocking

down GLDC in cells overexpressing PRL-3 reduced glycolysis, however not to the level in mock cells, suggesting the involvement of additional factors contributing to PRL-3-mediated glycolysis [19²²,21].

A transcriptomic analysis of two multiple myeloma cell lines overexpressing PRL-3 identified enrichment of several interferon I (IFN-I) signaling genes (ISGs) in PRL-3-overexpressing cells compared to the mock control cells. It is known that IFN-I stimulation leads to phosphorylation of transcription factors STAT1 and STAT2. Phosphorylated STAT1 and STAT2 together with Interferon regulatory factor (IRF)9 form a heterotrimer that translocates to the nucleus and leads to activation of interferon-stimulated genes. PRL-3 overexpression led to activation of STAT1 and STAT2 independently of IFN-I. Knocking down these two transcription factors reduced PRL-3-mediated glycolysis in myeloma cells, similarly to what we saw after knockdown of GLDC. Interestingly, glucose deprivation inhibited the activation of STAT1 and 2, and subsequently blocked PRL-3-driven stimulation of ISGs, suggesting that PRL-3 initiates a positive feedback loop involving increased glucose consumption and expression of ISGs through activation of STAT1 and -2 [21,22]. Interestingly, while PRL-3 increased acidity of the microenvironment through lactate production, a recent study by Funato *et al.* indicated that PRL-3-overexpressing cells can better tolerate an acidic environment by preventing the interior of cells from becoming acidic in environments with low pH. Generally, it is known that extracellular pH decreases during cancer progression. Cancer cells can survive and continue to proliferate in such acidic and harsh environments. The pH in the microenvironment adjacent to normal tissues is strictly maintained around 7.4 when in homeostasis. In Funato's study, a CRISPR-Cas9 loss-of-function screen revealed genes associated with lysosomal exocytosis to be involved in the acidic pH preference of the PRL-3 cells. Lysosomal exocytosis sustained the intracellular pH level in cells overexpressing PRL-3 by actively expelling hydrogen ions (H⁺) from lysosomes to the extracellular environment. The mechanism underlying the acid-addicted phenotype was that PRL-3 augmented intracellular Mg²⁺ by its interaction with CNNM, which led to concomitant increase of intracellular ATP and ROS levels. ROS activated TRPML, a lysosomal Ca²⁺ channel, and the release of Ca²⁺ to the cytosol triggered lysosomal exocytosis and H⁺ extrusion [23²²,24,25].

Another aspect of PRLs' role in metabolism is the influence on phosphatidylinositol 3-kinase (PI3K)/AKT, a signaling pathway playing vital roles in diverse cellular processes, including metabolism,

