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Databases and ontologies

MeLAD: an integrated resource for metalloenzyme-ligand associations

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Abstract

Motivation: Metalloenzymes are attractive targets for therapeutic intervention owing to their central roles in various biological processes and pathological situations. The fast-growing body of structural data on metalloenzyme-ligand interactions is facilitating efficient drug discovery targeting metalloenzymes. However, there remains a shortage of specific databases that can provide centralized, interconnected information exclusive to metalloenzyme-ligand associations.

Results: We created a *M*etallo*e*nzyme-*L*igand *A*ssociation *D*atabase (MeLAD), which is designed to provide curated structural data and information exclusive to metalloenzyme-ligand interactions, and more uniquely, present expanded associations that are represented by metal-binding pharmacophores (MBPs), metalloenzyme structural similarity (MeSIM) and ligand chemical similarity (LigSIM). MeLAD currently contains 6086 structurally resolved interactions of 1416 metalloenzymes with 3564 ligands, of which classical metal-binding, non-classical metal-binding, non-metal-binding and metal water-bridging interactions account for 63.0%, 2.3%, 34.4% and 0.3%, respectively. A total of 263 monodentate, 191 bidentate and 15 tridentate MBP chemotypes were included in MeLAD, which are linked to different active site metal ions and coordination modes. 3726 and 52 740 deductive metalloenzyme-ligand associations by MeSIM and LigSIM analyses, respectively, were included in MeLAD. An online server is provided for users to conduct metalloenzyme profiling prediction for small molecules of interest. MeLAD is searchable by multiple criteria, e.g. metalloenzyme name, ligand identifier, functional class, bioinorganic class, metal ion and metal-containing cofactor, which will serve as a valuable, integrative data source to foster metalloenzyme related research, particularly involved in drug discovery targeting metalloenzymes.

Availability and implementation: MeLAD is accessible at https://melad.ddtmlab.org.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Metalloenzyme is a generic term normally used for the enzymes containing one or more functionally essential active site metal ions. More than one-third of all known enzymes can be categorized as metalloenzymes, which are critical to a wide variety of biological processes, including metabolism, epigenetic regulation, immune modulation, antimicrobial resistance and many others. Metalloenzymes also are involved in the genesis, development and/or propagation of human diseases, such as cancer and cardiovascular diseases (Chen *et al.*, 2019; Cohen, 2017). Consequently, metalloenzymes represent a rich and attractive target space for drug discovery and development. To date, more than 60 small-molecule metalloenzyme inhibitors have been approved by U.S. Food and Drug Administration (FDA) (Chen *et al.*, 2019; Cohen, 2017; Yang *et al.*, 2016), and a large number of inhibitors targeting newly validated druggable metalloenzymes are in preclinical and clinical development phase (Bush and Bradford, 2019; Gupta and Wish, 2017; Krajnc *et al.*, 2019; Platten *et al.*, 2019). Nevertheless, a large discrepancy between the number of pharmacologically relevant metalloenzymes and the number of clinically useful drugs developed for metalloenzymes still exists,

exposing a knowledge gap in metalloenzyme focused research and particularly inhibitor development (Cohen, 2017).

The fast-growing body of experimental data on metalloenzyme-ligand interactions is fostering metalloenzyme-centric drug discovery and drug repositioning. Online resources and databases, such as the PDB (Burley *et al.*, 2019; wwPDB consortium, 2018), BRENDA (Chang *et al.*, 2019), MetalPDB (Putignano *et al.*, 2018), ChEMBL (Mendez *et al.*, 2019) and MetLigDB (Choi *et al.*, 2011), contain a wealth of information of metalloenzymes and their ligands/inhibitors. However, a specific database that can provide centralized, interconnected information exclusive to metalloenzyme-ligand associations has been lacking. We created the *M*etallo*e*nzyme-*L*igand *A*ssociation *D*atabase (MeLAD, https://melad.ddtmlab.org) for use as a general platform in assisting metalloenzyme inhibitor development and related studies. MeLAD provides curated structural data, e.g. minimal structural units (MSUs) of metalloenzyme-ligand interactions, and associated information, including ligand-metal coordination manner, interaction mode, bioinorganic information, active site metal ions and metal-containing cofactor, which were not included in other related databases. Given the distinctiveness of metal-containing active sites and ligand binding features, we further expanded metalloenzyme-ligand associations with the aim of providing new perspectives into unexploited space for rational drug design and metallome specificity examination. We compiled various chemical moieties responsible for binding with the active site metal ion(s), namely, metal-binding pharmacophores (MBPs) (Chen *et al.*, 2019; Cohen, 2017; Credille *et al.*, 2018; Jiang *et al.*, 2019), which are important links to establish relationships of structurally different ligands with various metalloenzymes/active site metal ions. Many recognized and unexpected metalloenzyme-ligand associations identified by analyses of metalloenzyme structural similarity (MeSIM) and ligand chemical similarity (LigSIM) are apparent in MeLAD. An online server for metalloenzyme profiling is available for uses to predict possible metalloenzyme targets for small molecules of interest. Moreover, MeLAD offers simple, easy-to-use, new data visualization and access, which will be useful to develop databases for proteins or nucleic acids with specific functions or structural features.

