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Nuclear inositide signaling and cell cycle

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ABSTRACT

Phosphatidylinositols (PIs) are responsible for several signaling pathways related to many cellular functions, such as cell cycle regulation at different check-points, cell proliferation, cell differentiation, membrane trafficking and gene expression. PI metabolism is not only present at the cytoplasmic level, but also at the nuclear one, where different signaling pathways affect essential nuclear mechanisms in eukaryotic cells. In this review we focus on nuclear inositide signaling in relation to cell cycle regulation. Many evidences underline the pivotal role of nuclear inositide signaling in cell cycle regulation and cell proliferation associated to different strategic physiopathological mechanisms in several cell systems and diseases.

1. Introduction

Phosphatidylinositols (PIs) are lipid molecules characterized by a hydrophilic inositol ring bound to a hydrophobic tail of glycerol and two fatty acid chains, that are involved in many signaling pathways. PIs play several pivotal roles in cell cycle regulation at different check-points, cell proliferation, cell differentiation, membrane trafficking and gene expression (Cocco et al., 2015a). The kinases and phosphatases related to the PI pool are present at both cytoplasmic and nuclear level showing that PIs can modulate different cellular functions in relation to their specific topography. This nuclear PI metabolism includes PI-Phospholipases C (PI-PLCs), a group of enzymes that hydrolyze Phosphatidylinositol 4,5-biphosphate (PI[4,5]P2) to Inositol 1,4,5-trisphosphate (Ins[1,4,5]P3) and Diacylglycerol (DAG), key second messengers involved in the activation of Protein Kinases C (PKCs), and that are phosphorylated by Diacylglycerol Kinases (DGKs) (Cocco et al., 1994; Baldanzi, 2014; Follo et al., 2015; Tu-Sekine et al., 2015; Tanaka et al., 2016). It is known that oscillations of the lipid nuclear pool and cell cycle progression are strictly associated (Irvine, 2003; Banfic et al., 2016). There have been several documented evidences on the role of nuclear inositide signaling in cell cycle regulation and cell proliferation that could pave the way to new fields of research related to different strategic physiopathological mechanisms in many cell systems and diseases (Ratti et al., 2017; McCubrey et al., 2017; Abrams et al., 2017). Cell cycle regulation is strictly controlled and regulated by a group of enzymes: cyclins, cyclin-dependent-kinases (Cdks), retinoblastoma protein (pRb) and Cip/Kip inhibitors (p16, p21, p27). Interestingly, each cell cycle phase is related to specific cyclins. For instance, Cyclins D/E control G1/S transition and Cyclins A/B control G2/M progression (Bloom and Cross, 2007). The role of nuclear inositide signaling in cell cycle regulation is therefore extremely fascinating and challenging at the same time.

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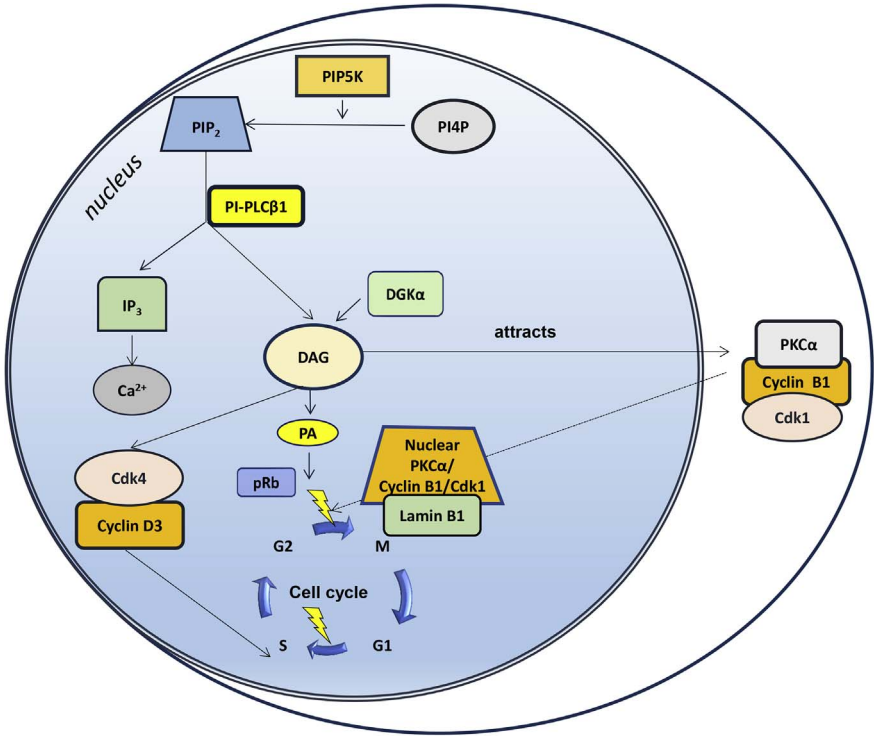