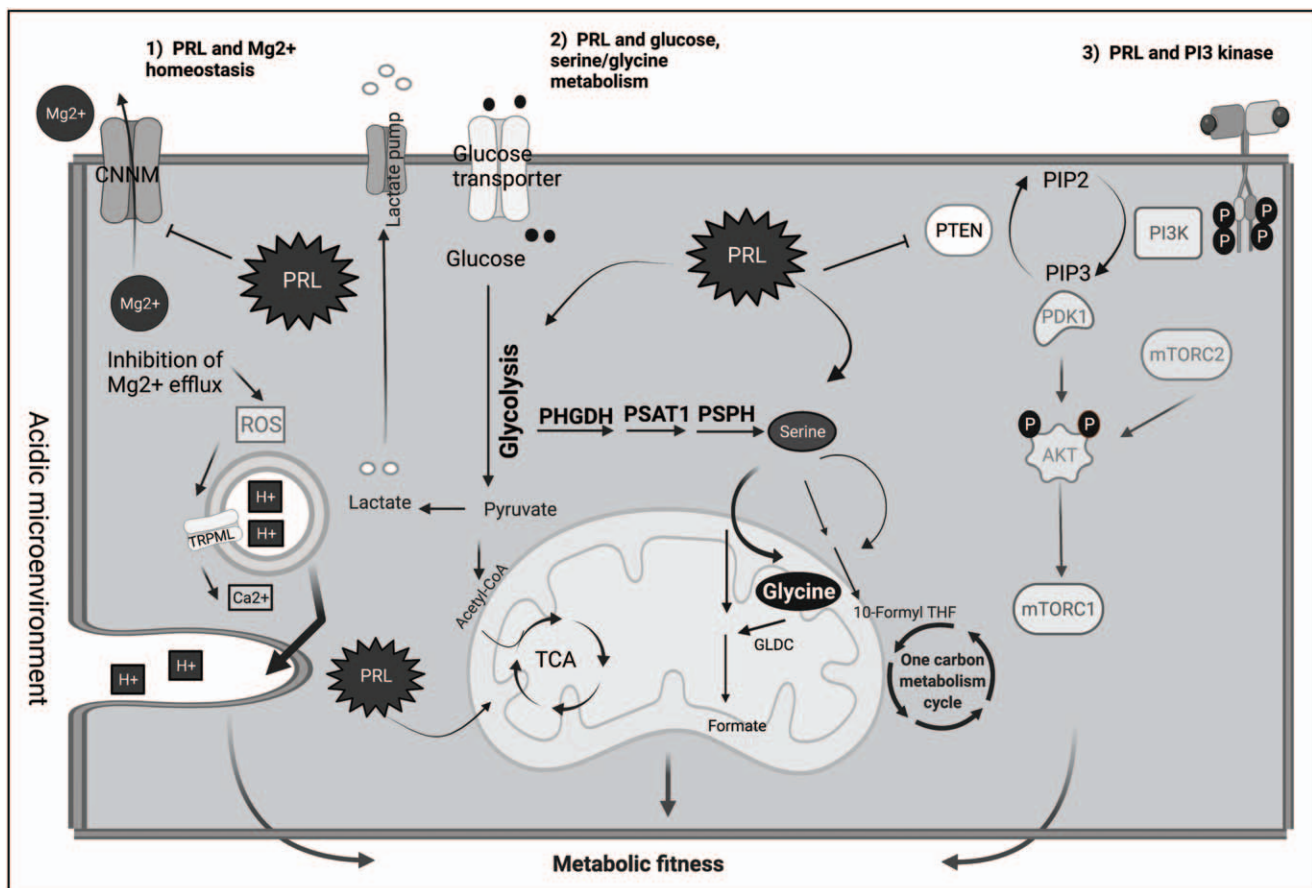


FIGURE 1. Overview of PRL's mechanism in regulating metabolism. PRLs' role in metabolic reprogramming is mediated by (1) shifting Mg^{2+} homeostasis by interacting directly with the magnesium transporter family CNNM, (2) shifting the energy source preference to glucose consumption and promotion of the serine/glycine synthesis pathway and (3) regulating PI3 kinase/mTORC pathway by inhibiting PTEN. The figure was created with Biorender.com. PRL, phosphatases of regenerating liver.

cell survival and growth. PI3K phosphorylates the phospholipid phosphatidylinositol (4,5)-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP3). Accumulation of PIP3 leads to activation of AKT by phosphoinositide-dependent protein kinase (PDK1) and mTORC2. AKT regulates the nutrient sensor, mTOR, and glucose, glutamine and fatty acid metabolism. Influence on the PI3K pathway by PRLs is mediated by negative regulation of the phosphatase PTEN (phosphatase and tensin homolog). PTEN is a well-known tumor suppressor that antagonizes PI3K by dephosphorylating PIP3 to PIP2 [26–28]. Li *et al.* identified PTEN as a direct substrate of PRLs. PRL-2 dephosphorylates PTEN at tyrosine 336 leading to PTEN ubiquitination and proteasomal degradation. Haplo-deficiency for PTEN leads to increased incidence of tumor development. Consistent with the impairment of AKT activity, deletion of PRL-2 in $PTEN^{+/-}$ mice protects these animals from developing tumors and

dramatically increases their overall survival. They did not find differences in Mg^{2+} concentration between tumor, kidney, and serum samples from $PTEN^{+/-}$ and $PTEN^{+/+}$; $PRL2^{-/-}$ mice nor any significant difference in CNNM expression between the two groups [29].

Figure 1 shows an overview of PRLs' mechanism in regulating metabolism.