2 Materials and methods

2.1 Structural data collection and preparation

We began by mining data from the PDB database (Burley *et al.*, 2019; wwPDB consortium, 2018) (by January 1, 2019) to obtain structural details for metalloenzyme-ligand interactions. Only crystal structures (3 Å resolution or lower) and Nuclear Magnetic Resonance (NMR) structures were analysed using an *in-house* programme, termed ML-TOOL, which was developed to distinguish metalloenzyme-ligand complex structures and generate prepared structures. The ML-TOOL procedure is briefly described as follows: (i) examine whether a given structure is a protein structure, and if so, proceed to the next step; (ii) examine whether this structure contains any metal ion (including Zn, Fe, Cu, Mn, Co, Ni, Mo, Mg, Ca, K and Na ions) that is positioned to coordinate with at least two protein N/O/S atoms (with the distance $\leq$2.5 Å), and if so, it is labelled as a 'metalloenzyme' and proceed to the next step; (iii) examine whether the metalloenzyme contains any metal-containing cofactor (e.g. heme cofactor, see Supplementary Table S1) and if so, it is labelled as 'cofactor-containing metalloenzyme' and proceed to the next step; (iv) examine whether this structure contains any eligible heterogen ligand within 6 Å around active site metal ions or cofactors, and if so, it is labelled as 'metalloenzyme-ligand complex'; (v) save separately the metalloenzyme (with metal ions or metal-containing cofactor) and ligand coordinates; and (vi) extract coordinates of intact active site residues and metal ions/metal-containing cofactors within 6 Å are of the ligand as MSU files. The resulting structures were then visually inspected to confirm active site metal ions and metal-containing cofactors and exclude undesirable complex structures.

2.2 Metalloenzyme/ligand information curation

Comprehensive metalloenzyme information, including metalloenzyme name, gene name, species, enzyme classification, enzyme commission (EC) number and enzyme function, were collected from the PDB (Burley *et al.*, 2019; wwPDB consortium, 2018), BRENDA (Chang *et al.*, 2019) and UniProt (UniProt Consortium, 2018) and manually checked. The bioinorganic classification of metalloenzymes was annotated according to the rules proposed by Degtyarenko (2000), and metalloenzyme-related diseases were manually collected from references. The canonical SMILES strings of ligands were generated using OpenBabel (O'Boyle *et al.*, 2011) from the 3D ligand coordinates extracted by ML-TOOL, and cLogP/cLogS values were calculated using the ALOGPS 2.1 programme (Tetko *et al.*, 2005).

The associated information regarding metalloenzyme-ligand interactions, including active site metals, number of metal ions and metal-containing cofactor, were obtained (manually checked) by ML-TOOL; binding data were collected from PDBbind (Liu *et al.*, 2015) and references therein. The interaction modes were annotated as four types, i.e. classical metal-binding, non-classical metal-binding, non-metal-binding and metal water-bridging interactions, according to the distance between the ligand atoms and the active site metal ions. The classical metal-binding interaction type denotes that at least one O/N/S/F/Se atom of the ligand is positioned to coordinate with active site metal ion(s), i.e. the ligand atom(s) are usually $\leq$2.8 Å from the metal ion(s) (Fig. 1A). Non-classical metal-binding includes acidic groups or π-systems involved in direct metal coordination (Fig. 1B). By contrast, non-metal-binding interactions do not involve direct metal coordination, i.e. all of the atoms of the ligand are >3 Å from the active site metal ion(s). In some complex structures, a ligand with a hydrated carbonyl group complexes the metal ion *via* on of its hydroxyl groups (typically with a distance $\leq$2.5 Å) (Fig. 1C); such complex structures were annotated as metal water-bridging type interactions.

