Ecotoxicology and Environmental Safety 140 (2017) 279–287

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

The evolution of environmental metalloproteomics over the last 15 years through bibliometric techniques

Rachel Ann Hauser-Davis[a,*], Renato Matos Lopes[b], Fábio Batista Mota[c], Josino Costa Moreira[a]

[a] Centro de Estudos da Saúde do Trabalhador e Ecologia Humana, Fundaçao Oswaldo Cruz, Rio de Janeiro, Brazil
[b] Laboratório de Comunicaçao Celular, Instituto Oswaldo Cruz, Fundaçao Oswaldo Cruz, Rio de Janeiro, Brazil
[c] Vice-Presidência de Pesquisa e Laboratórios de Referência, Fundaçao Oswaldo Cruz, Rio de Janeiro, Brazil

ARTICLE INFO

Keywords:
Environmental Metalloprotemics
Data mining
Bibliometrics
Ecotoxicology

ABSTRACT

Metalloproteomic studies in environmental scenarios are of significant value in elucidating metal uptake, trafficking, accumulation and metabolism linked to biomolecules in biological systems. The advent of this field occurred in the early 2000s, and it has since become an interesting and growing area of interdisciplinary research, although the number of publications in Environmental Metalloprotemics is still very low compared to other metallomic areas. In this context, the evolution of Environmental Metalloprotemics in the last decades was evaluated herein through the use of bibliometric techniques, identifying variables that may aid researchers in this area to form collaborative networks with established scientists in this regard, such as main authors, published articles, institutions, countries and established collaborations involved in academic research on this subject. Results indicate a growing trend of publications over time, reflecting the interest of the scientific community in Environmental Metalloprotemics, but also demonstrated that the research interactions in this field are still country- and organization-specific. Higher amounts of publications are observed from the late 2000's onwards, related to the increasing technological advances in the area, such as the development of techniques combining atomic spectroscopy and biochemical or proteomic techniques. The retrieved publications also indicate that the recent advances in genomic, proteomic and metallomic areas have allowed for extended applications of Environmental Metalloprotemics in non-model organisms. The results reported herein indicate that Environmental Metalloprotemics seems to now be reaching a more mature stage, in which analytical techniques are now well established and can be routinely applied in environmental scenarios, benefitting researchers and allowing for further insights into this fascinating field.

1. Introduction

The very recently developed field of metallomics investigates metal and metalloid species present in cells or tissues, according to their identity, quantity and location. The term “metallome” was first coined in 2001, by Williams, who referred to it as elemental distribution and equilibrium concentrations of free metal ions, or, in other words, the free element content in a cellular compartment, cell, or organism (Williams, 2001). In 2004, the term “metallomics” was coined by Haraguchi to denote the entire ensemble of research fields related to metals of biological interest, including metal-bound biomolecules. This field considers that biomolecules that show the capability to bind to metals and metalloids constitute a considerable amount of all molecules involved in cellular metabolism and behaviour, and that identifying a metal cofactor of a protein can greatly assist its functional assignment and positioning in known cellular pathways (Haraguchi, 2004). In this context, the focus of metalloproteomics is the study of these metal-bound proteins, also known as metalloproteins, concentrating on elucidating their structural and functional characterization, identification and quantification in living organisms (Andreini et al., 2009; Mounicou et al., 2009; Shi and Chance, 2008, 2011). Thus, this field of knowledge is known as interdisciplinary, combining analytical, inorganic and biochemical studies, with the ultimate goal of elucidating metal uptake, trafficking, accumulation, actions and metabolism in biological systems and their connection to biomolecules (Ge and Sun, 2009; Sun and Chai, 2010).

