Databases and ontologies

The SwissLipids knowledgebase for lipid biology

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Abstract

Motivation: Lipids are a large and diverse group of biological molecules with roles in membrane formation, energy storage and signaling. Cellular lipidomes may contain tens of thousands of structures, a staggering degree of complexity whose significance is not yet fully understood. High-throughput mass spectrometry-based platforms provide a means to study this complexity, but the interpretation of lipidomic data and its integration with prior knowledge of lipid biology suffers from a lack of appropriate tools to manage the data and extract knowledge from it.

Results: To facilitate the description and exploration of lipidomic data and its integration with prior biological knowledge, we have developed a knowledge resource for lipids and their biology—SwissLipids. SwissLipids provides curated knowledge of lipid structures and metabolism which is used to generate an in silico library of feasible lipid structures. These are arranged in a hierarchical classification that links mass spectrometry analytical outputs to all possible lipid structures, metabolic reactions and enzymes. SwissLipids provides a reference namespace for lipidomic data publication, data exploration and hypothesis generation. The current version of SwissLipids includes over 244 000 known and theoretically possible lipid structures, over 800 proteins, and curated links to published knowledge from over 620 peer-reviewed publications. We are continually updating the SwissLipids hierarchy with new lipid categories and new expert curated knowledge.

Availability: SwissLipids is freely available at http://www.swisslipids.org/.

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Supplementary information: Supplementary data are available at Bioinformatics online.
1 Introduction

Lipids are a large and diverse group of biological molecules that perform a wide variety of biological functions (Sud et al., 2007). They comprise the bulk of membrane bilayers (Holthuis and Menon, 2014; van Meer et al., 2008) and energy stores (Lass et al., 2011), provide markers for the recognition and sorting of distinct organelles (Balla, 2013), and regulate processes such as cell proliferation and death (Morad and Cabot, 2013), immunity (Knowelden and Georas, 2014; Simmons and Ishii, 2014), angiogenesis, cardiogenesis and neurogenesis (Mendelson et al., 2014) and inflammation (Ji et al., 2011). The lipid complement or ‘lipidome’ of individual cells may include hundreds of thousands of lipid structures whose occurrence is tightly regulated in response to changes in the cellular environment and lipid availability (Gross and Han, 2011; Shevchenko and Simons, 2010). Disregulation of the lipidome is a feature of many pathological conditions including cardiovascular disease (Siguener et al., 2014), hypertension (Graessler et al., 2009), diabetes (Meikle et al., 2014) and Alzheimer (Bennett et al., 2014; Mapstone et al., 2014), for which lipids may comprise an important source of biomarkers. Pathogens also manipulate the host lipidome in order to facilitate their own persistence and replication (Loizides-Mangold et al., 2014; Lyn et al., 2014).

Elucidating the roles of lipids in biological systems requires the integration of quantitative measurements of lipid composition with knowledge of lipid metabolic pathways, enzymes and interacting proteins. Lipidome composition may be analyzed using mass spectrometry (MS) and tandem mass spectrometry (MS/MS)-based approaches which are able to quantify hundreds of lipid species over a broad dynamic range (da Silveira Dos Santos et al., 2014). These approaches provide information on the atomic composition of intact lipids and their component parts (such as acyl chains) which can be mapped to prior knowledge of lipid structures using a standardized hierarchical notation (Liebsch et al., 2013). One of the foremost sources of such knowledge is the LIPID MAPS Structure Database (LMSD), which provides a comprehensive classification of over 37 000 lipid structures grouped in 8 major lipid categories—fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, prenol lipids, polyketides and saccharolipids (Fahy et al., 2007). Other resources and tools for the analysis of lipidomic data include LipidBlast, which provides a library of 120 000 lipid structures (some derived from LIPID MAPS) and associated theoretical tandem mass spectra (Kind et al., 2013), LipidHome, a database of over 36 million hypothetical glycerolipid and glycerophospholipid structures specifically designed for MS data integration (Foster et al., 2013) and Visualization and phospholipid identification (VaLID) which provides a search engine for a library of hypothetical glycerophospholipid structures somewhat similar to those of LipidHome (Blanchard et al., 2013). Specialized software for annotating MS data include LipidXplorer (Herzog et al., 2013), mzmine (Pluskal et al., 2010) and Lipid Data Analyzer (Hartler et al., 2011). A common feature of all these resources and tools is that they focus mainly on the classification and identification of lipids. Knowledge of lipid biology, including links to metabolic pathways and enzymes, may be found in public knowledge resources such as BRENDA (Chang et al., 2015), HMDB (Wishart et al., 2013), KEGG (Kanehisa et al., 2014), MetaCyc (Caspi et al., 2014) and Reactome (Croft et al., 2014). Although KEGG has been used as basis for computational approaches for matching hypothetical structures to pathways (Yetukuri et al., 2007), these knowledge resources do not aim to provide comprehensive coverage of the hundreds of thousands of lipids that may exist in nature.

