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REVIEW

Emerging role for PLCβ1 MiRNA and disease

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Nuclear inositides are independently regulated and their regulation is completely independent from the plasma membrane correspondent, hinting that the nucleus represents a specialized distinct compartment of inositol lipids metabolism. This points out that nuclear inositol lipids themselves can influence nuclear key events as transcription and pre-mRNA splicing, growth, proliferation, cell cycle regulation and differentiation. Phospholipase C β1 (PLCβ1) is the most significant enzyme for nuclear inositide signaling. Very recently it has been highlighted that the role of PLCβ1 during erythropoiesis is linked to that of miR-210. Moreover, PLCβ1 signaling is linked to gene regulation and changes in microRNAs (miRNAs) occur with PLCβ1 expression. Molecular targets of PLCβ1 have been found to be important during myogenesis and hematopoiesis. In addition, PLCβ1 signaling has been demonstrated to be impaired in diseases affecting both myogenic differentiation and affecting the hematopoietic system.

Keywords: miRNA; PLCβ1; nucleus

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Introduction

The roles of phosphoinositide-specific phospholipase C (PLC) have been extensively investigated in diverse cell lines and pathological conditions. It is clear today that lipid signaling molecules take part of the highly complex process that allows one extracellular signal to be transduced inside the cell, to the nucleus. In the nucleus, lipid signaling induces reactions that modulate the regulation of gene transcription, DNA replication or repair, and DNA cleavage, finally stemming in cellular differentiation, proliferation, apoptosis, or several other cellular functions [1-4]. PLCβ1 catalyzes the hydrolysis of the signaling lipid phosphatidylinositol 4, 5-bisphosphate (PI-4,5P2) to produce the second messengers inositol 1, 5, -trisphosphate (IP3) and diacylglycerol (DAG). In general, PLCβ1 is activated by G-protein coupled receptor (GPCR) through several mechanisms at the plasma membrane whilst in the nucleus its activation depends on MAP kinase [5]. In fact, the nucleus has a phosphoinositol lipid signaling pathway that is independent of the one found on the plasma membrane and PLCβ1 is the major PLC in the nucleus. The function of PLCβ1 in the nucleus still remains an intriguing question even if it has been studied in great detail up to now. Other independent laboratories has thoroughly demonstrated that the phosphoinositide cycle and its related correspondent is also present in the nucleus, and may be relevant for several nuclear events such as mRNA export, DNA repair and gene transcription [6-9]. Recent evidences have revealed the importance of investigating the nuclear protein network behind PLCβ1 role and identifying the associated protein targets, thus giving more enlightenment into the interactors and downstream molecular effectors that even further elucidate its nuclear signaling cascade. PLCβ1 gene is present as alternatively spliced variants β1a and β1b, which differ in their C-terminal residues [10]. PLCβ1a seemed to be localized preferentially in the cytosol, but PLCβ1b was found mainly in the nuclei [11]. The subcellular localization denote a different physiological

role for PLCβ1, in normal cell proliferation or differentiation [12,13], which could result in a different role in pathogenesis. Here we review the emerging role of PLCβ1 in physiology and disease highlighting the importance of understanding the network behind PLCβ1 function and downstream target effectors. In this review we will confine our focus to the nuclear PLCβ1 and in particular, we will review the most updated literature on PLCβ1.

