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Review

Phospholipids: "Greasing the wheels" of humoral immunity ☆

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ABSTRACT

Phospholipids are major structural components of all cellular membranes. In addition, certain phospholipids execute regulatory activities that affect cell behavior, function and fate in critically important physiological settings. The influence of phospholipids is especially obvious in the adaptive immune system, where these macromolecules mediate both intrinsic and extrinsic effects on B and T lymphocytes. This review article highlights the action of lysophospholipid sphingosine-1-phosphate as a lymphocyte chemoattractant, the function of phosphatidylinositol phosphates as signaling conduits in lymphocytes and the role of phospholipids as raw materials for membrane assembly and organelle biogenesis in activated B lymphocytes. Special emphasis is placed on the means by which these three processes push humoral immune responses forward. This article is part of a Special Issue entitled Phospholipids and Phospholipid Metabolism.

1. Introduction

In humoral immunity, the host is defended by antibodies that neutralize and eliminate extracellular microbes and microbial toxins. Antibodies are produced by B lymphocytes and are composed of covalently assembled immunoglobulin (Ig) heavy chain (H) and Ig light chain (L) proteins. Each B cell expresses a single type of Ig H chain and L chain and, therefore, produces antibody of single specificity. A highly diverse B cell repertoire provides an arsenal of antibodies specific for a wide array of molecules including proteins, polysaccharides and lipids, thereby affording protection against a variety of foreign agents [1].

There is a division of labor in humoral immunity as different B cell subsets manifest antibody responses to distinct types of antigens [2]. Follicular B cells, the largest B cell subpopulation, reside in the follicles of lymphoid tissue and are primarily responsible for antibody responses against protein antigens [3,4]. Successful responses to protein antigens require the assistance of helper T cells (T_H) and involve the development of germinal centers, specialized microenvironments within follicles [5]. Germinal center events allow for antibody isotype switching, generation of high-affinity antibodies and development of immunologic memory [6,7]. Thus, follicular B cells supply long-lasting, protective humoral immunity throughout the body against diverse types of pathogens and toxins. In contrast, marginal zone B cells [8] localize adjacent to the splenic marginal sinus and B-1 B cells [9] are enriched in the peritoneal cavity and mucosal tissues. These two smaller B cell subsets are predominant in the recognition of non-protein antigens like polysaccharides and mount rapid, mainly IgM antibody responses to such T cell-independent antigens. As such, marginal zone and B-1 B cells furnish a front-line humoral defense against bacterial pathogens [10].

In the simplest of terms, a successful humoral immune response requires that B cells be in the right place at the right time, become activated by a specific antigen, proliferate and differentiate into antibody-secreting cells. A myriad of molecular mechanisms orchestrate these processes including signal transduction cascades, gene expression programs and changes in cellular metabolism. In this article, the spotlight is on different types of phospholipids that play pivotal roles in B cell trafficking, activation and differentiation.

2. B cell trafficking: sphingosine-1-phosphate shows the way

Lysophospholipids are minor lipid components as compared to abundant membrane phospholipids like phosphatidylcholine (PtdCho),

Abbreviations: AP-1, activator protein-1; BLNK, B cell linker protein; BTK, Bruton's tyrosine kinase; CCT, choline cytidylyltransferase; CDP-choline, cytidine diphosphocholine; CEPT1, choline/ethanolamine phosphotransferase 1; Cer, ceramide; CK, choline kinase; CPT1, choline phosphotransferase 1; CRAC, Ca^{2+}-release activated entry channel; DAG, diacylglycerol; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; FA, fatty acid; FOXO, forkhead box subgroup O; FDC, follicular dendritic cell; H, heavy chain; T_H, helper T cell; Ig, immunoglobulin; $InsP_3$, inositol(1,4,5)-trisphosphate; IRE1, inositol requiring enzyme 1; ITAM, immunoreceptor tyrosine-based activation motif; KLF, Kruppel-like factor; LPS, lipopolysaccharide; MEK, mitogen-activated protein kinase/ERK kinase; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-kappa B; PH, pleckstrin homology; PLCγ2, phospholipase Cγ2; PKCβ, protein kinase Cβ; PtdCho, phosphatidylcholine; PtdEtn, phosphatidylethanolamine; PtdIns, phosphatidylinositol; $PtdIns(4,5)P_2$, PtdIns 4,5-bisphosphate; $PtdIns(3,4,5)P_3$, PtdIns 3,4,5-trisphosphate; PI-4K, PtdIns 4-kinase; PIP5K, PtdIns(4)P-5-kinase; PI3K, PtdIns 3-kinase; PTEN, phosphatase and tensin homolog deleted on chromosome ten; RASGRP, Ras guanyl nucleotide releasing protein; SM, sphingomyelin; S1P, sphingosine-1-phosphate; S1PR, S1P-receptor; Ser, serine; SH2, Src-homology 2 domain; SLP-65, SH2-containing leucocyte protein of 65 kDa; SHIP, SH2-containing inositol phosphatase; SPHK, sphingosine kinase; STIM1, stromal interaction molecule 1; TCR, T cell antigen receptor; Thr, threonine; TLR, Toll-like receptor; UPR, unfolded protein response; XBP1, X-box binding protein 1