2.3 Data analysis and expansion

Because most metalloenzyme-ligand interactions involve direct metal coordination, and many structurally different ligands contain common MBP chemotypes, we manually analysed and defined the key MBP chemotypes cross all the entries in MeLAD. These MBPs were catalogued as monodentate, bidentate and tridentate by their metal coordination nature (Fig. 1). To expand perspectives of metalloenzyme-ligand associations, we conducted structural similarity MeSIM analyses to classify different metalloenzymes using the MICAN programme (Minami *et al.*, 2013), which is capable of identifying the best structural alignment between metalloenzymes by disregarding the connectivity between secondary structure elements. The metalloenzymes were defined as similar if their structures had a root mean square deviation $\leq$2.5 Å. We also established chemical ligand similarity between different metalloenzymes based on the path- and substructure-based fingerprint similarity (namely LigSIM) (O'Boyle *et al.*, 2011). The metalloenzyme subsets were related to each other if their ligands had both path- and substructure-based similarity values larger than 0.4 and their targets are not in a same enzyme family;

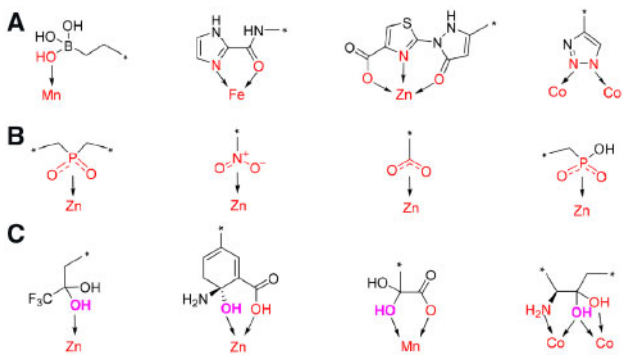

Fig. 1. Metal-ligand coordination modes. Examples of (**A**) classical metal-binding interactions, (**B**) non-classical metal-binding interactions and (**C**) metal water (water derived hydroxyl) bridging interactions

LigSIM-score is the average of these two-similarity metrics. An online server was established for users to query small-molecule compounds for metalloenzyme profiling on basis of chemical similarity and MBP features, further expanding the potential application of MeLAD.

3.4 Website development

To provide open access to the MeLAD database, we established a user-friendly website (https://melad.ddtmlab.org). The MeLAD database runs a cloud Linux server (Ubuntu 16.04), with the Nginx (version 1.10.3) as the web server and the MySQL programme (version 5.7.26) as the database server. The website was developed using Python programming language and the Flask framework (version 1.0.0). The web-frontend was designed with Vue.js and Bootstrap framework (version 4.3.1). The system was established based on the representational state transfer technology and the concept of model-view-controller pattern. The 3D metalloenzyme-ligand interactions can be visualized using the embedded NGL viewer (Rose *et al.*, 2018; Rose and Hildebrand, 2015). The website supports almost all modern browsers, such as Chrome, Firefox, Edge and Internet Explorer.

3 Results

3.1 Database statistics

MeLAD currently included 6086 structurally determined associations of 1416 metalloenzymes with 3563 ligands, which are graphically shown in Figure 1 and Supplementary Figure S1. Cross-enzyme inhibitors are observed not only for metalloenzymes in the same family [e.g. metallo-β-lactamases (MBLs), matrix metalloproteinases (MMPs) and N-methyl lysine demethylases (KDMs)] but also for structurally and mechanistically distinct metalloenzymes [e.g. between MBL and angiotensin-converting enzymes (ACEs)] (Fig. 1). Approximately 40% of these metalloenzymes have at least two structures with structurally different ligands (Supplementary Fig. S2), and 125 metalloenzymes have $\geq$10 structures in complex with ligands in the database, such as carbonic anhydrase 2 (CA2) and nitric oxide synthase (Nos1) (Fig. 1). These metalloenzymes consist of various mono-, bi- and poly-nuclear metal sites, covering all the six EC classes (Supplementary Fig. S3), and many of them are related to human diseases. We observe that 82.2% ligands in MeLAD are only bound to a single metalloenzyme (Supplementary Figs S1 and S2). Nevertheless, some ligands (e.g. BES, CAP, ICT, PQQ and TDP, Fig. 1) that bear non-specific or multiple metal-binding motifs and bind to more than five metalloenzymes should be seriously considered.