Outline of PLCβ1 targets and pathology

Skeletal muscle differentiation is characterized by terminal withdrawal from cell cycle, activation of muscle-specific genes and morphological changes, including myoblast alignment, elongation and fusion of mononucleated myotubes. Nuclear PLCβ1 is a key player in myoblast differentiation, and functions as a positive regulator of this process. Interestingly, it has been demonstrated that the differentiation of C2C12 mouse myoblasts in response to insulin stimulation is characterized by a marked increase in nuclear PLCβ1, which then appears to be a key player in the skeletal muscle differentiation program, by targeting cyclin D3 [14,15]. Cyclin D3 expression plays a critical role in the Myo-D-mediated arrest of the cell cycle, which precedes myoblast differentiation. In C2C12, PLCβ1 resides predominantly in the nucleus and activates cyclin D3 promoter during the differentiation of myoblasts to myotubes, indicating that its function and nuclear localization are crucial regulator of the mouse cyclin D3 gene and that PLC signaling induced by insulin activates at least a lipid-dependent signaling pathways. Cyclin D3 gene expression is regulated by PLCβ1 induction of the cyclin D3 promoter *via* the activation of the c-jun/AP1 transcription factor [16]. In fact, C2C12 cell fusion into myotubes is significantly inhibited by the knockdown of both PLCβ1 which is necessary for efficient muscle differentiation. Moreover, cyclin D3 promoter activation is under the control of molecular events that depend not only on PLCβ1expression levels and activity, but also on the nuclear localization of PLCβ1, because the over-expression of a PLCβ1 mutant for the nuclear localization sequence, which localizes only in the cytoplasm, inhibits both the promoter activity and the induction of differentiation [13]. Nuclear PLCβ1signalling has been demonstrated to be involved in diseases showing an altered myogenic differentiation. These findings, obtained mostly by in vitro studies, resulted to have a great impact in pathophysiology, as the deregulation PLCβ1/cyclin D3 signaling has been associated also with myogenic diseases [17]. Moreover, while cyclin D3 and cdk4 are elevated in normal myotubes, Myotonic dystrophy 1 (DM1) differentiating cells do not increase these proteins [18]. Myotonic dystrophy (DM) is a myogenic disease characterized by an impaired myogenic differentiation and is the most prevalent form of muscular dystrophy in adults. At the onset, DM can appear as DM type 1 (DM1) or type 2 (DM2), both dominantly inherited multisystem disorders. We know today that DM is not elicited by the presence of a mutated protein. Conversely, DM is the first acknowledged case of an RNA-mediated disorder. The presence of the mutated gene produces an expanded repeat RNA that is highly noxious to cells. The mutant RNA is accumulated in the nucleus compartment, originating ribonuclear clusters in pathological tissue [19] . There are two types of DM caused by microsatellite expansions in two different genes. DM type 1 (DM1) is produced by the repetition of a trinucleotide (CTG) reiteration in exon 15 in the 3' untranslated region (UTR) of the DM protein kinase (DMPK) gene. Instead, DM (DM2) is caused to the expansion of a tetranucleotide (CCTG) repeat in intron 1 of the zinc finger protein 9 (ZNF9) gene [20]. Given the data obtained in C2C12 cells and data dealing with the reduction in expression of cyclin D3 in DM1, we evaluated whether an alteration of PLCβ1 levels of could give rise to a correct differentiation in DM1 and DM2. The expression of PLCβ1 in myogenesis of DM cells significantly decreases. Overexpression of PLCβ1*a* and PLCβ1*b* in differentiated cells from control contributors and patients with DM1 or DM2 revealed that both isoforms were required for the correct expression of cyclin D3 and myogenin in this disease, as cyclin D3 levels increased only in differentiated cells from control participants, whereas in DM1 and DM2 cells the amount of cyclin D3 was reduced. In fact, the presence of a cluster of aberrant RNA in the nucleus can give rise to a delay of the correct event involved in translation. On the other hand, also cyclin D3 was low in DM1 differentiating cells, and this could be a crucial state acting to compromise myoblast fusion, as cyclin D3 plays a critical role in the Myo-D-mediated arrest of the cell cycle preceding myoblast differentiation [17]. These results furthermore emphasize that the PLCβ1 expression level is crucial in myoblast differentiation, acting as a positive regulator in the correction of compromised differentiation of skeletal muscle in DM human myoblasts. Very recently it has been demonstrated that a modulated expression of PLCβ1 into mithramycin (MTH) treated K562 cells is able to modify miR-210 profile expression. The DNA binding drug MTH is a potent inducer of γ-globin mRNA and fetal hemoglobin accumulation in erythroid cells from healthy human subjects and β-thalassemia patients [21]. miRNAs regulate a variety of cell functions such as cell proliferation, development, apoptosis, differentiation, and carcinogenesis [22,23]. They can control several cancer-relevant processes such as migration and invasion [24]. Recent studies also show that miRNAs play a key role in stem cell differentiation [25]. They can control the genesis of cancer stem cells (CSCs) [26,27] and the achievement of the epithelial–mesenchymal transition (EMT) phenotype, [28] in that they are fundamentally connected with