PHOSPHATASES OF REGENERATING LIVER, PHOSPHATASES OR PSEUDO-PHOSPHATASES

Finding a common substrate for PRLs has been unsuccessful until now [13,15,16]. As for other cysteine-based protein phosphatases, PRL family members have a conserved cysteine in their catalytic subunit, which mediates the phosphatase reaction by accepting a phosphate group from the substrate. Analyses of PRLs' enzymatic activity using artificial

substrates revealed that the phosphatase activity of PRL-3 is low in comparison to other cysteine-based protein phosphatases [13]. The phosphate-cysteine intermediate is transient and is usually hydrolyzed to release the active enzyme. Uniquely to PRLs, the phospho-cysteine intermediate is stable with a half-life of over an hour, thus halting the catalytic cycle of the enzymatic reaction [13,17]. A new interesting topic in the field of PRLs is whether they are phosphatases or pseudo-phosphatases. Typically, pseudo-phosphatases have lost their catalytic activity by mutations in the active site. However, PRL phosphatases have an intact active site, and they are remarkably well conserved during evolution. The majority of endogenous PRLs are phosphorylated on the catalytic cysteine, which can only occur due to phosphatase activity. This indicates that PRLs are functional phosphatases. However, recently several phosphatase-independent activities of PRLs have been reported, which launched the theory that PRLs behave both as phosphatases and pseudo-phosphatases [17]. Most of the studies on PRLs and CNNMs included experiments with mutations of the catalytic cysteine to serine or alanine. These mutations disrupt the interaction between PRLs and CNNMs, but also abrogate phosphatase activity. Therefore, it is hard to distinguish between the contribution of the phosphatase activity versus the CNNM binding on the oncogenic effect of PRLs. Kozlov *et al.* substituted the catalytic cysteine (C) by the negatively charged aspartic acid (D) in PRL-3. This mutation retained the CNNM binding but was unable to catalyze the dephosphorylation reaction. In addition, they made another PRL mutation where they substituted arginine (R) in position 138, which is part of the CNNM-binding site, but outside of the catalytic site, to glutamic acid (E). This mutation blocked CNNM binding but not catalytic activity. *In vitro* experiments indicated that, in contrast to R138E, the C104D mutant was able to repress CNNM magnesium efflux as effectively as wild-type PRL-3. In addition, B16 cells transformed with the C104D mutant formed as many lung nodules as the wild type in an animal model of tumor metastasis, whereas R138E did not promote metastasis. Therefore, Kozlov *et al.* concluded that PRLs primarily act as pseudo-phosphatases [10¹¹,17]. Our group also reported phosphatase-independent bioactivity of PRL-3. Phosphatase-dead PRL-3 stimulated aerobic glycolysis to the same extent as wildtype PRL-3. However, this effect is likely to be independent of CNNM since the C104S also abrogates the CNNM binding. This indicates that some of both the phosphatase and the pseudo-phosphatase activity of PRLs is independent of the proposed role of PRLs in modulating Mg²⁺ homeostasis.

CONCLUDING REMARKS

Studies have found significant links between oncogenic cell signaling and aberrant metabolic phenotypes. This signaling enables cancer cells to adapt to environments with severe metabolic stress. The mechanisms of how PRLs act as oncoproteins remain elusive, even though several different signaling pathways are influenced by this family of phosphatases. PRLs' role in metabolic reprogramming through Mg²⁺ homeostasis and glucose metabolism seems to be a robust observation reported by several groups. Furthermore, the role of PRLs in promoting serine/glycine synthesis pathway is a novel observation and it would be interesting to see if this is specific to multiple myeloma or is applicable to other cancer entities.

Whether the role of PRLs in metabolism is mediated by CNNM binding needs additional investigation with appropriate mutation models, as proposed by Kozlov *et al.* In addition, most of the studies with PRLs are performed *in vitro* with cell lines of specific cancer origin. Therefore, to find a consensus function for PRLs, it is essential to test them in various cell types both *in vitro* and *in vivo*. Moreover, despite high homology among PRL members, there are differences in expression patterns of the three PRL members in between cancer cells and normal cells. Most of the reported studies on PRLs are limited to only one of the PRL family members. For instance, it is not known whether PRL-1 and 2 are able to regulate glucose metabolism as PRL-3 does. Therefore, it is crucial to investigate if each function described is unique to only one or is common for all the PRL family members.

CONCLUSION

In conclusion, PRLs are oncoproteins that enable cancer cells to sustain cell proliferation by providing metabolic plasticity. Interestingly, both the phosphatase and non-phosphatase activity of PRLs appears to be important for their role in the regulation of metabolism. The discovery of PRLs' role in metabolism opens new possibilities for targeting this family of phosphatases.

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Conflicts of interest

There are no conflicts of interest.

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