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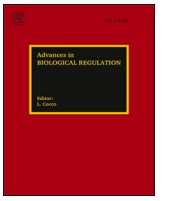

Advances in MDS/AML and inositide signalling

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ABSTRACT

Aberrant signaling pathways regulating proliferation and differentiation of hematopoietic stem cells (HSCs) can contribute to disease pathogenesis and neoplastic growth. Phosphoinositides (PIs) are inositol phospholipids that are implicated in the regulation of critical signaling pathways: aberrant regulation of Phospholipase C (PLC) beta1, PLCgamma1 and the PI3K/Akt/mTOR pathway play essential roles in the pathogenesis of Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML).

1. Introduction

Aberrant signaling pathways regulating proliferation and differentiation of hematopoietic stem cells (HSCs) can contribute to disease pathogenesis and neoplastic growth. HSCs usually live within the bone marrow (BM) niche, in balance between quiescence and activation. The transition between these two processes is a continuous developmental process driven by several signaling molecules, including cell-cycle regulators, transcription factors, epigenetic factors, and niche factors (Chen et al., 2022).

Phosphoinositides (PIs) are inositol phospholipids that are implicated in the regulation of critical signaling pathways (Cocco et al., 2015a). PIs play an important role in the regulation of cell proliferation, cell differentiation, and gene expression. PIs are regulated by kinases and phosphatases, localized both at the plasma membrane and the nucleus, as well as within distinct nuclear compartments (i.e., the nuclear speckles), with important implications in pathogenesis (Owusu Obeng et al., 2020).

2. Nuclear inositides: Phopsholipases C

Phosphoinositide-specific phospholipases C (PI-PLCs) are a group of inositide-dependent enzymes that cleave phosphatidylinositol 4,5-biphosphate (PIP_2) (Faenza et al., 2008; Martelli et al., 2005) to produce inositol 1,4,5-trisphophate (IP_3) and diacylglycerol (DAG) that, in turn, are key second messengers regulating cell proliferation, apoptosis, activation of immune cells and stem cell differentiation, through the release of intracellular calcium ions and activation of protein kinase C (PKC), respectively (Faenza et al., 2008; Martelli et al., 2005; Poli et al., 2018). Evidence accumulated over the past 30 years showed that an autonomous inositol lipid

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metabolism is located within the nucleus and suggests that lipid signaling molecules exert essential functions regulating cell metabolism (Ramazzotti et al., 2011). Interestingly, the regulation of the nuclear PI pool is totally independent from the plasma membrane counterpart, suggesting that the nucleus constitutes a functionally distinct compartment of inositol lipids metabolism (Cocco et al., 1999). For instance, nuclear PLCbeta1 appears to play a key role in cell cycle, acting as a check point in the G_1 or the G_2/M phase of the cell cycle. In fact, overexpression of nuclear PLCbeta1 is directly correlated to the overexpression and activation of the cyclin D3-cdk4 complex, which is known to stimulate progression through G_1 rather than promote the G_1-S transition. Nuclear PLCbeta1 is activated even during the G_2/M phase, involving PKC and some mitogen-activated protein kinases, such as Jun N-terminal kinase and extracellular signal-regulated kinase (ERK)1/2 (Faenza et al., 2013; Fiume et al., 2009). Interestingly, two PLCs (PLCbeta1 and PLCgamma1) were associated with normal and pathological hematopoiesis, especially the one of myelodysplastic syndromes (MDS) (Fig. 1).

3. PLCs in MDS/AML

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematological malignancies characterized by peripheral blood cytopenia, an aberrant myelopoiesis and a variable risk of acute myeloid leukemia (AML) progression (Sekeres and Taylor, 2022). Although the therapy regimen for MDS patients has seen improvements in recent years, there are no therapies to quickly eradicate the disease, except allogeneic stem cell transplantation. The first line of treatment for MDS is an epigenetic therapy which involves the use of demethylating agents, administered alone or in combination with other drugs. However, MDS patients at higher risk of AML evolution can become resistant to this therapy. Recently, a molecular study has linked a few inositide-related genes to the lack of response to epigenetic therapy (Follo et al., 2019). However, the mechanisms of appropriate inositide-dependent interactions and regulatory signals that alter several critical cellular events implicated in MDS, such as cell proliferation or apoptosis, are still not fully understood, although PLCbeta1 and PLCgamma1 seem to be implicated (Table 1) (Follo et al., 2006, 2012).

PLCbeta1 regulates several critical cellular processes, both at the nuclear and cytoplasmic levels. It is involved in both G_1/S and G_2/M cell cycle phases by modulating different proteins, such as cyclin D3, cyclin E, and lamin B1 (Ramazzotti et al., 2017, 2019a; Cocco et al., 2008). Moreover, it is associated with hematopoietic differentiation, particularly in MDS, that showed an increase of PLCbeta1 during myeloid differentiation and a reduced expression during erythroid differentiation (Cocco et al., 2015b; Follo et al., 2020; Xian et al., 2020).

