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Making sense of the yeast sphingolipid pathway

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Abstract

Sphingolipids (SL) and their metabolites play key roles both as structural components of membranes and as signalling molecules. Many of the key enzymes and regulators of SL metabolism were discovered using the yeast Saccharomyces cerevisiae, and based on the high degree of conservation, a number of mammalian homologs were identified. Although yeast continues to be an important tool for SL research, the complexity of SL structure and nomenclature often hampers the ability of new researchers to grasp the subtleties of yeast SL biology and to discover modulators of this intricate pathway. Moreover, the emergence of lipidomics by mass spectrometry has enabled rapid identification of SL species in yeast and rendered analysis of SL composition under various physiological and pathophysiological conditions readily amenable. However, the complex nomenclature of the identified species renders much of the data inaccessible to non-specialists. In this review, we focus on parsing both the classical SL nomenclature and the nomenclature normally used during mass spectrometry analysis, which should facilitate understanding yeast SL data and might shed light on biological processes in which SLs are involved. Finally, we discuss a number of putative roles of various yeast SL species.

Highlights:

1. The Yeast (Saccharomyces cerevisiae) sphingolipid metabolic pathway is introduced and the levels and roles of dihydro and phyto forms are highlighted.
2. Yeast sphingolipid nomenclature is clarified and compared to other standard nomenclatures.
3. Levels of various sphingolipid species in the branches of the metabolic pathways are discussed.
4. Distinct roles for hydroxylation, acyl chain length and unsaturation are discussed based on the biophysical properties of the lipids.
Keywords: Yeast, *Saccharomyces cerevisiae*, sphingolipids, nomenclature, classification, phytosphingolipids, dihydrosphingolipids, shotgun lipidomics.

Abbreviations
SL, sphingolipids; Cer, ceramide; CerS, Cer synthase; E-MAPs, epistatic miniarray profiles; 3KDS, 3-ketodihydrosphingosine; ER, endoplasmic reticulum; SPT, serine palmitoyltransferase; LCB, long chain base; DHS, dihydrosphingosine (sphinganine); PHS, phytosphingosine (4-OH sphinganine); LCB-P, LCB-phosphates; IPC, inositol phosphoryl Cer; MIPC, mannosyl inositol phosphoryl Cer; M(IP)2C, mannosyl diinositol phosphoryl Cer; FB1, Fumonisin B1; AbA, Aurobasidin-A; Rf, retention factor; TLC, thin layer chromatography.
Introduction

Sphingolipids (SLs) and their metabolites play vital roles in cell physiology both as structural elements of membranes and as signalling molecules [1-3]. The functional diversity of SLs is due to structural modifications, such as phosphorylation, hydroxylation and desaturation, each of which can dramatically change their biochemical and biophysical properties. Interconversion of SL species results in rapid changes in membrane properties including curvature, thickness, and rigidity which can each significantly impact cellular properties, such as permeability, vesicle formation, fission and fusion.

The yeast, *Saccharomyces cerevisiae*, is one of the most useful eukaryotic model organisms for studying SL biology because of its experimental tractability and due to the conservation of a large number of genes and pathways between yeast and mammals, including humans [4,5]. Indeed many of the enzymes of SL metabolism, and a number of regulators of this pathway, were first discovered in yeast and later identified in mammals based on their homology to yeast proteins. One of the best examples is the discovery of the ceramide synthases (CerS), Lag1p and Lac1p, in yeast [6-9], which led to the identification of the six mammalian CerS [10-13]. In terms of regulators, Orm1p/2p were discovered in yeast [6,10] to regulate the first enzyme in the pathway of SL biosynthesis, serine palmitoyl transferase (SPT). Similar studies in mammals confirmed that the ORM family also regulates SPT and suggests that this is why mutations in ORMs affect the propensity to be affected by asthma [14,15]. Thus, study of the regulation of SL metabolism in yeast has led to discoveries that might impact human health.