Here, we describe the development of a new knowledge resource that is designed to help connect lipidomics and lipid biology—SwissLipids. Our aim in creating SwissLipids was to provide a comprehensive reference database that can be used to describe mass spectrometry-based lipid identifications and link them to curated knowledge of lipid structures, metabolic reactions, enzymes and interacting proteins. SwissLipids was created through an iterative process in which prior knowledge of lipid structures and metabolism curated from published literature is used to generate an in silico library of all feasible structures for common lipid categories. These structures form the basis for a hierarchical lipid classification that is consistent with currently accepted lipidomic data notation and the classification of LIPID MAPS. The result is a reference namespace for lipidomic data publication, data exploration and hypothesis generation, allowing users to ask questions such as ‘where has this lipid species been seen before?’, ‘what structures might this lipid species have?’, ‘what are the relevant metabolic reactions?’ and ‘what proteins are known to interact with these putative structures?’

2 Methods

2.1 Curation of lipid structures and metabolism

We performed systematic curation of experimental knowledge of lipid structures using the chemical ontology ChEBI (Hastings et al., 2013) and of lipid metabolism using the annotated reaction database Rhea (Morgat et al., 2015) for several of the most common lipid categories including glycerophospholipids, glycerolipids, fatty acyls and sphingolipids. We focused mainly on lipids and enzymes of Homo sapiens, Mus musculus, Caenorhabditis elegans and Saccharomyces cerevisiae, but information from other species was also included when required to complete metabolic pathways (as in the desaturation of polysaturated fatty acids or PUFAs). Enzymatic reactions were curated in the SwissLipid database by linking UniProtKB (UniProt Consortium, 2014) protein accession numbers to Rhea reaction identifiers. All annotations in SwissLipids are associated with supporting evidence which includes a mandatory evidence type, represented by a code from the Evidence Codes Ontology (ECO) (Chibucos et al., 2014) and supporting source text and literature citation where applicable (articles from the scientific literature are represented as PubMed records). All annotations were checked for accuracy and consistency by a second curator.

2.2 Generation and annotation of lipid structures

Curated knowledge of experimentally characterized lipid structures and metabolism was used to design and create a library of theoretically feasible lipid structures in silico. Lipid structures were generated using the Java application SMILib v2.0 (Schuller et al., 2007) which combines SMILES (Weininger, 1988) representations of chemical substructures. Each structure was annotated with a standard name and abbreviations (created using a custom Perl script that follows accepted naming conventions of LIPID MAPS), as well as lipid class and fatty-acyl/alkyl components (including mappings to ChEBI) and their positions on the glycerol backbone. Formula, InChI and InChI key (Heller et al., 2013) and masses were calculated using the MolConvert and cxcalc tools (http://www.chemaxon.com), and exact m/z values for the following selected adducts were also calculated: [M]⁺, [M + H]⁺, [M + K]⁺, [M + Na]⁺, [M + Li]⁺, [M + NH₄]⁺, [M – H]⁻, [M + Cl]⁻, [M + OAc]⁻. Mappings to
Table 1. The hierarchical classification used in SwissLipids

| Level                        | Example                                                                 |
|------------------------------|-------------------------------------------------------------------------|
| Category                     | Glycerophospholipid                                                     |
| Class                        | Glycerophosphocholine                                                   |
| Species                      | PC(O-36:5)                                                              |
| Molecular subspecies         | PC(O-16:1,20:4)                                                         |
| Structural subspecies        | PC(P-16:0/20:4)                                                         |
| Isomeric subspecies          | PC(P-16:0/20:4(5Z,8Z,11Z,14Z))                                         |

