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Review

Sphingolipid homeostasis in the web of metabolic routes ☆

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ABSTRACT

Sphingolipids play a key role in cells as structural components of membrane lipid bilayers and signaling molecules implicated in important physiological and pathological processes. Their metabolism is tightly regulated. Mechanisms controlling sphingolipid metabolism are far from being completely understood. However, they already reveal the integration of sphingolipids in the whole metabolic network as signaling devices that coordinate different metabolic pathways. A picture of sphingolipids integrated into metabolic networks might help to understand sphingolipid homeostasis. This review describes recent advances in the regulation of *de novo* sphingolipid synthesis with a focus on the bridges that exist with other metabolic pathways and the importance of this crosstalk in the control of sphingolipid homeostasis. This article is part of a Special Issue entitled New Frontiers in Sphingolipid Biology.

1. Introduction

Sphingolipids (SLs) are essential structural components of membranes and critical signaling molecules whose levels must be tightly regulated. Most sphingolipids contain a ceramide *i.e.* a long chain sphingoid base attached to a fatty acid through an amide linkage. Ceramides are the simplest sphingolipids and the precursor onto which different head groups can be added to form either phospho- or glycosphingolipids [1].

Regulation of SL homeostasis is of fundamental importance for cells and, to a larger extent, for multicellular organisms. Indeed, many biosynthetic intermediates, in addition to the SL end products, are bioactive molecules whose accumulation or absence can severely influence cell functions [1–3]. As a consequence, several mechanisms contribute to the control of enzymes at different steps of SL synthesis and breakdown. Recently, an interesting review extensively summarized these mechanisms [4]. Some of these mechanisms operate by the sensing of non-sphingolipid metabolites that are functionally or metabolically coupled to SL biosynthesis [4]. Indeed, SL synthesis is strongly influenced by substrate availability and therefore coupled to other metabolic routes. Coordination of metabolic routes is particularly observable when cells undergo differentiation, for example, a shift between stationary to proliferative phase in yeast [5], transformation into cancer cells in mammals [6] or during development. This coupling and its importance in the control of SL balance is increasingly highlighted in recent studies. For instance, during the heat stress response Chen and coworkers describe concomitant changes between SL concentrations and the activity of all enzymes participating in SL metabolism [7].

In this review, we provide an overview of the regulation of SL homeostasis. We focus particularly on bridges that exist between the *de novo* SL synthesis pathway and other metabolic routes, and how they are coupled.

2. Sphingolipid metabolism in eucaryotes: an overview

2.1. De novo sphingolipid synthesis

The SL biosynthesis pathway shows elements of conservation in all eucaryotes. A complete description of the SL pathways in different organisms is not the scope of this review but the reader can find a detailed description in recent references [1,8–11]. An overview of the basic pathway is shown in Fig. 1. *De novo* SL synthesis begins in the endoplasmic reticulum (ER) with the condensation of serine and palmitoyl CoA into 3-ketodihydrosphingosine by serine palmitoyltransferase (SPT). This product is reduced to generate sphinganine, the precursor of long-chain bases (LCBs). LCBs vary in chain length, degree of unsaturation and hydroxylation. Combinations of these three parameters define the specific species of LCBs for each organism [12]. At the ER, LCBs can be phosphorylated by a kinase or condensed by a ceramide synthase with fatty acyl-CoA, giving dihydroceramides. The number of C atoms of the amide-linked fatty acid usually ranges from 14 to 26 and can extend to 36 carbons (Table 2). The very long chain fatty acids (VLCFA) are produced by specific enzymatic complexes called

Abbreviations: CPE, Ceramidephosphoethanolamine; DG, Diacylglycerol; ER, Endoplasmic reticulum; EtnP, Phosphoethanolamine; FA, Fatty acid; GPL, Glycerophospholipid; LCB, Long chain base; LCB-P, Long chain base phosphate; LCFA, Long chain fatty acid; LD, Lipid droplet; PA, Phosphatidic acid; PC, Phosphatidylcholine; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; SL, Sphingolipid; SM, Sphingomyelin; SPL, Sphingosine-1-phosphate lyase; SPT, Serine palmitoyltransferase; TG, Triacyglycerol; VLCFA, Very long chain fatty acids

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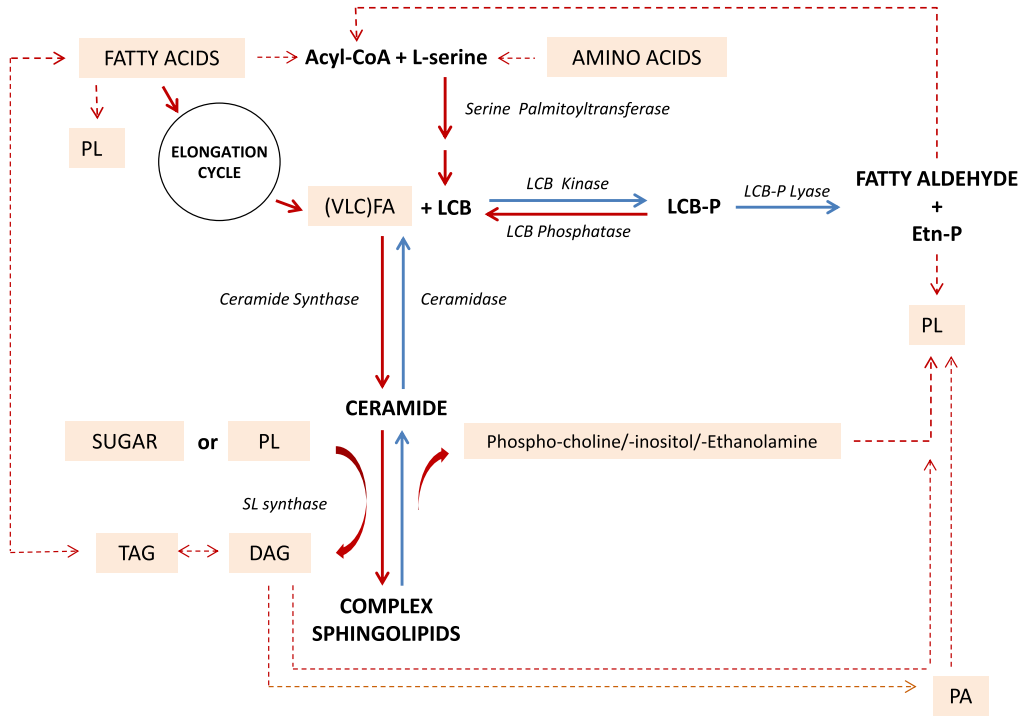