Despite the many advantages of working with the yeast SL pathway, the nomenclature of yeast SLs is cumbersome and often impedes dialogue with the mammalian SL community. In the current review, we provide a platform that should facilitate understanding of yeast SL nomenclature, and attempt to systematise this nomenclature with the somewhat intricate (although accurate) nomenclature suggested by the LipidMaps consortium.
(www.lipidmaps.org) [16,17]. This is particularly important since shotgun lipidomics by mass spectrometry [18,19] is being used by more and more laboratories, generating huge data sets comprising large numbers of SL species in any one experiment. Moreover, it is relatively common for different laboratories to use different nomenclatures, making comparison of large data sets problematic. In our opinion, the best way to permit reproducible handling of lipidomics data and metabolomics data in general is to use unique identifiers for each metabolite. This path has already been initiated in the systematic lipidomics approach [20,21] where each lipid species was identified in the ChEBI database (https://www.ebi.ac.uk/chebi/) by a unique identifier.

Another initiative, SwissLipid (www.swisslipid.org), is a good example for how data can be merged from different databases although it is still lacking yeast SLs. In the future, such approaches will permit bioinformatic handling of lipidomic and metabolomics data without ambiguity and increased possibilities to find synonyms and interrelationships between species. Here, we nevertheless document the various approaches to SL nomenclature in yeast in order to increase its understanding, as well as to provide tools to facilitate navigation of the pathway.

Finally, we suggest a functional classification of the yeast SL pathway based on three characteristics that determine the biophysical properties of specific SLs, namely hydroxylation, saturation and acyl chain length. Our goal is to establish a framework that will simplify cross-talk between the yeast and mammalian SL communities and attract more scientists to the yeast SL field.

The yeast SL biosynthetic pathway

As in mammals [22,23], yeast SL biosynthesis (Fig. 1) begins in the endoplasmic reticulum (ER) with the condensation of serine and palmitoyl CoA to form 3-ketodihydrosphingosine (3-KDS), by serine palmitoyltransferase (SPT), a complex consisting of two subunits, Lcb1p [24,25] and
Lcb2p [24,26]. SPT is part of a larger complex, the SPOTS complex (serine palmitoyltransferase, Qrm1p/2p, Tsc3p, and Sac1p) [10,27] which regulates the rate of 3-KDS production, and as a result, the levels of sphingoid long chain bases (LCBs). LCBs are not only intermediates in SL metabolism, but also act as potent biologically-active molecules, necessitating strict regulation of their levels. 3-KDS is subsequently reduced by Tsc10p [28,29] to form sphinganine (also called dihydrosphingosine, DHS). LCBs can also be phosphorylated by two kinases, Lcb4p and Lcb5p, to form LCB-phosphates (LCB-P), which can be dephosphorylated by Lcb3p, Ysr3p, Lpp1p or Dpp1p, and subsequently irreversibly degraded by the LCB-P lyase, Dpl1p [30] to form acyl aldehydes and phosphoethanolamine. The latter step connects the SL pathway with glycerophospholipid metabolism through the Kennedy pathway [31,32].

Subsequent to LCB formation, the SL pathway divides into two distinct arms, the dihydro (non-hydroxylated) and the phyto (hydroxylated) branches (Fig. 1). The critical enzyme regulating levels of these two branches is the C4-hydroxylase, Sur2 [33]. DHS can be N-acylated by the CerS, Lag1p [7] and Lac1p [34,35] to form dihydroCer (known as ‘Cer-A’ based on the classical yeast SL nomenclature, see below) [31]. In Saccharomyces cerevisiae Lag1p and Lac1p require an additional protein, Lip1p [36] whose precise function is unknown. Alternatively, DHS is hydroxylated by Sur2 at the C4 position (Fig. 1) to form 4-OH sphinganine (also called phytosphingosine, PHS), which can also be N-acylated by Lag1p and Lac1p, generating phytoCer (Cer-B). Hence, phytoCer might be formed by two alternative pathways, either by formation of PHS and N-acylation to phytoCer, or by hydroxylation of dihydroCer by Sur2p. The yeast CerSs are localized to the ER, with a concentration in the peri-nuclear parts [36].