Most metalloenzyme-ligand interactions identified in MeLAD involve classical or non-classical metal-binding, accounting for 65.3% of chemotypes; non-metal-binding and metal water-bridging interactions account for 34.4% and 0.3%, respectively. A total of 469 MBP chemotypes were identified (Supplementary Table S2), of which 56.1% are monodentate MBPs, 40.7% are bidentate MBPs and 3.2% are tridentate MBPs. Many MBPs such as hydroxamic acid and imidazole (Supplementary Table S2) were observed as common core scaffold of inhibitors for different metalloenzymes, suggesting that they are important pharmacophores for fragment-based drug design. Notably, in some cases, multiple MBPs are involved in

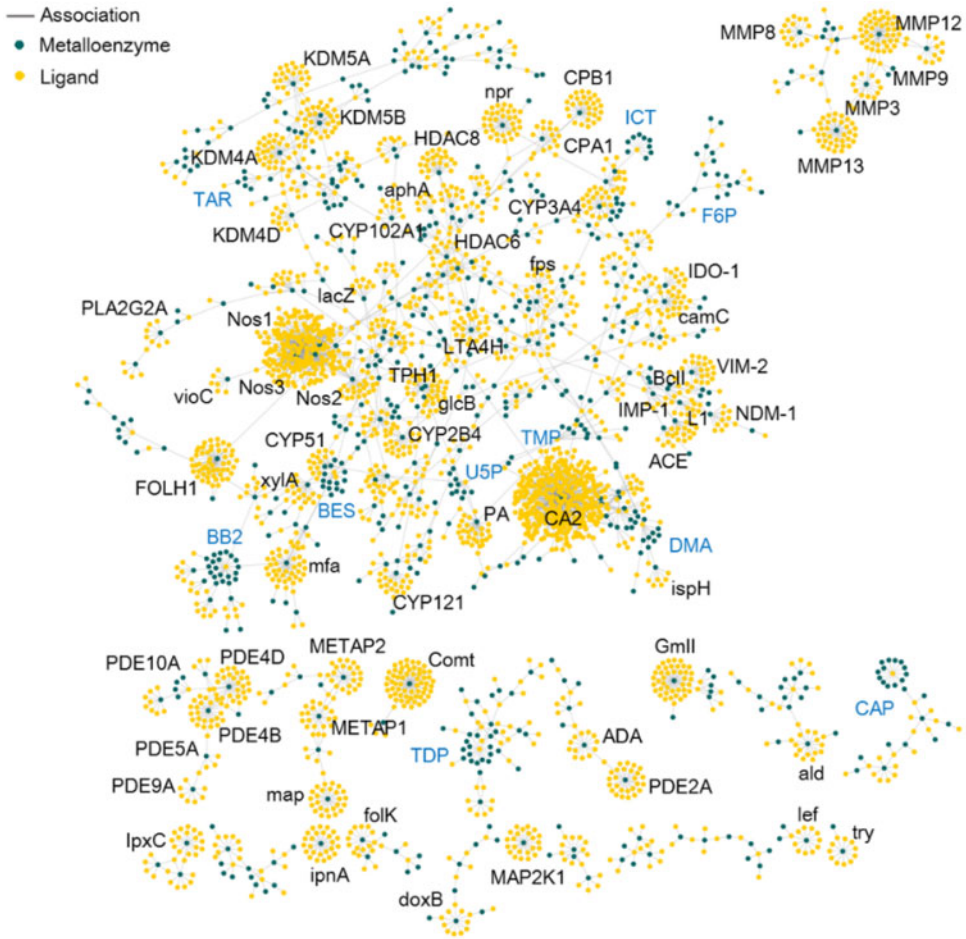

Fig. 2. The metalloenzyme-ligand network. Each ligand (gold) is linked to its metalloenzyme target (teal) by a grey edge. Each edge represents a structurally solved metalloenzyme-ligand association. Some representative metalloenzymes are labelled (black), and some ligands that bind with more than five metalloenzymes are also labelled (blue) (Color version of this figure is available at *Bioinformatics* online.)

a single compound (Fig. 2), which will increase promiscuous 'off-target' metalloenzyme intentions, suggesting that MBP analysis could be useful for metallome selectivity investigations.