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phosphatidylethanolamine (PtdEtn) and sphingomyelin (SM). Originally considered as nothing more than metabolic intermediates in the *de novo* biosynthesis of various phospholipids, lysophospholipids have been found to exert regulatory activity, including acting as extracellular signaling factors. One of the most important lysophospholipids is sphingosine-1-phosphate (S1P) which is generated exclusively via the phosphorylation of sphingosine, a central element of all sphingolipids (Fig. 1A) [11]. Ceramidases remove one fatty acid tail from ceramide (Cer), a sphingolipid, yielding the long-chain amino alcohol sphingosine [12]. Sphingosine kinases (SPHK1 and SPHK2) phosphorylate sphingosine, producing S1P [13]. S1P can be de-phosphorylated back to sphingosine by either S1P phosphatases [14,15] or lipid phosphate phosphatases [16,17] and then recycled for use in sphingolipid biosynthesis. Alternatively, S1P can be degraded by S1P lyase [18,19] into hexadecenal and phosphoethanolamine, a precursor for synthesis of PtdEtn. Hence, S1P is produced inside cells and serves as an intermediate in sphingolipid metabolism. However, S1P, an amphiphilic molecule, is also exported outside of cells by a mechanism likely involving ATP-binding cassette transporters and members of the spinster family of transporters [20–22]. Extracellular S1P engages five S1P receptors (S1PR1–S1PR5), all of which are cell surface heterotrimeric G protein-coupled receptors [23,24], and has been implicated in several biological processes including lymphocyte trafficking [25].

2.1. Lymphocytes on the move

Adaptive immunity, including humoral immune responses, relies upon the mobility of B and T lymphocytes. Newly made B and T cells must migrate from the bone marrow and thymus, respectively, to secondary lymphoid tissues including the spleen, lymph nodes and mucosal Peyer's patches. Lymphocytes enter these tissues from the blood by a complex mechanism involving selectins, chemokines and integrins that coordinate their transmigration across the endothelium [26]. Once inside a secondary lymphoid tissue, naïve B and T cells are in position to encounter foreign antigens. If, after several hours of duty in a given lymphoid tissue, these cells have not been activated by cognate antigen, they will exit the site and move into position in another secondary lymphoid organ. From the spleen, lymphocytes exit back into the blood, whereas from the lymph nodes and Peyer's patches, they exit into the lymph. Cells in lymph come back to the blood as lymph drains into the thoracic and right lymphatic ducts. This dynamic process allows the diverse specificities within the B and T cell repertoires to survey more than one anatomic site each day. However, during an infection, this process stops transiently for the involved lymphoid organ, allowing more time for potential antigen recognition by cognate B or T cells. When activated by an antigen, responding lymphocytes no longer quickly exit the secondary lymphoid tissue to patrol another site. Rather, activated lymphocytes remain for a longer period to proliferate and differentiate into effector cells that will eventually leave the lymphoid tissue to combat the infection at peripheral sites. As all of these events unfold, S1P plays a key role in directing lymphocyte movement.