DihydroCers and phytoCers can be degraded by two ceramidases, Ydc1p, which preferentially hydrolyses dihydroCers versus phytoCers, and Ypc1p which preferentially
hydrolyses phytoCer [37,38]. Ypc1p and Ydc1p are both localized to the ER [39]. Dihydro- and phytoCers can also be hydroxylated at the C2 position of the acyl chain (often referred to as the \( \alpha \) position) by Scs7p [33] to generate \( \alpha \)-hydroxyl-dihydroCer (Cer-B') or \( \alpha \)-hydroxyl-phytoCer (Cer-C). In contrast to the Sur2 hydroxylase, the Scs7 hydroxylase contains a cytochrome b5-like domain [40] indicating that the mechanisms of electron transfer for catalysis are substantially different. Cer-C can be further hydroxylated on the acyl chain at an undefined position to form \( \alpha \)-x-hydroxyl-phytoCer (Cer-D); Ccc2p is somehow involved in this latter step [41] although it might not be directly involved in catalysis but rather related to an aspect of copper transport [41]. The identity of the hydroxylase itself is unknown.

Accordingly, yeast contains five ceramide species, dihydroCer (Cer-A), \( \alpha \)-hydroxyl-dihydroCer (Cer-B'), phytoCer (Cer-B), \( \alpha \)-hydroxyl-phytoCer (Cer-C) and \( \alpha \)-x-hydroxyl-phytoCer (Cer-D). These ceramide species form the backbones of complex SLs (Fig. 1). Thus, inositol phosphoryl Cers (IPCs) are formed upon addition of inositol phosphate by Aur1p [42,43] and Kei1p [4]; the cellular localization of this reaction is likely to be the Golgi apparatus [44] although Aur1 is found mostly in the ER in steady state so some conversion may also occur at the ER [39]. IPCs are then further metabolized to mannosyl IPCs (MIPCs) by the catalytic subunits, Sur1p and/or Csh1p [20] and Csg2p, a supposed regulatory subunit [41,45]. Mannosyl di-inositol phosphoryl ceramides (M(IP)\(_2\)Cs) are formed by Ipt1p [46].

It has been suggested that a significant proportion of Cers used in SL biosynthesis are generated from the turnover of complex SLs, catalysed by Isc1p [47]. Isc1p is localized in the ER in the early logarithmic growth phase, but after diauxic shift, relocalizes to mitochondria [48], where its activity might be enhanced by the mitochondrial lipids, phosphatidylglycerol and cardiolipin [49]. \( \alpha \)-OH-phytoCer (Cer-C) levels are enriched in mitochondria and loss of
Isc1p leads to a drastic reduction in the post-diauxic shift levels of \( \alpha \)-OH-phytoCer (Cer-C) and impaired mitochondrial function [50].

There are a number of similarities, but also some important differences, between SL metabolism in yeast and in mammals. While the steps leading to dihydroCer are similar, no homologs of Sur2 are found in mammals and thus the phytoCer branch is only found at very low levels [51], and when found, is formed via the action of DES2 (by hydroxylating dihydroCer at the C4 positon) [52,53]. Mammalian Cers, similar to yeast, can be hydroxylated on both the long chain base and on the fatty acid. \( \alpha \)-hydroxyl-dihydroCer (known as 2’-OH dihydroCer in mammals) is formed via a different route in mammals than in yeast with hydroxylation occurring prior to formation of dihydroCer by FA2H [54,55]. The hydrophilic head groups of mammalian SLs are completely different to those in yeast, leading to formation of sphingomyelin and glycosphingolipids, rather than IPCs and MIPCs, but their site of formation and their trafficking and largely similar [56]. In both mammals and yeast, an additional layer of complexity results from modification of the LCBs and of ceramide; thus, the LCB can consist of 18 or 20 carbons, the acyl chain, although most commonly C26 in yeast, can be of varying chain length, and the hydroxylation and saturation state of the two chains can also be altered.