drug resistance. MicroRNAs can target up to several hundred mRNAs, which makes them very powerful regulators and an aberrant miRNA expression can influence a multitude of cell signaling pathways. Hundreds of studies lead to the realization that miRNA profiles can diversify between normal and pathologiacl tissue, characterize tissues of origin and discriminate distinct subtypes of a specific type of cancer or even particular oncogenic abnormalities [29]. Furthermore, miRNAs are important indicators for drug resistance, as the expression of miRNAs in chemoresistent cancer cells often differs from that in their parental chemosensitive cells [30]. Recent studies found a different expression of circulating miRNAs in the serum of cancer patients [31,32]. These findings highlight the importance of these small molecules as potential clinical biomarkers for diagnostic, predictive and prognostic purposes. Finally, current studies moved toward the application of microRNAs in cancer therapy as a new approach to interfere with the molecular mechanism of malignancies [33]. Deregulation of miRNA expression results in haematological malignancies [34]. A single miRNA targets many genes and it is not clear whether targeting a single gene or multiple genes leads to hematological malignancies. MiRNAs can function through several pathways which are involved in disease manifestations. Gain of function and loss of function experiments could give a better idea about the clinical use of miRNAs. In particular, the miR-210 is related with the high expression level of fetal γ-globin in K562 cells treated with mithramycin [35,36]. Moreover, miR-210 levels were elevated during mouse fetal liver erythroid cell differentiation in vitro [37]. MiR-210 is a predominant miRNA induced under hypoxic condition in several types of cancers, and has contributed to cellular adaptation to hypoxic environment [38]. It is known that miR-210 levels were elevated during mouse fetal liver erythroid cell differentiation in vitro [37]. Novel data suggest a novel role for PLCβ1 in regulating miR-210 and hint at the fact that, in human K562 erythroleukemia cells, the modulation of PLCβ1 expression is able to exert an impairment of normal erythropoiesis as assessed by γ-globin expression [39]. PLCβ1 protein and mRNA content decreased in MTH-treated K562 cells in parallel with the induction of the differentiation process. Whilst PLCβ1 overexpression inhibits differentiation of the erythroid lineage K562 cell line, knockdown of PLCβ1 causes a significant up-regulation of γ-globin expression. To investigate the PLCβ1 effect on miRNA-210 expression after MTH treatment, experiments were performed in wild type K562 cells, in cells in which the PLCβ1 was overexpressed and in cells in which PLCβ1 was knocked-down. In proliferating K562, cells transfected with PLCβ1 show no significant difference in the level of miR-210 compared to vector transfected cells. On the other hand, K562 cells silenced for the expression of the PLCβ1 show an increase of miR-210 levels. PLCβ1 overexpression led to a loss of induction of miR-210 expression after MTH treatment. Moreover, K562 cells silencing for the expression of the PLCβ1 induces an increase of miR-210 levels. Enhanced PLCβ1 level and reduced miR-210 level accompanies erythroid differentiation. This suggest that the role of PLCβ1 during erythropoiesis is linked to that of miR-210. Furthermore, transfection of K562 cells with anti-miR-210 caused a significant down-regulation of miR-210 expression and determination of γ-globin in the presence of anti-miR-210 showed a limited but appreciable reduction of γ-globin mRNA levels under the MTH treatment, suggesting that PLCβ1 signaling is implicated in the erythroid differentiation event. PLCβ1 can regulate miR-210 levels through PKCα signaling pathway. PKCα levels decreased in cells where PLCβ1 was overexpressed and silencing PKCα by RNAi technique, leads to a decrease in miR-210 and γ-globin expression levels as well as to a severe slowdown of cell differentiation in K562 cells. Understanding new PLCβ1 molecular targets, different from proteins, such as miRNA could result to new signaling pathway in physiology and pathology (and aberrant expression of miRNAs may contribute to abnormal erythropoiesis). In tumor tissues such as breast cancer and head and neck cancers, miR-210 expression levels have been demonstrated to be correlated with hypoxia gene signatures, which suggested a direct connection between miR-210 expression and hypoxia. However, paradoxically opposing results were documented with regard to whether miR-210 is an oncogene or a tumor suppressor, and whether it is a positive or negative prognostic biomarker [40]. PLCβ1 has been connected with several human diseases such as leukemia [41] and Alzheimer's disease [42]. It is notable that losses of PLCβ1 are found in patients with neurological disorders such as epileptic encephalopathiess and schizophrenia which are recapitulated in Knock-out mice [43,44]. PLCβ1and G protein signaling are linked to gene regulation. PLCβ1 can affect the siRNA activity of genes for two metabolic enzymes, GAPDH and LDH, through its interaction with TRAX [45]. The studies here suggest that genes whose levels are regulated by microRNAs with structures allowing rapid hydrolysis by C3PO are vulnerable to secondary regulation by cytosolic levels of PLC. These results show that the level of PLCβ1 affects the cellular amount of small RNAs and that it can reverse the siRNA activity of two cellular proteins involved in metabolism. It has been demonstrated that PLCβ1 reduces the nuclease activity of C3PO and TRAX by an amount that depends on RNA sequence and structure. Changes in microRNAs (miRNAs) occurs with PLCβ expression and some miRNAs are significantly down-regulated when PLCβ1 is over-expressed in HEK29 cells are closely linked to various leukemias and lymphomas in that PLCβ1 expression is directly linked to these diseases [45,46]. A group of researchers