Fig. 1. Connection between *de novo sphingolipid* pathway and related metabolites. Several interconnected pathways link SL metabolism to other metabolisms. Main entries and exits of *de novo* pathway are shown. SL metabolites are highlighted in black. Red and blue arrows indicate the anabolic and catabolic SL pathways respectively. Dotted lines represent the connections with non-sphingolipid metabolites.

elongases. In many species the dihydroceramide can be desaturated to form ceramide. The ceramides can then be modified in the ER to produce ceramide phosphoethanolamine or galactosylceramides, or travel to the Golgi through vesicular and non-vesicular transport routes. The mode of transport seems to determine the subsequent fate of the ceramide; conversion to glucosylceramide or sphingomyelin [13]. Once in the Golgi, diverse head groups are attached to the C-1 hydroxyl group of the ceramide backbone. The head group donor can be a glycerophospholipid (GPL) or nucleotide sugars to generate either phosphosphingolipids, with simultaneous release of diacylglycerol (DG), or glycosylsphingolipids with release of a nucleotide. The initial sugar of glycosphingolipids, usually glucose, can be extended to more complex glycan structures. Finally, complex SLs travel through the secretory pathway to the plasma membrane, endosomes and lysosomal/vacuole system where their concentration is sensed and regulated.

2.2. Turnover and breakdown

Many reactions of sphingolipid metabolism can be reversed allowing for the rapid interconversion of different metabolic intermediates (Fig. 1). Nonetheless, some steps are irreversible: the initial step catalyzed by SPT and the degradation of long chain base phosphates (LCB-P) by an ER-localized lyase to acyl aldehydes and phosphoethanolamine (EtnP). Deficiencies in both steps have severe consequences in SL metabolism [14]. Apart from these two reactions, there are several possible interconversions between SLs along their metabolic route. For instance, ceramidases regenerate LCBs from ceramides but they can also make ceramides through acylation of LCBs when ceramide synthase activity is compromised [15–17]. The activity of glycohydrolases or sphingomyelinases produces ceramides from complex SLs that can be recycled again into the sphingolipid pathway [18]. As in the anabolic pathway, enzymes responsible for SL turnover have an organelle-specific distribution in cells. For instance, in mammals, members of ceramidase and sphingomyelinase families localize in different cell compartments, such as mitochondria, ER, Golgi, lysosome/vacuole and plasma membrane [19]. In *Saccharomyces cerevisiae*, Isc1p, which removes inositol-containing head groups, changes its localization from ER to mitochondria depending on yeast growth phase [20]. Localization is thought to allow the production of local pools of bioactive SLs, such as ceramides, LCBs and their phospho-derivatives. Several interesting reviews highlight the importance of these degradative pathways in the production of bioactive lipids [18,21]. Sphingolipid turnover, named the salvage route, is also used to feed the sphingolipid synthesis pathway. In mammals, the salvage pathway can be responsible for 10% to 90% of sphingolipid synthesis [22]. In *Leishmania* parasites, it is essential to capture host SLs for infection [23,24]. Moreover, also in *Leishmania* this route can be used to compensate insufficiencies in SL biosynthesis. Similarly, in neurons deficient in sphingosine-1 phosphate lyase, complex SL production is mainly performed using products of the salvage pathway at the expense of *de novo* synthesis [25]. How cells coordinate *de novo* and salvage pathway to generate the proper amounts of bioactive or structural SLs is an interesting field of research. The complexity of the sphingolipidome might differentiate between these two functions. Growing evidence supports the importance of substrate specificity of enzymes belonging to the degradation pathway in production of bioactive SLs. Recent observations in *S. cerevisiae* support the role of a specific ceramide species generated by Isc1p (yeast ceramidase) in the resistance to hydroxyurea [26]. In mammals, bioactive sphingosine is mainly produced by ceramidase activity [21] and in plants, the alkaline ceramidase also presents a defined substrate selectivity [17]. Most of the enzymes of SL metabolism show specific subcellular localization. Therefore, spatial organization of the salvage pathway could be another discriminatory mechanism to differentiate between fates of products and to distinguish between structural and bioactive SLs. Interestingly, several enzymes of signaling pathways involved in SL metabolism are regulated by LCBs or ceramides [27,28]. This raises intriguing questions about the relative importance of the *de novo* and salvage pathways in the creation of bioactive sphingolipids to control their own synthesis. Indeed, the turnover of SLs in multicellular eucaryotes is vital for