The SL pathway can be interrogated by use of inhibitors of specific enzymes (Fig. 1), many of which also inhibit SL synthesis in mammals [57]. Myriocin inhibits SPT [58], CerS are inhibited by Fumonisin B1 (FB1) [59] or Australifungin [60] (although FB1 can be removed from yeast by active transport limiting its use \textit{in vivo}), and Aureobasidin A (AbA) [42,43,61,62] inhibits IPC formation.

**Yeast SLs nomenclature**

The classical nomenclature of yeast SLs was originally established based on their retention factor (Rf) on thin layer chromatography (TLC). For instance, in a particular TLC solvent
system, Cer-A has a higher Rf than Cer-B, which has a higher Rf that Cer-C, and so forth [33]. While such nomenclature was useful when TLC was the main technique for separating and identifying yeast SLs and is still useful due to its brevity, it might not be optimal in the current climate in which mass spectrometry is the preferred method of SL separation. Nevertheless, the classical yeast nomenclature remains in common use to this day, and therefore necessitates some explanation. Cer-As are dihydroCers (DHCer) which have no hydroxylation either on the LCB or on the acyl chain (Fig. 1). Cer-B are phytoCers (PHCer) with a hydroxyl group on the C4 position of the LCB; when Cers are hydroxylated only on the α-position of the acyl chain, they are known as Cer-B’ (α-hydroxylated-dihydroCers). Cer-Cs are α-hydroxylated-phytoCers, and when further hydroxylated, are known as Cer-D [33]. The nomenclature of complex SLs is based on their Cer structure, as documented in Table 1, which shows the most common SLs and also provides information on their short name, their yeast acronym, their LipidMaps ID, LipidMaps common name, LipidMaps systematic name, formula and mass. LipidMaps was a consortium created to identify and quantitate all known lipid species, and based upon this identification, systematic names were given to each lipid species, not only in mammals but also in yeast. For a more precise identifier taking into account various acyl chain length see the ChEBI database. However, as is often the case with systematic or chemical nomenclature, the systematic names are frequently unwieldy and not suitable for day-to-day use, although the LipidMaps common name are very useful (see below).

The advent of shotgun mass spectrometry of SLs by simple infusion and high mass accuracy resolution marked a major breakthrough as it enabled in-depth analysis of overall changes and identification of many individual SL species in one experimental run [19]. However, as the technology became more and more common, a plethora of names emerged, with each group using its own favorite nomenclature, making it difficult to compare datasets obtained from different laboratories (Fig. 2). It should be stressed that these different
nomenclatures reflect, to some extent, the limitations of mass spectrometry setups that use precursor scan only, compared to mass spectrometry that use fragmentation as part of the identification [63]. For instance, mass spectrometry without fragmentation can detect the total chain length of SLs but cannot distinguish between the contribution of the LCB and the acyl chain, whereas fragmentation can resolve these contributions, but usually does not determine the position of double bonds (Fig. 2a). Thus, shotgun lipidomics without fragmentation uses a nomenclature that echoes its limitations in definitively determining structural parameters (Fig. 2c). By way of example, a C44:1 ceramide detected by shotgun lipidomics without fragmentation could contain a C26:1 acyl chain and a C18:0 LCB, or alternatively, a C26:0 acyl chain and a C18:1 LCB. To attempt to overcome these inherent limitations, three laboratories have each suggested a nomenclature system (Fig. 2c). The first [19] is very similar to the common name, inasmuch as the lipid (i.e. IPC, Fig. 2b) is first named, followed by the LCB (i.e. 18:0) and then the fatty acid (i.e. 26:0), along with the hydroxylation state; note that the length of the LCB and acyl chain in this case was identified by an additional second ionization step and lipid fragmentation. The second nomenclature [21,64-67] uses the classical yeast nomenclature (i.e. IPC-B) based on TLC separation, to indicate the hydroxylation state of the lipid followed by the d/t 44:0 designation, where d/t indicates that the lipid is either α-OH-dihydro (d indicates dihydroxyl) or phyto (t indicates trihydroxyl). The third system [6] uses a similar nomenclature but focuses on designation of the number of OH groups, i.e. 3 OH groups at undefined positions of the lipid. In fact the third system uses the same principle as the first system but encompasses a lower level of detail (lipid species instead of molecular subspecies). Hence with fragmentation information the nomenclature would be: IPC 18:0;2/26:0;1, while it would be only IPC 44:0;3, when this information is unavailable. Moreover, these notations can be combined to IPC 44:0;3 (18:0;2/26:0;1).