The hierarchy includes seven levels that are illustrated below with a single example. The hierarchy is compatible with that of LipidHome (Foster et al., 2013) but uses only known components in the generation of the base isomeric subspecies. The hierarchy is fully mapped to ChEBI at all levels. The prefix ‘O’ indicates an alkyl bond, the prefix ‘P’ a 1Z-alkenyl bond and the absence of a prefix an ester bond. PC, phosphatidylcholine.

2.3 Generation of the lipid hierarchy
Glycerolipid and glycerophospholipid structures were used as the basis for the generation of a hierarchy of analytical outputs from mass spectrometry experiments (Liebisch et al., 2013). The lipid hierarchy was generated using custom software that takes as input a set of structures and a template file that specifies the required annotations for each of the corresponding higher levels and the relations that link them (Table 1). These annotations include lipid nomenclature and human readable descriptions, ChEBI identifiers for lipid parent classes and parent components, SMILES representations, formula, mass and m/z values for adducts, and InChI and InChI keys where applicable.

2.4 Curation of the lipid hierarchy
The lipid hierarchy was curated using experimental literature on the occurrence of lipids in biological systems. Qualitative annotations take the form of a link between a lipid identifier (generally one of Species, Molecular subspecies or Structural subspecies), a term from the Gene Ontology (GO) (Blake et al., 2013) or the cross-species tissue and cell ontology Uberon (Mungall et al., 2012), and a taxonomic identifier (NCBI Resource Coordinators., 2014). As with other annotation types, all annotations of lipid occurrence in SwissLipids are associated with supporting evidence represented by a code from the Evidence Codes Ontology (ECO) and supporting source text and literature citation where applicable.

2.5 Databases
SwissLipids data is organized in a set of MySQL tables. Data from external reference resources such as ChEBI (Hastings et al., 2013), Rhea (Morgat et al., 2015), UniProtKB (UniProt Consortium, 2014), GO (Blake et al., 2013), Cellosaurus and Uberon (Mungall et al., 2012) is sourced from local copies synchronized on a weekly basis.

2.6 Website development
The SwissLipids website has been developed using the AngularJS (http://www.angularjs.org) framework and server side PHP scripts (http://www.php.net). SVG images of molecules are generated from their mol representations using MolConvert (http://www.chemaxon.com).

3 Results and discussion
3.1 SwissLipids content
SwissLipids includes over 2000 curated enzymatic reactions which directly link more than 800 proteins (UniProtKB) and 1500 reactions (Rhea) and supporting evidence. These annotations cover a variety of lipid categories including glycerophospholipids, glycolipids, sphingolipids, sterols, fatty acids, fatty alcohols and wax esters. As the number of experimentally characterized lipid structures constitutes only a small fraction of the number of possible structures that may exist in nature (Gross and Han, 2011; Shevchenko and Simons, 2010), the curated knowledge available in SwissLipids was used to design and generate an in silico library of feasible lipid structures for selected common lipid categories. The current version of this library features 244 155 structures—hereafter referred to as isomeric subspecies—from 38 classes of glycerophospholipid and 13 classes of glycerolipid (Supplementary Table S1) including 80 fatty acids and 18 fatty alcohols (Supplementary Table S2). Forthcoming versions of SwissLipids will generalize this approach to other lipid categories for which curated data is available, including more classes of glycerophospholipid as well as sphingolipids. Structures are arranged in a hierarchical classification consistent with the latest lipid notation (Liebisch et al., 2013) that includes 91 124 structural subspecies (which assume knowledge of lipid class and the composition and positions of individual fatty acyl groups), 45 571 molecular subspecies (which assume knowledge of lipid class and the composition of individual fatty acyl groups) and 5508 species (which assume knowledge of lipid class and the sum composition of all fatty acyl groups) (Table 1). The SwissLipids hierarchy includes curated lipid identifications from published literature for over 300 species, molecular subspecies and structural subspecies.

