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Review

Phospholipid – Driven gene regulation

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ABSTRACT

Phospholipids (PLs), well known for their fundamental role in cellular structure, play critical signaling roles via their derivatives and cleavage products acting as second messengers in signaling cascades. Recent work has shown that intact PLs act as signaling molecules in their own right by modulating the activity of nuclear hormone transcription factors responsible for tuning genes involved in metabolism, lipid flux, steroid synthesis and inflammation. As such, PLs have been classified as novel hormones. This review highlights recent work in PL-driven gene regulation with a focus on the unique structural features of phospholipid-sensing transcription factors and what sets them apart from well known soluble phospholipid transporters.

1. Introduction

1.1. Phospholipids

PLs are ubiquitous to all forms of life serving as the major constituent of the membranes that isolate and protect cells from their external environment, and segregate organelles from the greater cellular milieu. PLs are composed of two hydrophobic tails, donated by a diacylglycerol (DAG), and a hydrophilic head group containing a phosphate, which is frequently conjugated to an additional hydrophilic metabolite (Fig. 1). This amphipathic, bipartite structure drives their spontaneous assembly into bilayers, which compartmentalize the cell and harbor an assortment of proteins, glycans, and other lipids that play critical roles in cell structure, function, metabolism, and signaling.

1.1.1. PLs as signaling molecules

Though best known for their role in membrane construction, PLs play integral roles in a number of cellular signaling cascades at and within the membrane bilayer [1]. Arguably the most familiar of these are the IP_3/DAG and Akt cascades. In the former, membrane-bound PI-bisphosphate (PIP_2) is cleaved by PLC to yield inositol trisphosphate (IP_3) and DAG; IP_3 is released into the cytoplasm and triggers the release of Ca^{2+} from the endoplasmic reticulum, while DAG remains in the plasma membrane and activates PKC [2]. PI-trisphosphate (PIP_3) is instrumental in recruiting Akt to the plasma membrane, where it is activated by PDK-1 [3]. In more recent years, additional PL derivatives have been implicated in cell signaling. Lysophospholipids, single-chain PLs that include sphingosine-1-phosphate (S1P) and lysophosphatidic acid (LPA), were found to bind and activate G protein coupled receptors (GPCRs) upstream of Ras homolog gene family, member A (RhoA) activation, affecting numerous signaling responses [4]. Furthermore, a family of tail-oxidized PLs are now known to play central roles in the regulation of the plasma membrane and the innate immune system [5]. PLs have therefore emerged as key players in the signal cascades that control many vital biological processes.

1.1.2. PLs outside the membrane

A significant fraction of the cellular PL pool resides outside of the membrane, particularly inside the nucleus. While some of this subpopulation may have structural roles as part of chromatin or the nuclear lamin [6], it is now evident that there is a PL signaling system distinct from that which occurs within the membrane bilayer [7]. PIs again are at the core of the known nuclear lipid signaling pathways [8], and while the nature of nuclear PLs remains enigmatic, it is now understood that PI and PIPs have important functions in the regulation of protein–chromatin interactions [9]. The close association of PLs with DNA [10] suggests that, in addition to their roles in cell structure and signal transduction, PLs play a role in driving gene expression and regulation.

1.1.3. PLs are a new class of hormone

Ernest Starling coined the term "hormone" in 1905, long before the isolation of the first nuclear receptor (NR) in 1958, to describe a substance that is able to travel throughout an organism serving as

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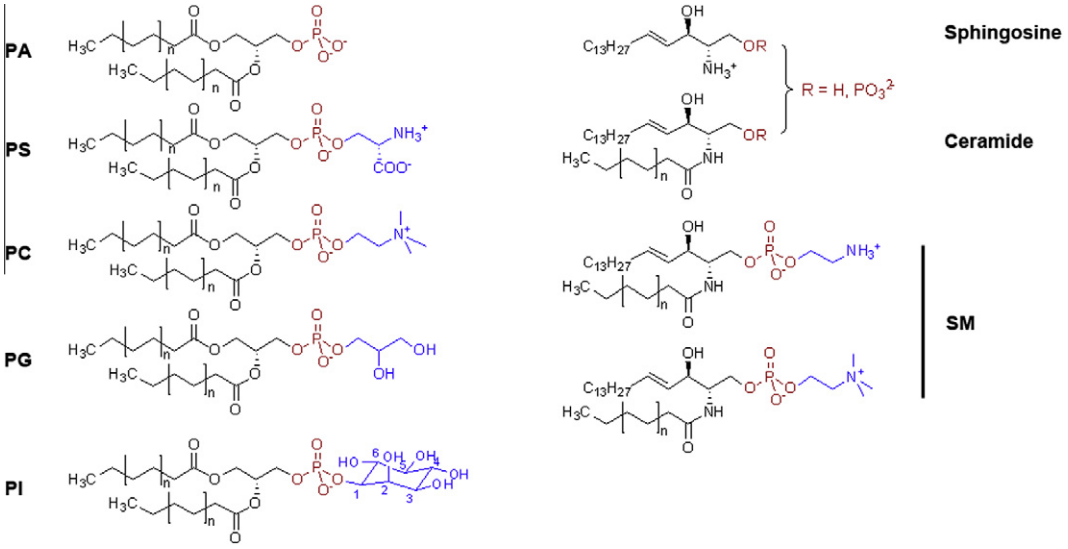