Each of these different nomenclatures has inherent advantages and limitations. The LipidMaps
name (rather than the LipidMaps systematic name) might be the best compromise, in which inositol phosphoryl \( \alpha \)-OH-dihydroCer and inositol phosphoryl phytoCer are designated PI-Cer(d18:0/26:0(2OH) and PI-Cer(t18:0/26:0), respectively (Fig. 2b and Table 1). As an alternative, the first system described above is highly useful as it is less complicated to write and fully applicable to other lipids (for example PC 17:0;0/17:0;0).

**Abundance of yeast SL species and flux through the SL metabolic pathway**

Despite the tremendous advances made by shotgun lipidomics [19], the lack of appropriate internal standards specific for yeast complex SLs has hindered precise quantification of the complex SL species, and data are better presented in a comparative manner, within species, rather than as absolute values. Even the best internal standards [19] lack hydroxylation, which could potentially have consequences on the detection by mass spectrometry, in particular, concerning loss of water. Based on such analyses and estimations and considering these limitations, PhytoSLs comprise >90% of yeast SLs, and consist mainly of two species, t18:0/26:0(2OH) and t20:0/26:0(2OH). Cers are thought to comprise <1% of the sphingolipidome while IPCs are the most abundant SL species, comprising ~65% of total SLs (Fig. 3), and MIPCs and M(IP)\(_2\)Cs are ~15% and ~20%, respectively [19,67]. These amounts of complex SLs are consistent with determinations by long-term 32P labelling and TLC [8]. A variety of commonly used growth conditions have dramatic effects on the yeast lipidome (including SLs) [68].

The relatively low abundance (<1%) of Cer is likely to be due to its toxicity; for instance, growing cells in AbA leads to Cer accumulation and death [8,69]. This may explain why \( \Delta lag1\Delta lac1 \) and \( \Delta lip1 \) strains, that do not form ceramide, are resistant to AbA [36]. Ceramide toxicity strongly depends on the chain length because substitution of yeast CerS with an heterologous CerS from cotton leads to AbA resistance despite an enormous accumulation of
Cer (t18:0/18:0) [1].

Analysis of steady state levels of SLs by mass spectrometry cannot, by definition, address issues related to flux, and for this, alternative methods are needed, such as metabolic labelling with radioactive (i.e. $^3$H-serine, $^3$H-DHS, $^3$H-myoinositol, $^{14}$C-palmitate or $^{32}$P-phosphate) precursors. NBD-DHS, a fluorescent LCB, is also commercially-available, but is not taken-up by yeast (unpublished data); in contrast C6-NBD-Cer can be used for metabolic labelling [4] although ideally, the yeast lipids, NBD-dihydro- or NBD-phytoCer should be used; it should be emphasized that similar to the lack of internal standards for mass spectrometry for yeast SLs, radioactive, fluorescent or stable isotope derivatives of yeast SLs are often not commercially available. Combining shotgun lipidomics with the use of SL analogs takes advantage of the best of both worlds; thus, C17-dihydrosphingosine (C17-DHS) or C17-phytosphingosine (C17-PHS) can be fed to cells and their incorporation into Cer and more complex SLs monitored by mass spectrometry enabling pulse-chase analyses and flux measurements [6]. However, metabolism of C17-DHS is less efficient than C18-DHS and C17-DHS is also less effective to sustain growth of yeast cells that cannot make LCBs (unpublished observations). Using C17-DHS labeling, ∆orm1∆orm2 strains [10] display major differences in steady state SL levels but no differences in the rate of synthesis [6]. A variety of other tools to analyze metabolic flux through the yeast SL pathway are slowly becoming available [14].