Although the study of metal content in many different organisms and many different circumstances, both regarding metal exposure in the laboratory and environmental settings, has been conducted for many decades, these types of studies, although extremely valuable in an environmental setting, cannot be considered metalloproteomic studies, since they do not exactly take into account metal distribution or their

* Corresponding author.
E-mail address: rachel.hauser.davis@gmail.com (R.A. Hauser-Davis).

http://dx.doi.org/10.1016/j.ecoenv.2017.02.024
Received 27 December 2016; Received in revised form 14 February 2017; Accepted 16 February 2017
0147-6513/

link to biomolecules, only compare total metal burden between organs and state that there is more or less of a certain element in said tissue, focusing only on metals and their speciation into the environment without discussing the biological system or biochemical aspects. These studies are indeed useful in indicating metal detoxification routes and bioaccumulation (Hauser-Davis et al., 2012; Kehrig et al., 2016), as well as inter-site and trophic level comparisons (Guedes et al., 2014), in addition to showing value in risk assessment and public health concern evaluations (Cherfi et al., 2016; Khoei and Bastami, 2013; Reichmuth et al., 2010). However, the interactions between biomolecules and metals are not taken into account in studies of this type, and functional assignments and the elucidation of metalloprotein structural and functional characterization, identification and quantifications are also not evaluated.

With the advent of the metallomics field in the early 2000's, the first studies focusing on metalloproteins in an environmental context began to be published, with reviews appearing as early as 2003 and 2004 (Gómez-Ariza et al., 2004; Szpunar et al., 2003). However, these reviews focused mainly on the techniques available to conduct metallomic studies. The first real applications in Environmental Metalloproteomics appeared only in 2011, published by a group from Spain (Gonzalez-Fernandez et al., 2011). That study was conducted on free-living mice *Mus spretus* collected from polluted and non-polluted sites in Spain and analyzed by size-exclusion chromatography coupled with UV spectroscopy and ICP-MS (SEC-HPLC-ICP-MS) to investigate different molecular mass fractions from brain and liver. In addition, the study also evaluated the metalloproteomic effects of *in vivo* subcutaneous administration of Cd in the subcellular fractions by the same analytical technique. Previous studies by this group in 2008 had already investigated metal-binding molecules in the organs of *Mus musculus* by SEC-HPLC-ICP-MS, but in laboratory rats with no exposure to contaminants, in a first step to characterize the metalloproteome of these animals, which was unknown until then (González-Fernández et al., 2008). Following these papers, more studies regarding metalloproteins, especially in the search for biomarkers of environmental contamination, were published, beginning the trend for Environmental Metalloproteomics.

Some conventional biomarkers that happen to be metalloproteins, such as metallothionein and superoxide dismutase (SOD), have been studied for decades. However, the advent of the metallomics field allowed for integration of these responses in a broader manner. So, studies in this regard can be technically considered metalloproteomics studies if they take into account not only alterations in the amounts expressed in organisms but also considerations of the global role of all metals/metalloids in the biological system (Koppenaal and Hieftje, 2007). However, this has not been the norm, and only with the advent of the metalloproteome field is their full potential now being realized.

In *de facto* metalloproteomics studies, metal-binding proteins, both those in which the metal binds to proteins with high-affinity interactions and those in which the metal-protein interactions are of lower affinity, are increasingly being used successfully as environmental exposure biomarkers (López-Barea and Gómez-Ariza, 2006), where metalloproteins differ not only in their relative abundances, but in which metals are bound to them, and also the amount of each metal (Garcia et al., 2006). Metalloproteins linked to oxidative stress, for example have been indicated as relevant biomarkers because their expression and abundance relative are modified in different situations, and, with metallomic approaches, can be further investigated not only regarding concentrations, but also speciation and concerning different isoforms (Arruda et al., 2011). Recent studies on the characterization of metalloproteins from bioindicator organisms have led to further insights in this regard, although studies are still scarce and in their infancy, since many are conducted in the field (Garcia-Sevillano et al., 2012; Hauser-Davis et al., 2012; Lavradas et al., 2016), which is more challenging due to exposure to environmental mixtures and not only one contaminant at a time as is routinely performed in the laboratory.

However, the number of discoveries and studies in metalloproteomics is still much lower than in proteomics, due to several unique issues that must be considered. These include, mainly, the difficulty in preserving metalloproteins native states during analysis. According to Lothian et al. (2013), traditional proteomic approaches are mostly incompatible for the evaluation of metal–protein interactions, since conditions for protein analyses require denaturing conditions and enzymatic digestion. This in turn disrupts the comparatively weak ionic interactions that are present in most metalloprotein bonds. In addition, the very low concentrations of trace-elements in biological tissues (generally lower than $1\ mg\ g^{-1}$) and the complexity of the biological matrices are also of note (Gomez-Ariza et al., 2004). These aspects make the analysis of metals bound to biomolecules difficult and challenging. The continued development of novel analytical techniques has aided in this regard, leading to new possibilities in this field of research (Michalke, 2016; Prange and Profrock, 2005).