The combinatorial generation of lipid structures described here and elsewhere (Blanchard et al., 2013; Foster et al., 2013) may produce lipid structures that do not exist in nature, and SwissLipids includes significantly more glycerophospholipid and glycolipid structures than reference databases such as LMSD (which leverages the expert knowledge of the LIPID MAPS consortium). Although the existence of these extra structures is currently unproven, the use of known structural building blocks from the reference ontology ChEBI ensures that they are at least relevant to our current understanding of lipid structures and metabolism, and the procedure for brute force enumeration of structures is completely transparent. The SwissLipids library also provides a means to link structures from other databases such as HMDB and LMSD to published lipid identifications and to metabolic reactions (described using Rhea) and enzymes (UniProtKB), and is cross-referenced by the experimental lipidomics platform of the LipidX consortium (www.lipidomes.org).

3.2 SwissLipids website and access
The SwissLipids website at www.swisslipids.org provides a simple interface to search for lipids (by identifiers, names, synonyms, abbreviations, formulae, m/z values for common adducts and SMILES, InChI and InChI key representations). Users may also browse the SwissLipids hierarchy at http://www.swisslipids.org/#/browse, beginning at Species level with the selection of the desired lipid class and the number of carbon atoms and double bonds in the acyl chains (Fig. 1). This returns a list of all possible molecular subspecies, structural subspecies and isomeric subspecies. Exploration of the result lists is facilitated by a simple icon system that indicates the available information for each lipid entry (Fig. 1). Individual lipids
as well as complete result lists may be selected for the identifier mapping service (http://www.swisslipids.org/#/mapper), which maps lipid identifiers from SwissLipids, ChEBI, HMDB and LMSD to each other as well as to the corresponding biochemical reactions from Rhea and curated enzymes from SwissLipids. Individual lipid entry pages provide key information including structure, cheminformatics descriptors, nomenclature, classification, reactions, enzymes, and subcellular and tissular location (Fig. 2). Enzyme names link to protein entry pages that list all curated information from SwissLipids, such as Rhea reactions and citations (not shown). SwissLipids may also be searched and accessed through the ExPASy bioinformatics resource portal (http://www.expasy.org) (Artimo et al., 2012).

4 Conclusions
SwissLipids provides a core of curated information on lipid structures and metabolism which serves as the base for the generation of a library of all feasible lipid structures (according to our current knowledge of the relevant lipid structural classes) and their corresponding analytical outputs for MS and MS/MS. The curation of
information using ChEBI, Rhea and UniProtKB provides a ready-made mapping of SwissLipids to these widely used resources and others that reference them such as the MetaboLights repository for metabolomic studies (Haug et al., 2013), the IntEnz resource for enzyme nomenclature and classification (Fleischmann et al., 2004), the MetaNetX.org platform for the analysis of metabolic models (Bernard et al., 2014; Ganter et al., 2013) and the genome annotation platform MicroScope (Vallenet et al., 2013). As well as

**Fig. 2. A SwissLipids entry.** SwissLipids entry pages provide information on lipid structure and nomenclature (top panel), cheminformatics descriptors (second panel), lipid classification and components (third panel), reactions (Rhea) and enzymes (UniProtKB) (fourth panel), and subcellular (GO) and tissue (Uberon) location (not shown) which can be navigated through distinct tabs. Links to other databases such as ChEBI, HMDB and LIPID MAPS are also provided. The lipid classification indicates the structural class of lipid (here, 1-O-(1Z-hexadecenyl)-2-(5Z,8Z,11Z,14Z-eicosatetraenooy)-sn-glycero-3-phosphocholine) and its ‘analytical parent’ (the Structural subspecies Phosphatidylcholine (P-16:0/20:4)) as well as the individual components (hexadecanol-1-ol and 5Z,8Z,11Z,14Z-eicosatetraenoate) and the annotations available for each. The underlying evidence for curated assertions can be viewed by clicking on ‘see evidence’ (see fourth panel)
enriching SwissLipids with new lipid categories, structures and curated information, we plan to provide enhanced search options that include common isotopes and fragmentation patterns, and to improve interoperability by providing annotations and structures using the W3C standard RDF, a mainstay of large bioinformatics resources like UniProtKB.

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