Physiological functions of hydroxylation, chain length and saturation of SLs

The development of techniques for rapidly measuring the structural heterogeneity of SLs has resulted in a number of attempts to understand the precise roles of specific SL species in yeast. However, very few studies have shed light on this area, and this illustrates that the technology to measure SL species is more advanced than the translation of this quantitative data into tangible results demonstrating the function of specific SL species in yeast. Specifically the main
reasons for heterogeneity are:

*Hydroxylation*: PhytoCers comprise >90% of the total yeast sphingolipidome. This raises the issue of the function of the less common SLs, i.e. the dihydroSLs. DihydroSLs are not required for yeast viability because the *lcb1Δ* mutant can be grown by feeding PHS (unpublished results). One possible role for dihydroSLs might be regulation of yeast mating [16] in which a reduction in SL flux (in the temperature sensitive *lcb1ts* or *Δlag1Δlac1*) causes defects in mating, although *Δsur2* strains do not show such a phenotype [18]. The abundance of phytoCers implies that they are of major structural and presumably regulatory function, which is supported by the vital place of Sur2p in the biosynthetic pathway and the preferential specificity of some enzymes towards phytoCer rather than dihydroCer (i.e. Ypc1 and Ydc); Csh1/Csg2 has a preference towards dihydro-IPCs while Csg1/Csg2 use both phyto- and dihydro-SLs [20]. Likewise, the three *Arabidopsis thaliana* CerS isoforms display differential specificity towards the LCB [22], which might mimic the situation in yeast. Together, it is apparent that yeast make a great effort to maintain the correct balance between phyto- and dihydro-SLs although, except for one or two examples, the precise biological rationale remains to be discovered. One example of the obvious functional differences between species concerns toxicity [24], in which growth arrest upon repression of *AUR1* was enhanced by deletion of *SCS7* (the hydroxylase of the acyl chain) and attenuated by deletion of *SUR2* (the hydroxylase of the LCB), such that Cers containing α-hydroxylated fatty acids were less toxic than those containing non-hydroxylated fatty acids, and ceramides containing a PHS backbone were more toxic than those containing a DHS backbone [24]. PhytoSLs are also involved in regulating the diffusion barrier in the ER between the mother and the bud [27]. The role of SL hydroxylation in biological functions involving sterols has been elegantly shown by genetic analyses [28]. For example, combination of an *erg2* mutation with a *scs7* mutation, but not a *sur2* mutation showed synthetic lethality in presence of low concentrations of caffeine or rapamycin, due to a
decreased TOR (Target Of Rapamycin) complex 2 function in the double mutant. In contrast, combination of the \textit{erg4} mutation with the \textit{sur2} mutation, but not the \textit{scs7} mutation caused synthetic lethality in the presence of sorbic or benzoic acids due to loss of activity of the weak organic anion exporter, Pdr12p, despite it being properly localized to the plasma membrane. Thus, the hydroxylation of SLs plays important roles, in combination with sterols, in a diverse set of functions.

\textit{Chain length}: The chain length of SLs depends on both the length of the LCB and the acyl chain. Unlike mammals, which contain a wide variety of chain lengths for both moieties [51], yeast contain a more limited range of chain lengths. However, this does not mean that the chain lengths of yeast SLs are of no importance. For instance, upon heat shock, SL levels increase in yeast [70-72], which might be related to a possible role of SLs in regulating membrane rigidity. Under these conditions C20-phytoCer levels increase more than C18-phytoCers [71], as also occurs when yeast enter the stationary phase [73] or upon acid treatment [66]. Such changes might be related to biophysical differences between the slightly longer phytosphingosine backbones (i.e. C20) and the shorter ones (i.e. C18), which could impact membrane rigidity. Likewise, small quantities of C24, C22, C20, C18 and C16 acyl chains, in addition to the much more common C26, are also found. When CerS are absent the residual ceramides are most likely formed by reversal of the ceramidases and the main species have C16 and C18 acyl chains [74]. It was shown that vesicles of the secretory pathway are specifically enriched with the low-abundance C46 and C42 SL species compared to total cell extracts [75]. Study of the role of the LCB and acyl chain length in yeast is a fruitful area for further research.