Even PLCgamma1 is implicated in MDS hematopoietic differentiation, being increased during erythroid differentiation of MDS cells (Schnöder et al., 2015; Parisi et al., 2021). In untreated MDS cells, the expression level of PLCgamma1 is significantly lower in MDS

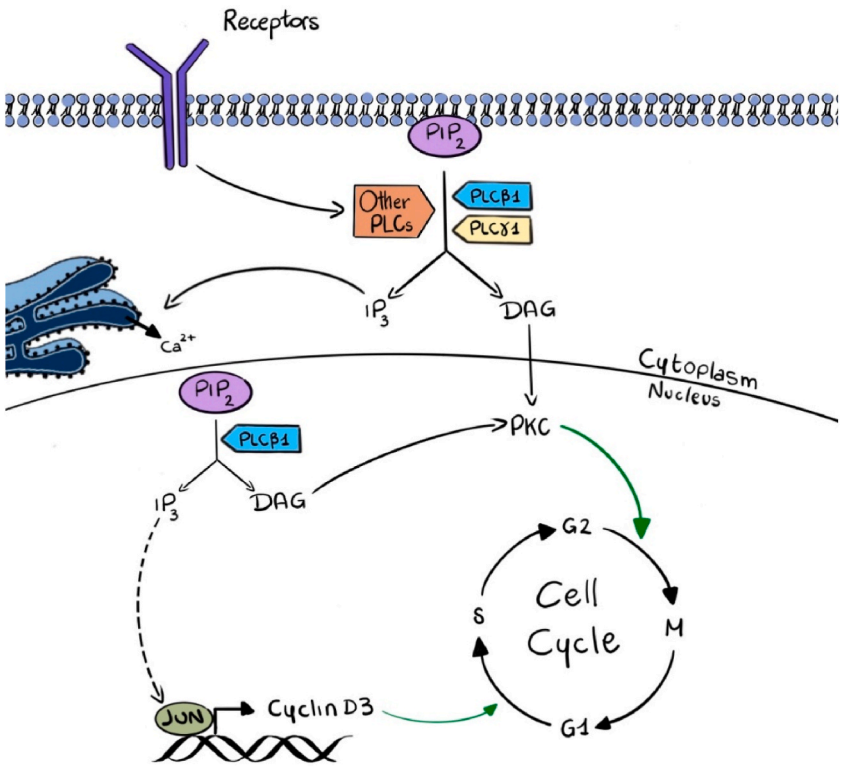

Fig. 1. Schematic representation of PLCs pathway. PIP_2 is cleaved by various PLCs to generate second messengers involved in cell cycle regulation and Ca^{2+} release. The image shows nuclear PLCbeta1, that is totally independent from the plasma membrane counterpart.

Table 1
Principal altered pathways and functions of involved molecules in Myelodysplastic Syndromes (MDS).

Principal altered pathways	Involved Molecules	Function
PLCs pathway	PLCβ1	Regulation of G_1/S and G_2/M cell cycle phases (through cyclin D3, cyclin E, lamin B1) Regulation of hematopoietic differentiation
	PLCγ1	Regulation of hematopoietic differentiation Maintenance of AML1-ETO in LSCs
PI3K/AKT/mTOR pathway	GSK3β, SOS1, RASA1, MTCP1 AKT3, FOS	Regulation of BM microenvironment and of the relationship between MDS cells and MSCs Overexpression in MDS patients with poor prognosis

patients with del(20q), where PLCG1 gene is mapped, but can be reduced also in patients without del(20q) compared to the healthy subjects, which suggests that reduced PLCG1 expression is a common molecular event in MDS. Moreover, reduced PLCgamma1 was also associated with increased blast proliferation, paving the way to further studies on PLCgamma1 in leukemic stem cells (LSCs) (Shiseki et al., 2020).

In fact, PLCgamma1 is required for maintenance of AML1-ETO leukemic stem cells (LSCs) but is dispensable for normal HSC function. Indeed, LSCs with higher cell-cycle activity than normal HSCs are sensitive to PLCgamma1 inhibition, so that pharmacologic perturbation of Calcium-signaling inhibits AML1-ETO LSC function (Schnoeder et al., 2022).

