Bioinformatics, 35(22), 2019, 4849–4850
doi: 10.1093/bioinformatics/btz462
Advance Access Publication Date: 14 June 2019
Applications Note

OXFORD

Databases and ontologies

MetOSite: an integrated resource for the study of methionine residues sulfoxidation

Héctor Valverde, Francisco R. Cantón and Juan Carlos Aledo*

Departamento de Biología Molecular y Bioquímica, Universidad de Málaga, Málaga 29071, Spain

*To whom correspondence should be addressed.

Associate Editor: Alfonso Valencia

Received on December 28, 2018; revised on April 27, 2019; editorial decision on May 27, 2019; accepted on May 29, 2019

Abstract

Motivation: The oxidation of protein-bound methionine to form methionine sulfoxide has traditionally been regarded as an oxidative damage. However, growing evidences support the view of this reversible reaction also as a regulatory post-translational modification. Thus, the oxidation of methionine residues has been reported to have multiple and varied implications for protein function. However, despite the importance of this modification and the abundance of reports, all these data are scattered in the literature. No database/resource on methionine sulfoxidation exists currently. Since this information is useful to gain further insights into the redox regulation of cellular proteins, we have created a primary database of experimentally confirmed sulfoxidation sites.

Results: MetOSite currently contains 7242 methionine sulfoxide sites found in 3562 different proteins from 23 species, with *Homo sapiens*, *Arabidopsis thaliana* and *Bacillus cereus* as the main contributors. Each collected site has been classified according to the effect of its sulfoxidation on the biological properties of the modified protein. Thus, MetOSite documents cases where the sulfoxidation of methionine leads to (i) gain of activity, (ii) loss of activity, (iii) increased protein–protein interaction susceptibility, (iv) decreased protein–protein interaction susceptibility, (v) changes in protein stability and (vi) changes in subcellular location.

Availability and implementation: MetOSite is available at https://metosite.uma.es.

Contact: caledo@uma.es

1 Introduction

Research from a number of laboratories supports the notion that methionines in proteins serve as important cellular antioxidants (Drazic *et al.*, 2013), stabilize the structure of proteins (Valley *et al.*, 2012) and can act as regulatory switches through reversible oxidation and reduction of its sulfur atom (Veredas *et al.*, 2017).

Indeed, methionine residues from proteins are liable to reversible oxidation and reduction. Thus, methionine forms methionine sulfoxide (MetO) by addition of an oxygen atom to its sulfur atom in a reaction that can be or not enzymatically mediated. On the other hand, MetO is reduced back to methionine by methionine sulfoxide reductases. Depending on whether or not the added oxygen atom impacts the biological properties of the target protein, the reversible oxidation-reduction cycle may fulfill two well differentiated cellular functions, either as part of a signaling mechanism or as ROS scavengers, respectively.

There is a large body of evidence suggesting that those surface-exposed methionine residues that are oxidized without loss of catalytic activity, may serve as endogenous antioxidants. In this case, the enzyme-mediated recycling of MetO functions as a ROS scavenging mechanism, providing a catalytic amplification of the antioxidant potential of each methionine residue (Levine *et al.*, 1996). On the other hand, the mere addition of an oxygen atom to a single specific residue of methionine can cause drastic changes in the physicochemical properties of the whole protein, which, in turn, can affect the activity (Drazic *et al.*, 2013), the interaction with other cellular component (Lee *et al.*, 2013), the protein stability (Kanayama *et al.*, 2002) and/or the subcellular localization of the target protein (Gallmetzer *et al.*, 2015). This group of methionyl residues is potentially signaling-competent and collectively they may play important roles in the adaptation to oxidative conditions.

Given the relevance of methionine sulfoxidation to the redox biology, it is of great interest to identify, classify and document

sulfoxidized proteins/sites in different organisms and under different experimental conditions. A database that provides easy access to information on experimentally confirmed sulfoxidized methionine sites would be a valuable resource. Herein we describe MetOSite, a primary database that aims to fulfill such purpose.

2 Materials and methods

2.1 Curation and annotation of sulfoxidation sites

MetOSite is a manually curated database of experimentally verified methionine sulfoxidation sites. We have searched the literature to find those protein-bound methionine residues that have been detected as MetO. Those methionine sites for which strong experimental evidence could be collected were included in the database linked to their supporting publications.