identified PLCβ1 as a, expected, conserved target of miR-26b [47]. Cardiac hypertrophy is characterized by an upregulation of the transcription factor GATA4. GATA4 appears to have a fundamental action in myocyte growth and survival. Amplification of miR-26b expression decreased GATA4-dependent transcription, endothelin-induced hypertrophy, and made susceptible the cells to apoptosis. Moreover, miR-26b targeted PLCβ1, which, successively, prevent miR-26b expression increase, producing a double-negative feedback loop. Resultantly, overexpression of miR-26b in the heart prevented up-regulation of its targets and the improvement of hypertrophy. Nonetheless, knockdown of miR-26b is not enough adequate for promoting hypertrophy. More recently, we demonstrated that lipid signaling could be involved in the regulation of cyclin D3 and, in turn, of cell proliferation in human erythroleukemia cells, K562. Indeed, we observed that overexpression of PLCβ1 drove to an up-modulation of cyclin D3 and a down-regulation of PKCα expression [48]. This was followed by an accumulation of cells at G1/S transition. In particular, silencing of PKCα led to a very similar up-regulation of cyclin D3 compared to PLCβ1 overexpression [48]. PLCβ1 expression levels and cellular localization are necessary for the induction of erythroid differentiation. Nuclear PLCβ1 is down-regulated when Friend erythroleukemia cells treated with dimethysulfoxide differentiate and synthesize γ-globin. It was previously demonstrated that cyclin D3/cdk4 is a target of nuclear PLCβ1 signaling, which is able to activate cyclin D3 promoter transcription during differentiation [1,11,14,15]. Recently, it was shown a functional role for PLCβ1 in erythroleukemia K562 cells. More detailed investigations identified PLCβ1 targets and nuclear regulating molecules after the anticancer drug kinamycin F administration. Kinamycin F has been recently outlined as a powerful differentiating inducer of human erythroleukemia cells [49]. We explored the impact of the antibiotic kinamycin F on PLCβ1 expression and downstream targets of the its nuclear signal transduction pathway through an amplification or a withdrawal of the expression of both PLCβ1a and -β1b [50]. The results showed that whilst the levels of PLCβ1a decreases upon differentiation, the levels of PLCβ1b do not, consequently the action of the drug is primarily direct towards the expression of PLCβ1a. These data underline that kinamycin F acts preferentially on PLCβ1a protein and mRNA expression levels. PLCβ1a overexpression in K562 cells did not affect γ-globin expression after kinamycin F treatment, implying a delay in erythroid differentiation, whereas amplification of PLCβ1b expression significantly increased the amount of the erythroid marker. Generally the expression of cyclin D3 in wild type cells decreases but only the overxpression of the PLCβ1a and not that of PLCβ1b is able to produce high levels of cyclin D3 expression even after the cells have been exposed to the drug. The amplification of PLCβ1a expression is able to support the proliferative state of the cells and to the contrary, the expression of PLCβ1b already in itself favours the proceeding to differentiation. It is shown that the conflicting function of the two isozymes in the kinamycin F induced differentiation process occurs for their different topography within the cell since PLCβ1b has a significant higher expression restricted to the nuclear compartment as compared to PLCβ1a. Moreover it has been demonstrated that cells overexpressing PLCβ1a have a protective effect toward the process of apoptosis as assessed by flow cytometric analysis of Annexin V. Ultimately PLCβ1a and PLCβ1b are crucial regulators of erythropoiesis, having opposite action by means of a positive or a negative role in erythroid development, on the basis of their intracellular location. PLCβ1 has been studied also in the pancreatic β cells to find out if it had a role in the pathology of diabetes. In pancreatic MIN6 cells, PLCβ1 and PLCδ4 are isoforms localized in the nucleus and in the cytoplasm. The advancement of siRNA silencing technology offered the opportunity to evaluate the specific contribution of these two distinct PLC isoforms to insulin release and to distinguish between the effects of nuclear and cytoplasmic isoforms. In fact, they all affected glucose-induced insulin release in that by silencing each of them, it was consistently observed an inhibition of insulin release. Actually, nuclear PLCβ1 and PLCδ4 affected insulin secretion by regulating the expression of PPARγ and its responsive elements. The results identify a nuclear role for PLC in insulin secretion and adds PPARγ to the list of recognized molecular targets of nuclear PLCs [51]. PLCβ1 expression levels could be increased by the presence of α-synuclein through improvement from enzymes degradation such as μ-calpain. α-synuclein is a conserved protein that is a fundamental element in neurodegenerative plaques and mutations are correlated with infrequent forms of familial Parkinson's disease. The level of expression of α-synuclein increases the presence of PLCβ1 and this balance does not appear to be determined to alteration in transcription or in ubitquitin-mediated degradation [52]. While PLCβ1 and other α-synuclein binding partners could stabilize α-synuclein structure, it is possible that their absence or their interaction promotes α-synuclein aggregation and consequential pathogenesis. These results highlight the concept that by changing the cellular expression of specific enzymes, α-synuclein might improve PLCβ1 signaling pathways and events within the cells. Abnormal expression patterns of PLCβ1 in specific brain areas of patients with schizophrenia, and its high genetic linkage to the disorder implicated a pathogenetical involvement of PLCβ1 signaling system. In fact, PLCβ1 is expressed in select areas of brain such as cerebral cortex, hippocampus, amygdala, lateral septum, and olfactory bulb [53], and, therefore, is implicated