4. PI3K/AKT in MDS

The phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR signaling pathway plays an important role in the control of several cellular processes, such as cell growth, proliferation, survival, and neoplastic transformation (Ramazzotti et al., 2019b; Poli et al., 2020; Cocco et al., 2007) (Fig. 2). Several stimuli, including a range of growth factors and mitogens, activate cell surface tyrosine kinase receptors, which in turn determine the activation of PI3K. For further activation, Akt is phosphorylated by both PI3K-dependent kinase-1 (PDK1) and mammalian target of rapamycin (mTOR) to regulate cell metabolism and differentiation (Poli et al., 2020; Darici et al., 2021). In addition, the PI3K/Akt/mTOR pathway has some overlapped functions with PLCs and PKC (Steelman et al., 2020).

PI3K/Akt/mTOR pathway plays an important role in MDS (Table 1), where it can activate several downstream targets, especially involving the BM microenvironment and the relationship between MDS cells and mesenchymal stem cells (MSCs). Indeed, statistically significant downregulation of some PI3K/Akt targets (GSK3β, SOS1, RASA1, and MTCP1) was observed in BM-MSCs isolated from patients with de novo MDS, as compared with controls. Moreover, the expression of the GSK3β protein was reduced in MDS-derived MSCs and was associated with concomitant reduction of phosphorylation at Ser-9. Deregulation of genes involved in the PI3K/AKT signaling pathway may therefore contribute to the phenotypical abnormalities of MDS BM-MSCs (Falconi et al., 2016).

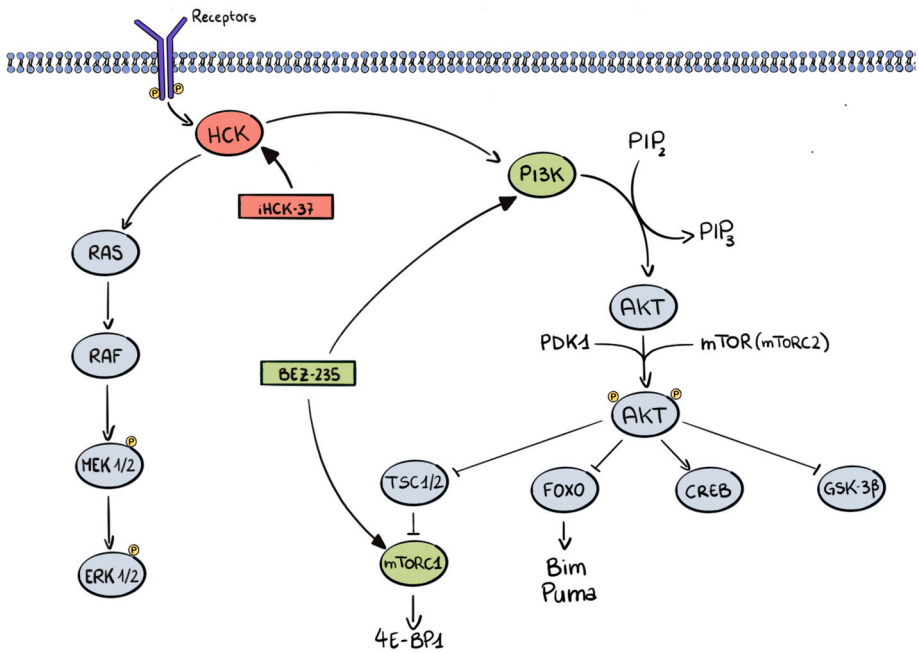

Fig. 2. Schematic representation PI3k/AKT/mTOR pathway. The pathways are activated by receptors, leading to the activation of several oncogenic process (cell growth, proliferation, and survival). Drugs are indicated in the rectangular shapes (red: iHCK-37; green: BEZ-235) and the related target are shown in the same colour in the circular shapes.

PI3K/Akt signaling in MDS was also associated with drug resistance, as thirty-eight candidate genes, including immune checkpoints and genes regulating myeloid cell differentiation, besides PI3K-Akt signaling, were identified as differentially regulated during decitabine therapy. Interestingly, two of the candidate genes, AKT3 and FOS, were overexpressed in MDS patients with poor prognoses (Kim et al., 2021).

Therefore, the PI3K/Akt axis is activated in MDS, although both p-mTOR and autophagy signaling (p-ATG1, p-AT6, ATG7, ATG12) were downregulated in MDS bone marrow. In fact, the PI3K/Akt/mTOR pathway does not rule over the process of autophagocytosis in HSCs of MDS bone marrow, as the isoflavanoid quercetin can remarkably restore autophagocytosis and normal hematopoietic oxidative status (Daw and Law, 2021).