Annotations are provided at both protein and residue levels. Thus, each MetO site present in the database has been assigned to one of three possible groups. Sites from group 1 have been detected as methionine sulfoxide in high-throughput studies and therefore the effect of such modification on the biological properties of the oxidized protein remains to be characterized. On the contrary, the effect of the modification of sites belonging to group 2 has been addressed but no apparent effect could be found, for which reason a role as ROS sink has been proposed for them. Finally, the sulfoxidation of any site from group 3 leads to changes of at least one biological property.

In this way, each site has been annotated with a functional category identifying the specific combination of properties known to be affected when that site is oxidized. In addition, the protein that hosts the modifiable methionine is also annotated and linked to UniProtKB. Further information related to other PTMs was collected from public sources such as PhosphoSitePlus and PhosPhAt.

2.2 Implementation

The MetOsite core consists in a MySQL database and a REST API built in PHP that provides access to the collection. In addition, it integrates (i) a user-friendly web interface for searching and browsing the data, (ii) a document repository offering relevant information related to the field and (iii) a documentation page of the REST API.

The source code of both back-end and front-end are published for possible contributors in Bitbucket (https://bitbucket.org/eebuma/metosite), as well as an issue tracker aimed to discuss and track future changes in the application. Hosting and infrastructure maintenance is provided by the University of Málaga.

3 Results

3.1 MetOSite web app

The app is a web-based client of the aforementioned REST API. It implements API calls and provides a user-friendly web interface to interact with the MetOSite database. The searches can be focused either on proteins or on sets of MetO sites grouped according to criteria such as functional effect, species or oxidants. In the first case, when the user is interested in a given protein, the data-resource is searched using the component *Scan*, which can take as argument the UniProt ID or the protein name. The server will return a detailed report containing general information about the protein, as well as specific information regarding the modifiable methionine residues. On the other hand, when we are interested in a set of oxidable methionine residues, the place to browse is *Search*, where users can set the parameters that will allow them to filter the data-resource to obtain a particular subset of MetO sites of interest.

3.2 MetOSite API and its R and Python clients

MetOSite also offers an API that provides a number of end-point functions that together aim to facilitate the management and analysis of the data contained in MetOSite. To this end, the API has been documented using Swagger. Thus, each user should be able to access these functions using the language of his/her choice. For R and Python users we also provide tutorials about how to access the API of MetOSite.

3.3 MetOSite content and maintenance

Currently, the database contains 7242 MetO sites distributed throughout 3562 different proteins belonging to 23 species. We plan to release two updates during 2019, around August and December.

4 Discussion

MetOSite is the first extensive database that provides information about MetO sites and their biological implications. MetOSite not only includes data from case-by-case studies but also integrates high-throughput data from proteomic studies. In the context of redox biology, we expect that MetOSite will be useful as a benchmark dataset for the development of computational prediction tools as well as for experimental researchers.

Acknowledgements

J.C.A. is in debt with Dr. Rodney L. Levine (NIH, Bethesda) for hosting during a mini-sabbatical and for providing useful comments. The authors also thank Alicia Esteban and Elena Aledo for their help with this project. The authors are also grateful to Ana M. García Olivencia for provisioning and maintaining the production servers.

Funding

This work was partially supported by the University of Málaga.

Conflict of Interest: none declared.

References

Drazic,A. *et al.* (2013) Methionine oxidation activates a transcription factor in response to oxidative stress. *Proc. Natl. Acad. Sci. USA*, **110**, 9493–9498.

Gallmetzer,A. *et al.* (2015) Reversible oxidation of a conserved methionine in the nuclear export sequence determines subcellular distribution and activity of the fungal nitrate regulator NirA. *PLoS Genet.*, **11**, e1005297.

Kanayama,A. *et al.* (2002) Oxidation of IκBα at methionine 45 is one cause of taurine chloramine-induced inhibition of NF-κB activation. *PLoS Genet.*, **11**, e1005297.

Lee,B.C. *et al.* (2013) MsrB1 and MICALs regulate actin assembly and macrophage function via reversible stereoselective methionine oxidation. *Mol. Cell*, **51**, 397–404.

Levine,R.L. *et al.* (1996) Methionine residues as endogenous antioxidants in proteins. *Proc. Natl. Acad. Sci. USA*, **93**, 15036–15040.

Valley,C.C. *et al.* (2012) The methionine-aromatic motif plays a unique role in stabilizing protein structure. *J. Biol. Chem.*, **287**, 34979–34991.

Veredas,F.J. *et al.* (2017) Methionine residues around phosphorylation sites are preferentially oxidized in vivo under stress conditions. *Sci. Rep.*, **7**, 1–14.