for participations in diverse critical functions related to forebrain diseases such as schizophrenia [54].

Thus, dysregulation of phospholipases contributes to a number of human diseases and primary PLCβ1 have been identified as therapeutic targets for prevention and treatment of diseases. The data reviewed here show that PLCβ1 signaling has a physiological and pathological role that is still not fully understood. More specific studies in the future, processed in terms of physiological conditions and in diseases, will increase knowledge about new PLCβ1 molecular targets and could give outcome to novel, original and unforeseen discoveries that are crucial for comprising the function and the importance of this pathway in physiology and in pathology.

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References

1. Cocco L, Faenza I, Follo MY, Billi AM, Ramazzotti G, Papa V, *et al*. Nuclear inositides: PI-PLC signaling in cell growth, differentiation and pathology. Adv Enzyme Regul 2009;49:2-10.
2. Faenza I, Bregoli L, Ramazzotti G, Gaboardi G, Follo MY, Mongiorgi S, *et al*. Nuclear phospholipase C beta1 and cellular differentiation. Front Biosci 2008;13:2452-2463.
3. Fiume R, Keune WJ, Faenza I, Bultsma Y, Ramazzotti G, Jones DR, *et al*. Nuclear phosphoinositides: location, regulation and function. Subcell Biochem 2012;59:335-361.
4. Yang YR, Follo MY, Cocco L, Suh PG. The physiological roles of primary phospholipase C. Adv Biol Regul 2013;53:232-241.
5. Faenza I, Fiume R, Piazzi M, Colantoni A, Cocco L. Nuclear inositide specific phospholipase C signalling - interactions and activity. Febs J 2013;280:6311-6321.
6. Irvine RF. Nuclear lipid signalling. Nat Rev Mol Cell Biol 2003;4:349-360.
7. Keune W, Bultsma Y, Sommer L, Jones D, Divecha N. Phosphoinositide signalling in the nucleus. Adv Enzyme Regul 2011;51:91-99.
8. Folkmann AW, Dawson TR, Wente SR. Insights into mRNA export-linked molecular mechanisms of human disease through a Gle1 structure-function analysis. Adv Biol Regul 2014;54:74-91.
9. Keune WJ, Jones DR, Divecha N. PtdIns5P and Pin1 in oxidative stress signaling. Adv Biol Regul 2013;53:179-189.
10. Faenza I, Billi AM, Follo MY, Fiume R, Martelli AM, Cocco L, *et al*. Nuclear phospholipase C signaling through type 1 IGF receptor and its involvement in cell growth and differentiation. Anticancer Res 2005;25:2039-2041.
11. Faenza I, Matteucci A, Bavelloni A, Marmiroli S, Martelli AM, Gilmour RS, *et al*. Nuclear PLCbeta(1) acts as a negative regulator of p45/NF-E2 expression levels in Friend erythroleukemia cells. Biochim Biophys Acta 2002;1589:305-310.
12. Martelli AM, Gilmour RS, Bertagnolo V, Neri LM, Manzoli L, Cocco L. Nuclear localization and signalling activity of phosphoinositidase C beta in Swiss 3T3 cells. Nature 1992;358:242-245.