5. PI3K/AKT in AML

In AML, one of the most common altered pathways is PI3K/Akt/mTOR. Indeed, in approximately 60% of AML patients, PI3K signals are enhanced, and 50–80% of patients have increased Akt signals in blasts and LSCs. In addition, almost all AML samples show high levels of mTOR signals, so that the inhibition of this pathway may be a potential therapeutic target (Nepstad et al., 2020). Therefore, the PI3K/AKT/mTOR pathway appears to be an appealing target, as it can promote MCL-1 expression at multiple levels, including transcription by activating the CREB transcription factor; mTORC1 activation and subsequent 4E-BP1 phosphorylation; and proteasome degradation by inhibiting GSK3-induced phosphorylation (Ratti et al., 2020). Moreover, the PI3K/AKT/mTOR pathway can also regulate the activity of MCL-1 by regulating the expression and phosphorylation of Bim and the expression of Puma. In AML patients, the abnormal activation of PI3K/AKT/mTOR pathway is often correlated to drug resistance and poor prognosis (Yakymiv et al., 2021). Therefore, several PI3K/Akt/mTOR multiple inhibitors are developed and tested (Table 2). This is the case of BEZ235, an ATP competitive inhibitor that can directly target the catalytic domain of both PI3K and mTOR [41] (Fig. 2). Interestingly, long-term use of BEZ235 can cause BCL2 up-regulation and lead to drug resistance. Therefore, new therapeutic approaches are studied, as the combination of BEZ235 and Venetoclax, a BCL-2 inhibitor (Liu et al., 2022).

Indeed, in AML, targeting PI3K/AKT/mTOR pathway is one of the novel strategies to enhance the anti-leukemia efficacy of Venetoclax (Liu et al., 2022).

This relies on *in vitro* data, showing that Venetoclax-resistant MV4-11 leukemic cells can activate the PI3K/Akt pathway, because of a metabolic reprogramming and redox adaptation for survival. Indeed, Venetoclax-resistant AML cells can accumulate metabolites associated with the PI3K/Akt pathway activation, shifting resistant AML MV4-11 cells towards glycolysis, and facilitating an increased redox potential, which ultimately favors cell survival. Altered metabolic networks in the resistant cells were also related to carbon energy metabolism, including the Warburg effect, glycolysis, the pentose phosphate pathway, glutamate, and the TCA cycle (Alkhatabi et al., 2022).

Finally, PI3K/Akt pathway is also correlated with other kinases, such as the Src family kinase (SFK). SFK may represent a molecular target, as the SFK member Hematopoietic Cell Kinase (HCK) is overexpressed in HSCs of de novo AML patients and involved in the MDS/AML oncogenic process. Interestingly, a novel chemical compound targeting HCK inhibition (iHCK-37), in combination with the most used drugs for the treatment of MDS and de novo AML, Azacitidine and Cytarabine, showed additive effects against leukemia cells, compared to either drug alone. iHCK-37 plus Azacitidine or Cytarabine treatment was thus able to reduce the activation of downstream oncogenic pathways, i.e., MAPK/ERK and PI3K/AKT, leading to reduction of ERK and AKT phosphorylation, increased BAX, and decreased BCL-XL protein expression (Table 2). Moreover, treatment with iHCK-37 reduced AML CD34-positive cell numbers inside a 3D-structure but did not affect normal CD34-positive cell numbers (Roversi et al., 2022).

6. Conclusions

The regulation of PLCs and PI3K/Akt/mTOR pathways is essential in MDS and AML. They can represent new therapeutic targets, but their comprehension can also be useful to understand the molecular mechanisms underlying MDS and AML pathogenesis and progression.

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Table 2
Novel therapeutic strategies targeting PI3K/Akt/mTOR axis in AML.

Inhibitors	Type	Functions	Pre-clinical studies	Long-term effects
BEZ-235	ATP competitive inhibitor	Inhibition of the catalytic domain of PI3K and mTOR	*in vitro* studies for the combination with Venetoclax	BCL-2 up-regulation and drug resistance
iHCK-37	Hematopoietic Cell Kinase (HCK) inhibitor	Reduction of the activation of downstream oncogenic pathways (i.e. MAPK/ERK, PI3K/Akt) Reduction of AML CD34-positive cell numbers	*in vitro*, *ex vivo* and *in vivo* studies for the combination with Azacitidine and Cytarabine	Unknown

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CRediT authorship contribution statement

Alessia De Stefano: Formal analysis, Investigation, Writing – original draft. Maria Vittoria Marvi: Validation, Writing – review & editing. Antonietta Fazio: Validation, Writing – review & editing. James A. McCubrey: Writing – review & editing. Pann-Ghill Suh: Writing – review & editing. Stefano Ratti: Funding acquisition, Supervision. Giulia Ramazzotti: Funding acquisition, Validation, Writing – review & editing, Supervision. Lucia Manzoli: Funding acquisition, Supervision. Lucio Cocco: Supervision. Matilde Y. Follo: Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

N/A

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