The MeSIM analyses identified 3726 pairs of structurally similar metalloenzymes in the database, of which 2902, 364 and 45 pairs are from mono-, bi- and poly-nuclear metalloenzymes, respectively, and particularly 415 pairs are from cross mono-, bi- and poly-nuclear enzymes (Supplementary Fig. S4). The LigSIM analyses resulted in 52 740 possible metalloenzyme-ligand associations. Among them, 64.08%, 2.91% and 0.29% ligand pairs are from mono-, bi- and poly-nuclear enzymes, respectively. Interestingly, 5932 similar ligand pairs are sharing the same MBP, mostly with LigSIM scores ranging from 0.5 to 0.7 (Supplementary Fig. S5).

3.2 Database features

The website involves six main sections, i.e. '*Search*', '*MBPs*', '*MeSIM*', '*LigSIM*', '*Profiling*' and '*Download*', which enables users to browse, search, compare and download all of the data covered, as well as conduct online computation. Each section was designed and developed to ensure an easy use without any prerequisite knowledge or experience.

In the '*Search*' page, users can retrieve all curated metalloenzyme-ligand interaction entries and associated information *via* basic annotations, such as metalloenzyme name, metal-containing cofactor, bioinorganic class, functional class, active site metal ions, number of metal ions and interaction mode. The detailed information page for a specific entry can be accessed by searching or clicking on the PDB code. The linked page mainly contains metalloenzyme information (gene name, species, enzyme functions, associated diseases, etc.), ligand information (ligand code, SMILES, clogP, clogS, etc.), metalloenzyme-ligand interaction information (3D interaction view, ligand-metal coordination mode, interaction mode, binding data, metal-containing cofactor, etc.), and links to references and other related databases (Supplementary Fig. S6). It also supports multiple-criteria searching to narrow search results and searching through links e.g. a ligand code, and download search results (at the bottom of the page).

The '*MBPs*' page contains chemical structures of all the monodentate, bidentate and tridentate MBP chemotypes. User can click each MBP entry to obtain detailed information of the matching metalloenzyme-ligand associations. For example, clicking on the MBP of ethanol (ID: MBP1-1-1) will lead to a list of 71 entries that involve this chemotype for metal binding, which are associated with a variety of metalloenzymes. User can further browse, search, compare and download all of these data.

On the '*MeSIM*' page, a total of 3726 structurally metalloenzyme-related associations catalogued by mono-, di- and poly-nuclear enzymes were provided (Fig. 3A). Users can obtain a specific metalloenzyme focused associations by keyboard input of the PDB code or mouse clicking of the enzyme colour circle. For example, searching with the PDB code of '5NDB', which is a SPM-1: inhibitor complex structure, will link to information on structurally related metalloenzymes for SPM-1, including the binuclear MBLs IMP-1, VIM-1, VIM-2, VIM-5, NDM-1, BlaB-1, BCII-1, Ccra, mononuclear MBLs CphA-1, SFH-1, phospholipase A2 (phoa) and cytochrome C1 (CYC1) (Fig. 3B); these enzymes are ranked by the structural similarity score (Fig. 3C). Users can further click to search for information about these enzymes, and can also view the superimposition of structures and their ligand binding modes (Fig. 3C).

In the '*LigSIM*' section, 52 740 metalloenzyme-ligand associations identified by the LigSIM analyses are available. Users can access the association data for any ligand in MeLAD by ligand code or mouse clicking on the colour circle. For example, searching ligand code of 'X8Z', which is a VIM-2 inhibitor, will result in a list of 87 chemically similar ligand pairs—correspondingly new possible metalloenzyme-ligand associations (Fig. 4A-B). More importantly, users can directly view and compare the binding modes and metal coordination modes of related set of ligands (Fig. 4C), providing centralized, valuable information for hit/lead identification, rational drug design and metallome selectivity examination.