Fig. 1. Nuclear inositide signaling and cell cycle: nuclear PI-PLCβ1 modulates Cyclin D3 activity affecting G1/S transition and Cyclin B1 activity affecting G2/M progression. DAG increase, related to PI-PLCβ1 activity, is responsible for PKCα nuclear translocation. The phosphorylation of Lamin B1, by PKCα/Cyclin B1/Cdk1 complex is essential for the mitosis. There are many other molecules involved in these processes such as DGKs that can be present inside the nucleus under different stimuli and in diverse cell lines with distinct effects on cell cycle. DGKα can affect cell cycle progression interacting with DAG and other molecules involved in cell cycle regulation such as pRb.

2. Nuclear PI-PLCs

PI-PLCs are a family of 13 isozymes, divided in six families: PI-PLC-β (1–4), - γ (1–2), δ (1, 3, and 4), - ε, - ζ, and η (1–2) (Gresset et al., 2012). All these PI-PLCs show conserved structural features that allow them to hydrolyze PI(4,5)P2 following several ligand bonds with cell surface receptors. Moreover, PI(4,5)P2 hydrolysis results in DAG and inositol-1,4,5- trisphosphate (IP3) synthesis. In turn, IP3 releases Ca2+ that, together with DAG, determines PKC activation and results in many cellular mechanisms. Indeed, PKCs can regulate cell cycle progression at all levels, interacting with many cell cycle regulatory molecules. Apart from the traditional cytoplasmic pathways, PI-PLCs localize also inside the nucleus and are independent from their cytoplasmic counterparts. A PI-PLC that seems to be located inside the nucleus is PI-PLCζ, a sperm protein associated with nuclear infertility mechanisms in relation to oocyte activation trough Ca2+ release via IP3 pathway (Amdani et al., 2016; Saunders et al., 2002). However, the most studied nuclear PI-PLC is PI-PLCβ1, whose gene is located on the short arm of chromosome 20 (20p12) and can determine two splicing variants: PI-PLCβ1a (150 kDa) and PI-PLCβ1b (140 kDa), differing one another for the C- terminal sequence (Bahk et al., 1998). Both isoforms have a Nuclear Localization Sequence (NLS), but PI-PLCβ1a also has a Nuclear Export Sequence (NES). Therefore, PI-PLCβ1a can also be found in the cytoplasm and PI-PLCβ1b is primarily inside the nucleus (Martelli et al., 2005; Follo et al., 2006). Nuclear PI-PLCs play pivotal roles at several levels, and nuclear PI-PLCβ1 is involved in cell cycle control at both G1/S transition and G2/M progression trough different molecules (Fig. 1). Moreover, nuclear PI-PLCβ1 has been associated with hematopoietic, osteogenic, myogenic, and adipogenic differentiation processes (Ramazzotti et al., 2016). During cell differentiation PI-PLCβ1 levels change: there is an increase in normal osteogenic and myogenic differentiation of C2C12 cells and in adipogenic differentiation of 3T3-L1 cells; whereas there is a decrease in erythroid differentiation in MEL and CD34 $^{+}$ cells with erythropoietin stimulation toward erythroid lineage and in Myelodysplastic Syndromes (MDS) cells, responding to erythropoiesis stimulating agents. These evidences indicate an inhibiting role of PI-PLCβ1 in erythroid differentiation in opposition of PI-PLCγ1 that increases in erythroid differentiation. Interestingly, it has been observed an increase in MDS cells during the myeloid differentiation induced by hypomethylating therapies, suggesting a different modulation of PI-PLCβ1 in hematopoietic regulation (Mongiorgi et al., 2016a). The possible positive role of PI-PLCβ1 in myeloid differentiation seems to be related to the Myeloid zinc finger-1 (MZF-1), a specific myeloid transcription factor, that is recruited during PI-PLCβ1 expression increase. At clinical level, the increase of PI-PLCβ1 expression in MDS patients treated with Azacitidine, a hypomethylating agent, have been related to a favorable clinical response, an improve of normal myeloid differentiation and a more durable response to the treatment. These data suggest a possible use of PI-PLCβ1 as a molecular marker able to define specific and personal therapeutic strategies in MDS patients (Manzoli et al., 2014; Mongiorgi et al., 2016b; Cocco et al.,