2.2. S1P, S1PR1 and lymphocyte movement

S1P signals lymphocytes to exit lymphoid tissues and influences lymphocyte positioning within lymphoid tissues. These processes require two essential ingredients: S1P receptors with nanomolar

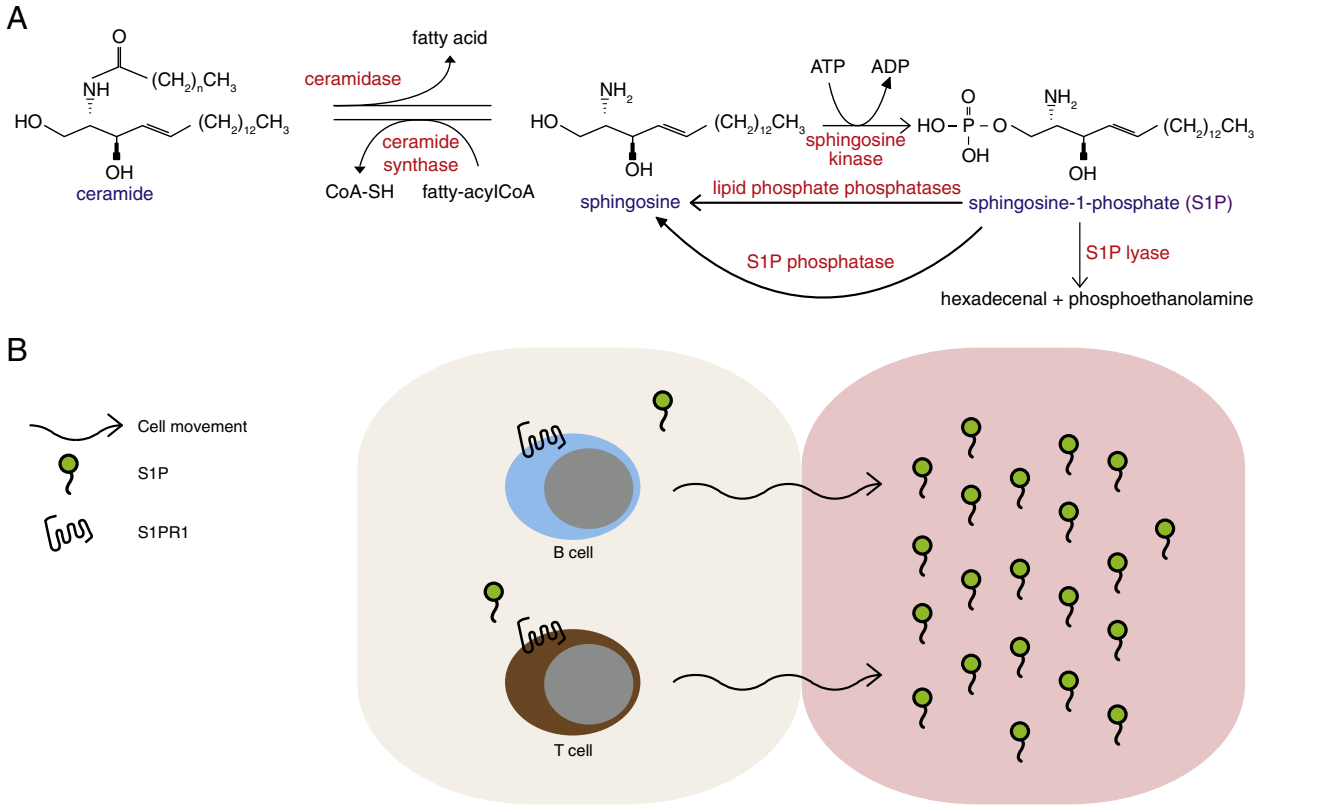

Fig. 1. The lysophospholipid sphingosine-1-phosphate (S1P) is a lymphocyte chemoattractant. A. Phosphorylation of sphingosine by the sphingosine kinase produces S1P, which can be de-phosphorylated by either lipid phosphate phosphatases or a S1P phosphatase. S1P can also be metabolized by S1P lyase, yielding hexadecenal and phosphoethanolamine. Sphingosine is derived from ceramide and used in ceramide synthesis by the actions of ceramidase and ceramide synthase, respectively. B. B and T lymphocytes express S1P receptors (S1PR), most prominently the Gαi-coupled S1PR1. In S1P-low environments, such as the bone marrow, thymus and secondary lymphoid tissues, S1PR1 is expressed on the cell surface and lymphocytes are attracted to increasing S1P concentrations in the blood and lymph.