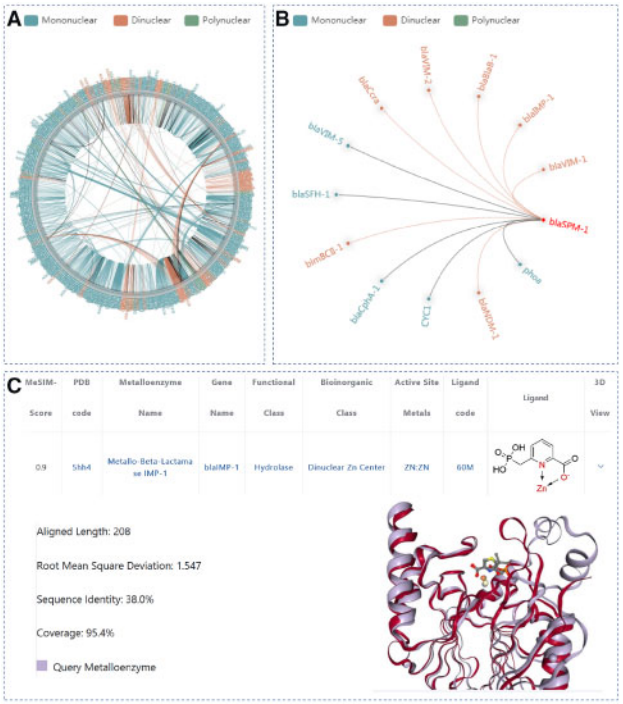

Fig. 3. Basic instructions for MeSIM. (**A**) A full picture of structurally metalloenzyme-related associations, indicating structural similarity appearing cross mono-, bi- and poly-nuclear metalloenzymes. (**B**) Structurally related metalloenzymes for the query enzyme, SPM-1. (**C**) Detailed information and superimposition view of the metalloenzymes ranked by MeSIM-Score

The user-friendly '*Profiling*' web server was provided to predict possible metalloenzyme-ligand associations for small molecules. The user can query a molecule using canonical SMILES strings or sd/sdf/mol2 files. Once a molecule is uploaded, clicking the 'PROFILING' tab will compute chemical fingerprint similarity scores of the query compound against all of the ligands in MeLAD, and output a prioritized list of similar ligands and associated information; an example of metalloenzyme profiling for Crisaborole, an FDA-approved PDE4 inhibitor, was shown in Supplementary Figure S7. This allows comparisons of chemical similarity and visual inspection of the MBP chemotypes, coordination and binding modes, which will, to a large extent, help to enhance the usefulness of metalloenzyme profiling.

Through the '*Download*' tab, users can access the executable ML-TOOL programme and its usage instructions, which can be used to prepare PDB coordinates offline, e.g. to generate MSU coordinates. Users can download ready-to-use files of the metalloenzyme-ligand complex, metalloenzyme, ligand and MSU coordinates that can be directly used in, e.g. scoring function development, virtual screening, bioinformatics and chemoinformatics. The associated data of metalloenzymes and ligands in MeLAD can be downloaded. All the curated data and computation tools are free of charge. We would appreciate it if users could fill a brief registration form to help analyse usage statistics.

4 Discussion

The rising interest in drug discovery targeting metalloenzymes will benfit from comprehensive analyses of specialized information regarding metalloenzyme-ligand interactions. We established the MeLAD database to provide a platform for efficiently analysing organized information about various metalloenzyme-ligand associations to assist inhibitor development and selectivity examination. The MeLAD database contains a large number of manually curated complex structures covering 1416 metalloenzymes, many of which are clinically relevant or validated therapeutic targets. An unique feature of MeLAD is the search parameters exclusive to