13. Ramazzotti G, Faenza I, Fiume R, Matteucci A, Piazzi M, Follo MY, *et al*. The physiology and pathology of inositide signaling in the nucleus. J Cell Physiol 2011;226:14-20.
14. Faenza I, Matteucci A, Manzoli L, Billi AM, Aluigi M, Peruzzi D, *et al*. A role for nuclear phospholipase Cbeta 1 in cell cycle control. J Biol Chem 2000;275:30520-30524.
15. Faenza I, Ramazzotti G, Bavelloni A, Fiume R, Gaboardi GC, Follo MY, *et al*. Inositide-dependent phospholipase C signaling mimics insulin in skeletal muscle differentiation by affecting specific regions of the cyclin d3 promoter. Endocrinology 2007;148:1108-1117.
16. Ramazzotti G, Faenza I, Gaboardi GC, Piazzi M, Bavelloni A, Fiume R, *et al*. Catalytic activity of nuclear PLC-beta(1) is required for its signalling function during C2C12 differentiation. Cell Signal 2008;20:2013-2021.
17. Faenza I, Blalock W, Bavelloni A, Schoser B, Fiume R, Pacella S, *et al*. A role for PLCbeta1 in myotonic dystrophies type 1 and 2. Faseb J 2012;26:3042-3048.
18. Salisbury E, Sakai K, Schoser B, Huichalaf C, Schneider-Gold C, Nguyen H, *et al*. Ectopic expression of cyclin D3 corrects differentiation of DM1 myoblasts through activation of RNA CUG-binding protein, CUGBP1. Exp Cell Res 2008;314:2266-2278.
19. Wheeler TM. Myotonic dystrophy: therapeutic strategies for the future. Neurotherapeutics 2008;5:592-600.
20. Huichalaf C, Sakai K, Jin B, Jones K, Wang GL, Schoser B, *et al*. Expansion of CUG RNA repeats causes stress and inhibition of translation in myotonic dystrophy 1 (DM1) cells. Faseb J 2010;24:3706-3719.
21. Bianchi N, Osti F, Rutigliano C, Corradini FG, Borsetti E, Tomassetti M, *et al*. The DNA-binding drugs mithramycin and chromomycin are powerful inducers of erythroid differentiation of human K562 cells. Br J Haematol 1999;104:258-265.
22. Shivdasani RA. MicroRNAs: regulators of gene expression and cell differentiation. Blood 2006;108:3646-3653.
23. Galasso M, Sandhu SK, Volinia S. MicroRNA expression signatures in solid malignancies. Cancer J 2012;18:238-243.
24. Baranwal S, Alahari SK. miRNA control of tumor cell invasion and metastasis. Int J Cancer 2010;126:1283-1290.
25. Heinrich EM, Dimmeler S. MicroRNAs and stem cells: control of pluripotency, reprogramming, and lineage commitment. Circ Res 2012;110:1014-1022.
26. Peter ME. Targeting of mRNAs by multiple miRNAs: the next step. Oncogene 2010;29:2161-2164.
27. Shimono Y, Zabala M, Cho RW, Lobo N, Dalerba P, Qian D, *et al*. Downregulation of miRNA-200c links breast cancer stem cells with normal stem cells. Cell 2009;138:592-603.
28. Adam L, Zhong M, Choi W, Qi W, Nicoloso M, Arora A, *et al*. miR-200 expression regulates epithelial-to-mesenchymal transition in bladder cancer cells and reverses resistance to epidermal growth factor receptor therapy. Clin Cancer Res 2009;15:5060-5072.