\textit{Desaturation}: The saturation state of SLs significantly impacts membrane properties, although few studies have systematically examined changes in saturation. One of the few studies in \textit{Saccharomyces cerevisiae} demonstrated that 18:1 phytoCer levels increased in an Isc1-dependent manner upon hydroxyurea treatment [76], which could be rescued by oleic
acid (18:1).

Concluding remarks
In this review, we have emphasized the importance of the yeast *Saccharomyces cerevisiae* as a model to study SL biology in eukaryotes. Yeast can be a rich source for discovering conserved enzymes, regulators, modifiers and biological pathways. To facilitate such research, the classical and mass spectrometry nomenclature that is used by the yeast SL community has been explained and the pathway, nomenclature and abundance of different lipid species as well as potential roles for different subspecies based on their biophysical properties, discussed. We hope that this review will facilitate navigation through the murky waters of the yeast SL pathway.

Conflict of interest
The authors declare no conflict of interest.

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Figure legends
*Fig. 1. Schematic of the yeast SL pathway.*
Lipid species (including the classical yeast nomenclatures) are in black, the enzymes are in blue, regulators in brown and inhibitors in red. The pathway is divided into two major branches, dihydro (blue background) and phyto (red background), which are related by Sur2.

**Fig. 2. The nomenclature of yeast SLs based on SL structure determined by mass spectrometry.**

The structure of two yeast SLs is given in panel (a), inositol phosphoryl α-OH-dihydroCer and inositol phosphoryl phytoCer, which are difficult to distinguish by shotgun lipidomics. PI refers to inositol phosphate, and the O(H) groups on the LCB (blue) and on the acyl chain (black) are indicated in red or magenta respectively. (b) The first row (i) gives the classical name of the lipids, and the second row (ii) the name designated by LipidMaps. In the second row (ii), each aspect of the name is indicated, i.e. di- or tri-hydroxyl (red), the number of C atoms (#C), the number of double bonds (#unsaturation), and whether or not there is an OH group on the C2-OH (magenta). (c) The nomenclatures given by three different yeast SL laboratories are shown: (i) The Ejsing laboratory, in which the number of hydroxyl groups (red or magenta respectively) are indicated after the length and saturation state of the LCB and of the fatty acid (red or magenta); (ii) The Riezman laboratory, which uses the yeast common name followed by d/t to indicate the whether the hydroxyl group is on the LCB or on the fatty acid, followed by the total number of carbons and level of unsaturation. (iii) The Schneiter laboratory, which simplifies the nomenclature even more by just giving the total number of carbons, saturation and number of hydroxyl groups in both chains.

For an exact correspondence of a specific lipid to a compound we suggest using unambiguous designations found in ChEBI.

**Fig. 3. The relative abundance of yeast SLs.**
Quantification of the relative amounts of SLs. Data is from [66]. The relative amounts of the major SL species (Cer, IPCs, MIPCs and M(IP)₂Cs) are shown as a pie chart, with the total SL level in arbitrary units.

**Table 1. Summary of nomenclature and structures of yeast SLs.**

All yeast SLs listed in Lipid Maps (www.lipidmaps.org) are shown, along with some additional SLs. The yeast acronym is commonly used by the yeast SL community. The SLs listed in the table all have a C18 LCB and C26 acyl chain; the structures shown in Fig. 2 take into account differences in the LCB and acyl chain, information which is largely derived from mass spectrometry.

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Figure 1
Figure 2
Figure 3
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Graphical abstract