Fig. 1. Structures of major phospholipid species. PLs consist of a hydrophobic diacyl tail (black), a phosphate (red), and a polar head group (blue). PA: phosphatidic acid; PS: phosphatidylserine; PC: phosphatidylcholine; PG: phosphatidyl glycerol; PI: phosphatidylinositol; SM: sphingomyelin.

a chemical messenger to alter cell behavior. PLs have long been thought of as synthesis material for some hormones, but new evidence suggests they are transmitting their own unique signals to alter transcriptional patterns. The vast majority of evidence for direct PL-mediated transcription is among the NR family of transcription factors.

1.2. Nuclear receptors: lipid regulated transcription factors

1.2.1. Nuclear receptor structure and function

NRs are a family of ligand regulated transcription factors that are activated by a diverse group of lipophilic ligands including fatty acids, cholesterol derivatives, steroid hormones, vitamins, dietary components, and xenobiotics [11–14]. These ligands, primarily derived from lipids, act as messengers by transmitting chemical information that reflects the body's nutritional and endocrine states [15]. This allows for the coordination of growth, reproduction, and homeostasis, and allows the body to appropriately respond to events, such as eating a meal, exercise, or stress.

NRs share a highly conserved multi-domain architecture including a variable N-terminal domain, often referred to as the activation function 1 (AF-1), a DNA binding domain (DBD), a flexible linker region, and a ligand binding domain (LBD) that contains a ligand sensitive transcriptional switch, the AF-2 [12,13]. Ligand dependent NR activation is centered on the LBD, a helical bundle containing a lipophilic cavity that can accommodate ligands. The hydrophobic pockets within NRs typically vary in size and shape to match their cognate hormone [13,14]. A mobile ligand sensing helix, termed the activation function helix (AF-H), responds to a bound ligand by rotating and packing against the LBD. This repositioning completes the AF-2 surface, enabling interaction with coactivator proteins contained in chromatin modifying complexes that promote gene transcription [12]. In the absence of ligand, NRs preferentially interact with corepressor complexes which displace the "active AF-H" from the body of the protein resulting in transcriptional repression [12]. Similarly, NR antagonists alter AF-H positioning to either prevent coactivator binding or promote binding of corepressor proteins to inhibit transcription.

NRs ligands are invariably hydrophobic and freely diffuse across membranes to allow for long-range signal transmission. In this way, hormones affect diverse groups of gene programs involved in pathophysiology ranging from diabetes to cancer making NRs ideal targets for pharmacological intervention. As such, NR-targeting drugs have a myriad of uses ranging from cancer treatments, and contraceptives, to treating allergic reactions and metabolic disorders and represent a major industrial and academic investment in basic research and drug development [14,16,17].

1.2.2. PL-driven NR activation

To date, four NRs have been identified as PL-binding proteins: liver receptor homolog 1 (LRH-1) and steroidogenic factor 1 (SF-1), members of the NR5a class of steroidogenic factor-like NRs; peroxisome proliferator-activated receptor alpha (PPARα), a member of the NR1 thyroid hormone receptor-like family of receptors; and ultraspiracle (USP), the insect homolog of the retinoid X receptor. This review will focus on the compelling evidence for PLs role in regulating these receptors, as well as a family of PL transporters that stimulate NR transactivation.

2. Case studies

2.1. LRH-1

LRH-1 is a member of the NR5, or Ftz-f1, subfamily of NR's, and regulates the expression of genes involved in development, lipid and glucose homeostasis, steroidogenesis, and cell proliferation [18,19]. During the early stages of development, LRH-1 is responsible for maintaining levels of OCT-4, considered to be a master regulator of pluripotency [20]. Disruption of the LRH-1 gene in mice leads to the loss of Oct4 expression in the epiblast, causing lethality at embryonic day 6.5 [21]. Over expression of LRH-1 is sufficient to reprogram murine somatic cells to pluripotent cells without simultaneous overexpression of OCT-4. This makes LRH-1 the only known transcription factor that can replace OCT-4 in the cellular reprogramming identifying it as a new stem cell factor [22]. It is unknown what role LRH-1 plays in OCT4 regulation beyond development, however, the receptor was recently shown to regulate OCT4 expression in human cancer stem cells [23].

In adults, LRH-1 is expressed in liver, pancreas, intestine, brain and sex glands such as the ovaries and placenta [18,24]. In the liver, LRH-1 is a master regulator of lipid homeostasis [19] regulating bile acid and cholesterol flux through regulation of CYP7A1, which catalyzes the rate-limiting step in bile acid synthesis [18]. LRH-1 also regulates the transcription a number of other lipid, bile,