29. Iorio MV, Croce CM. MicroRNA dysregulation in cancer: diagnostics, monitoring and therapeutics. A comprehensive review. EMBO Mol Med 2012;4:143-159.

30. Ma S, Tang KH, Chan YP, Lee TK, Kwan PS, Castilho A, *et al*. miR-130b Promotes CD133(+) liver tumor-initiating cell growth and self-renewal via tumor protein 53-induced nuclear protein 1. Cell Stem Cell 2010;7:694-707.

31. Rabinowits G, Gercel-Taylor C, Day JM, Taylor DD, Kloecker GH. Exosomal microRNA: a diagnostic marker for lung cancer. Clin Lung Cancer 2009;10:42-46.

32. Taylor DD, Gercel-Taylor C. MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. Gynecol Oncol 2008;110:13-21.

33. Acunzo M, Romano G, Wernicke D, Croce CM. MicroRNA and cancer - A brief overview. Adv Biol Regul 2014.

34. Gounaris-Shannon S, Chevassut T. The Role of miRNA in Haematological Malignancy. Bone Marrow Res 2013;2013:269107.

35. Bianchi N, Zuccato C, Lampronti I, Borgatti M, Gambari R. Expression of miR-210 during erythroid differentiation and induction of gamma-globin gene expression. BMB Rep 2009;42:493-499.

36. Bianchi N, Zuccato C, Finotti A, Lampronti I, Borgatti M, Gambari R. Involvement of miRNA in erythroid differentiation. Epigenomics 2012;4:51-65.

37. Kosaka N, Sugiura K, Yamamoto Y, Yoshioka Y, Miyazaki H, Komatsu N,*et al*. Identification of erythropoietin-induced microRNAs in haematopoietic cells during erythroid differentiation. Br J Haematol 2008;142:293-300.

