At variance with these databases, Metal-MACiE presents a detailed description of the functions of the metal(s) involved in an enzyme reaction in a step-by-step manner, and pulls together the 3D coordinates of the metal site(s) (wherever possible) for the various states along the reaction pathway.

Metal-MACiE, which exploits MACiE for the annotation of the reaction mechanisms, can be used to advance our understanding of the chemistry underlying metal-dependent catalysis, and thus can be helpful in several areas of research including enzymology, biochemistry and molecular pharmacology.

2 DATABASE DESIGN

Similarly to MACiE, Metal-MACiE entries correspond to enzyme catalytic mechanisms. The identification codes of Metal-MACiE entries are the same as in MACiE (e.g. M0004) to facilitate the communication between the two databases. Each Metal-MACiE entry contains annotation for all the metals involved in the catalysis. Basic information includes the type of center in which the metal is found (e.g. dinuclear, heme) and the identity of the metal in the functional, physiological form of the enzyme. It is reported when the physiological metal is under debate [e.g. for fumaroylacetacetase, M0180 (Bateman et al., 2001)] and when protein homologues from different organisms use different metals [e.g. for lactoylglutathione lyase, M0032 (Clugston et al., 1998)].

A detailed description of metal properties (e.g. oxidation state, coordination geometry) and functions (e.g. substrate activation) is given for every step of the enzymatic reaction. These data are retrieved or deduced from the available literature, for which references are provided. When a PDB structure is available for a given reaction state, information on the 3D structure of the first coordination sphere of the metal in that state is also reported.

3 DATABASE CONTENT

Metal-MACiE contains all the metalloenzymes currently annotated in MACiE. This release of Metal-MACiE includes 136 entries spanning 134 enzyme commission (EC) numbers, and contains annotations for 220 metals participating to a total of 605 reaction steps. About 23% of reaction states are associated with a PDB structure describing the metal environment in that state. Enzymes whose EC codes have the same first three digits (defining EC sub-sub-classes) generally share similar overall chemistry. Entries in MACiE and thus in Metal-MACiE are selected so as to cover as many EC sub-sub-classes as possible, i.e. to ensure the largest possible coverage of the EC reaction space. Currently, the PDB covers 188 EC sub-sub-classes, of which 144 include at least one metal-dependent enzyme (Andreini et al., 2008). The 134 EC sub-sub-classes currently covered span 134 enzyme commission (EC) numbers.
The information contained in Metal-MACiE is based on the manually checked. From the PDB structure with the highest resolution, and then on the metal first coordination sphere was automatically extracted representative protein structures of reaction states. The information MACiE dictionary (http://www.ebi.ac.uk/thornton-srv/databases/Metal-MACiE have been rigorously defined taking as reference the interface that involves data checking and validation. All the terms in available primary literature and is manually entered using a web reasons of exclusion (e.g. the catalytic mechanism is not defined) the database, queries based on EC number give information on the other pages of the entry, and to the corresponding entry in MACiE. Degtyarenko, K.N., et al. (2001) PROMISE: a database of bioorganic motifs. Nucleic Acids Res., 29, 370–382. Degtjarevko, K.N., et al. (1999) PROMISE: a database of bioorganic motifs. Nucleic Acids Res., 27, 233–236. Holliday, G.L., et al. (2005) MACiE: a database of enzyme reaction mechanisms. Bioinformatics, 21, 4315–4316. McDonald, A.G., et al. (2007) ExplorEnz: a MySQL database of the IUBMB enzyme nomenclature. BMC Biochem., 8, 14.

5 DATABASE ACCESS AND WEB INTERFACE

Metal-MACiE can be queried from the main page and from the advanced query page (Table S1). For enzymes not included in the database, queries based on EC number give information on the reasons of exclusion (e.g. the catalytic mechanism is not defined) and on what is known about their metal-binding capability.

Entry information is organized in four types of page, which share a common design composed of three sections (Boxes A, B and C in Fig. 1). Box A is the same in all page types, and contains links to the other pages of the entry, and to the corresponding entry in MACiE. Box B reports the scheme of the overall enzymatic reaction or of a reaction step. When the scheme exceeds the screen, it can be seen by horizontal scrolling. Box C reports the core data of Metal-MACiE on metals, and differs in each page type (Boxes C1, C2, C3 and C4 in Fig. S1). The four page types are:

- Entry home page: contains general information on the metal(s) involved in the catalysis and on its/their properties in the resting state enzyme.
- Step information page: contains detailed information on the properties and function(s) of the metal(s) in a reaction step. There is one for every reaction step. It can be accessed using the links in Box A (Fig. 1).
- First coordination sphere page: contains detailed information on the first coordination sphere of the metal(s) in a reaction state. There is one for every reaction state for which a representative PDB structure is available. It can be accessed using the links in Box C (Fig. S1). Spatial coordinates of the metal first coordination sphere can be downloaded as a PDB formatted file.
- Metal information page: contains an overview of metal properties and roles during the course of the reaction. There is one for every metal involved in the catalysis. It can be accessed using the links in Box C (Fig. S1).

6 FUTURE DEVELOPMENTS

The main future work will concern the extension of the Metal-MACiE coverage, to include alternative reaction mechanisms, as well as new mechanisms. Due to the intimate link between MACiE and Metal-MACiE, their datasets will grow in parallel. Other work will include adding statistics resulting from several analyses on the database, and creating FTP pages to allow data download.

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