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Review

Nuclear phospholipase C: Involvement in signal transduction

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Abstract

During the past years, several independent laboratories have highlighted the presence of nuclear signaling pathways based on lipid hydrolysis, which are not a mere duplication of those occurring at the plasma membrane. Among the enzymes of the cycle, nuclear phosphoinositide-specific phospholipase C (PI-PLC) has been analyzed quite extensively. In this context, PI-PLCβ_1 appears to play a key role as a check point in the G1 phase of the cell cycle. It has also been shown that its activation and/or up-regulation is upon the control of type 1 insulin-like growth factor receptor (IGF-R) in both mouse fibroblast and myoblasts, suggesting that its signaling activity is essential for the normal behavior of the cell, at least in culture. The recent discovery of a possible involvement of the deletion of PI-PLCβ_1 gene in the progression of myelodysplastic syndrome (MDS) to acute myeloid leukemia (AML) in humans strengthens the contention that nuclear PI-PLC signaling is essential for physiogical processes such as cell growth and differentiation. Even though PI-PLCβ_1 is present and does not translocate to eukaryotic nuclei, this organelle, even though only in some conditions contains also PI-PLCγ_1 which acts not only as a PI-PLC but also as guanine nucleotide exchange factor (GEF) for PI 3-kinase enhancer (PIKE) and is somehow linked to PI 3-kinase (PI3K) activity. Also members of PI-PLCδ family are shuttling from the nucleus to the cytoplasm and return and are possibly involved in the control of cell growth. We must also take into account the presence in the nucleus of other phospholipases such as phospholipase A2 (PLA_2) and phospholipase D (PLD), which also exert a signaling activity upon external stimuli.

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On the whole this review highlights the latest development in the PI-PLC cycle in the nucleus, which in terms of activation, regulation and down-stream targets differs substantially from that located at the plasma membrane.

Keywords: Inositol lipids; Inositol phosphates; Diacylglycerol; Protein kinase C; Proliferation; Differentiation

Contents

1. Introduction

For the first time, late in the eighties and early in the nineties, the evidence appeared that polyphosphoinositides (PIs), even though in a small amount, are present inside the cell nucleus and that their metabolism changes during cell growth and differentiation [1–4]. Going back in to the literature dealing with nuclear lipids, it looks like that the nuclear PI story stems from the evidences obtained during the seventies and the early eighties, by Manzoli and co-workers. In fact, they not only defined the composition of nuclear phospholipids but also made the first steps to establish a possible metabolic role of these molecules analyzing in vitro the relationship between nuclear phospholipids and DNA duplication, mRNA synthesis, and chromatin structural organization also in neoplastic cells [5–10]. That work constituted the background for new investigators who have focused their attention to the metabolic role of nuclear phospholipids and namely on the signaling activity exerted by all the players of the nuclear inositol lipid cycle.