38. Huang X, Le QT, Giaccia AJ. MiR-210--micromanager of the hypoxia pathway. Trends Mol Med 2010;16:230-237.

39. Bavelloni A, Poli A, Fiume R, Blalock W, Matteucci A, Ramazzotti G, *et al*. PLC-beta 1 regulates the expression of miR-210 during mithramycin-mediated erythroid differentiation in K562 cells. Oncotarget 2014;5:4222-4231.

40. Qin Q, Furong W, Baosheng L. Multiple functions of hypoxia-regulated miR-210 in cancer. J Exp Clin Cancer Res 2014;33:50.

41. Follo MY, Faenza I, Piazzi M, Blalock WL, Manzoli L, McCubrey JA, *et al*. Nuclear PI-PLCbeta1: an appraisal on targets and pathology. Adv Biol Regul 2014;54:2-11.

42. Albasanz JL, Dalfo E, Ferrer I, Martin M. Impaired metabotropic glutamate receptor/phospholipase C signaling pathway in the cerebral cortex in Alzheimer's disease and dementia with Lewy bodies correlates with stage of Alzheimer's-disease-related changes. Neurobiol Dis 2005;20:685-693.

43. Koh HY, Kim D, Lee J, Lee S, Shin HS. Deficits in social behavior and sensorimotor gating in mice lacking phospholipase Cbeta1. Genes Brain Behav 2008;7:120-128.

44. Manning EE, Ransome MI, Burrows EL, Hannan AJ. Increased adult hippocampal neurogenesis and abnormal migration of adult-born granule neurons is associated with hippocampal-specific cognitive deficits in phospholipase C-beta1 knockout mice. Hippocampus 2012;22:309-319.

45. Philip F, Sahu S, Caso G, Scarlata S. Role of phospholipase C-beta in RNA interference. Adv Biol Regul 2013;53:319-330.

46. Philip F, Guo Y, Aisiku O, Scarlata S. Phospholipase Cbeta1 is linked to RNA interference of specific genes through translin-associated factor X. Faseb J 2012;26:4903-4913.

47. Han M, Yang Z, Sayed D, He M, Gao S, Lin L, Yoon S, Abdellatif M. GATA4 expression is primarily regulated via a miR-26b-dependent post-transcriptional mechanism during cardiac hypertrophy. Cardiovasc Res 2012;93:645-654.

48. Poli A, Faenza I, Chiarini F, Matteucci A, McCubrey JA, Cocco L. K562 cell proliferation is modulated by PLCbeta1 through a PKCalpha-mediated pathway. Cell Cycle 2013;12:1713-1721.

49. O'Hara KA, Dmitrienko GI, Hasinoff BB. Kinamycin F downregulates cyclin D3 in human leukemia K562 cells. Chem Biol Interact 2010;184:396-402.

50. Bavelloni A, Dmitrienko GI, Goodfellow VJ, Ghavami A, Piazzi M, Blalock W, *et al*. PLCβ1a and PLCβ1b selective regulation and cyclin D3 modulation reduced by Kinamycin F during K562 cell differentiation. J Cell Physiol 2014. doi: 10.1002/jcp.24776.

51. Fiume R, Ramazzotti G, Faenza I, Piazzi M, Bavelloni A, Billi AM, *et al*. Nuclear PLCs affect insulin secretion by targeting PPARgamma in pancreatic beta cells. Faseb J 2012;26:203-210.

52. Guo Y, Rosati B, Scarlata S. alpha-Synuclein increases the cellular level of phospholipase Cbeta1. Cell Signal 2012;24:1109-1114.

53. Fukaya M, Uchigashima M, Nomura S, Hasegawa Y, Kikuchi H, Watanabe M. Predominant expression of phospholipase Cbeta1 in telencephalic principal neurons and cerebellar interneurons, and its close association with related signaling molecules in somatodendritic neuronal elements. Eur J Neurosci 2008;28:1744-1759.

54. Koh HY. Phospholipase C-beta1 and schizophrenia-related behaviors. Adv Biol Regul 2013;53:242-248.