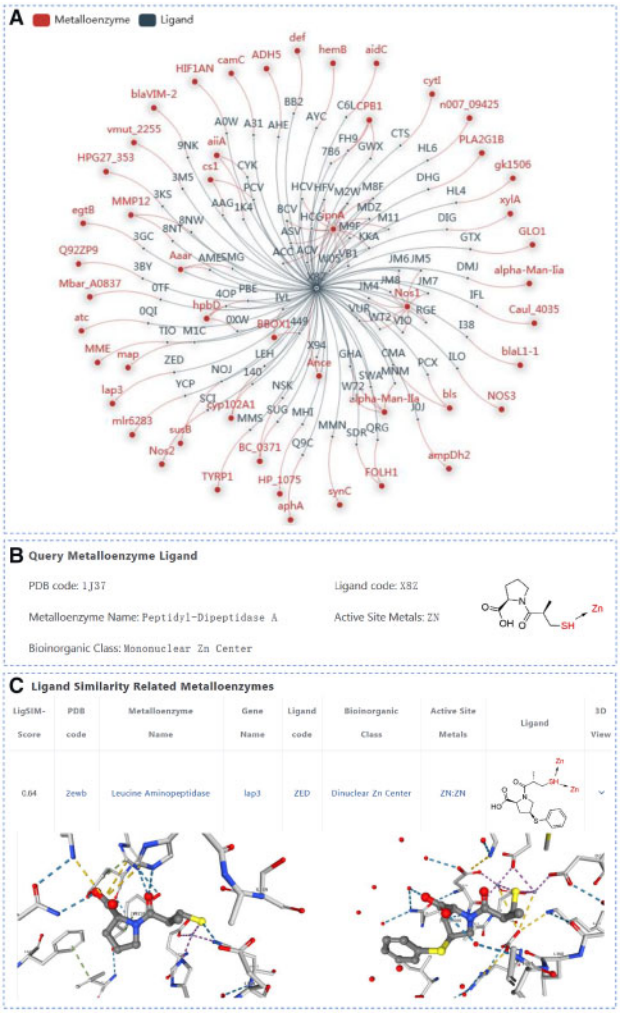

Fig. 4. Basic instructions for LigSIM. (**A**) An example of metalloenzyme-ligand network, in which ligands are similar to the query ligand (code: X8Z) in MeLAD. (**B**) Information for ligand X8Z. (**C**) Detailed information and comparison view of the resulted metalloenzyme-ligand associations

metalloenzyme-ligand interactions, e.g. interaction mode, active site metal ions, metal-containing cofactor, bioinorganic information and MBPs, which can be used to exclusively centralize metalloenzyme-ligand-centric associations, visually compare metal-containing active sites and inhibitor binding features, thereby boost structure-based drug discovery and related studies.

Analyses of metalloenzyme-ligand interactions indicate numerous widespread metal-binding modes and an abundant diverse set of MBP chemotypes. Some of the MBPs, e.g. hydroxamic acid and imidazole, have been used as privileged scaffolds for drug development and polypharmacological investigations, whereas some have not been widely used, such as oxiranes, cyclic boronates, cyano-, and thiurea-groups, which may prompt users to try these MBPs. Comparison of MBP-linked metalloenzyme-ligand associations may be an effective strategy for deriving new ideas for future inhibitor development. The available MBP dataset will also be helpful in developing privileged molecular collections or expanding the MBP chemical space, for example, *via* a fused bioinorganic and medicinal chemistry strategy proposed by Cohen and co-workers (Cohen, 2017; Dick and Cohen, 2018; Perez *et al.*, 2019). Notably, MeLAD contains a number of ligands that bear multiple metal-binding atoms/MBPs, and appear to non-specifically target several metalloenzymes; these ligands should be recognized and even labelled as alert structures to avoid generation of pan-assay interference compounds (PAINS) (Baell and Walters, 2014). Thus, MBPs may be used as an important index for metallome selectivity examination. In addition, many metalloenzyme inhibitors in the database have non-metal-binding modes, which are usually positioned to make key interactions with active site anchor residues and other catalytically important residues, and manifest substantial selectivity even to homologous metalloenzymes (Li *et al.*, 2017). This observation suggests that further mining and analysis of metalloenzyme ligand interactions will be productive.

MeSIM analysis enables users to compare inhibitor binding modes or consider inhibitor selectivity over homologous or similarly-folded enzymes. In addition, users can also obtain ligand chemical similarity related associations for ligands in the MeLAD database or any other small molecules of interest *via* an online server. These expanded relationships constitute another unique feature of MeLAD and substantially enriches knowledge of metalloenzyme-ligand associations. In particular, visual direct cross-comparison of experimental and inferred associations may help to improve data plausibility and success in drug discovery programmes.

We intend MeLAD will serve as a valuable, integrative platform, coupled with advances in medicinal chemistry, bioinorganic chemistry, computational chemistry, molecular/chemical biology, bioinformatics and many other fields, to fill the knowledge gap in metalloenzyme inhibitor development and nurture the development of metalloenzyme related subjects. In the future, to respond to the rapid growth of metalloenzyme related research, we will continue to update new metalloenzyme-ligand association data. We are developing new computational tools to make MeLAD even more resourceful and usable. As the first attempt to present the metalloenzyme-ligand association database, we sincerely are open to receiving support and advice from academic and industrial communities to improve MeLAD's usefulness.

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