Bibliometric studies are now applied in the mapping of scientific fields of knowledge to obtain information about the current state of research in particular areas and allow researchers to identify and undertake new lines of research (De Battisti and Salini, 2013). This allows for new insights on academic production and collaboration networks between authors and research institutions, and also in defining main areas of research and presenting the impacts of scientific article publications on the scientific community (De Pinho et al., 2015; Scott, 2010; Vasconcellos, 2012). Important bibliometric indicators in the investigation of research capacity and productivity in a given area include number of scientific publications, amount of peer-reviewed scientific journal articles, number of total citations, and type of publications, among other variables (Kira et al., 2011; Tess et al., 2009).

In this context, this study aims to evaluate the evolution of Environmental Metalloproteomics in the last decades through bibliometric techniques, identifying variables that may aid researchers in this area to form collaborative networks with established scientists in this regard, identifying main authors, published articles, institutions, countries and established collaborations involved in academic research on this subject.

2. Methodology

The topic of Environmental Metalloproteomics in the present study included research conducted on both animals and humans environmentally (including occupationally) and laboratory exposed to relevant environmental contaminants. Analytical validation studies were only included if they also reported data on biological matrices exposed to contaminants in order to validate their methodology on actual samples. It is important to note that some papers are categorized into specifically analytical applications, which may have led to omissions in papers regarding the topic of Environmental Metalloproteomics, since authors may have only analyzed a small amount of real samples but mostly report advances or novelties regarding increased sensitivity of certain techniques. In addition, papers applying mass spectrometry for the identification of differentially expressed proteins in lab or field situations are plentiful, identifying many metal-binding proteins in an environmental context. However, these studies are mostly classified as proteomic studies, not focusing specifically on metalloproteins, aiming at identifying whichever protein, regardless of structure or function, and were, therefore, not included herein. Furthermore, studies on determinations of only metal content in organisms were also not included, since they show no link to biomolecules in the organism and are mostly used as health risks assessments regarding ingestion of contaminated food, such as shellfish and fish, among others.

Bibliometric techniques were applied to generate qualified information on Environmental Metalloproteomics from scientific publications indexed at Thomson Reuters' Web of Science Core Collection (WoS). Encompassing a timespan from 1945 to 2016, the search was carried

Table 1
Bibliometric search strategy and results applied in the present study.

Subject	Environmental Metalloproteomics
Scientific database	Thomson Reuters' Web of Science Core Collection / Advanced search mode
Tag	Topic (TS = Title, Abstract and Keywords)
Descriptors and Boolean operators	((metallomic* OR metallome* OR metalloproteomic* OR metalloprotein*) AND (ecotoxicolog* OR toxicolog* OR pollution OR contamination* OR metal* OR biomarker*))
Language	English
Document types	Article OR Proceedings Paper
Research Areas	Plant Sciences OR Marine Freshwater Biology OR Chemistry OR Toxicology OR Environmental Sciences Ecology OR Fisheries OR Water Resources
Web of Science Categories	Environmental Sciences OR Fisheries OR Chemistry Analytical OR Chemistry Applied OR Marine Freshwater Biology OR Plant Sciences OR Ecology OR Toxicology OR Water Resources
Indexes	Science Citation Index Expanded (SCI-EXPANDED)
Timespan	All years (1945-September 2016)
Results	2366 records
Number of records after manual screening using WoS	66 records
Number of records imported to VantagePoint	66 records

out on September 2016 and retrieved 2366 records. In order to select only works directly related to the article's research interests, the records were manually screening by reading their titles and abstracts. After this methodological procedure, a final list of 66 records on Environmental Metalloproteomics was obtained. Table 1 depicts the search strategy and the results applied herein.

Retrieved data (n = 66) were imported from WoS as raw data files in plain text format to the data/text mining software VantagePoint 9.0, where procedures were applied to (a) remove possible duplicated records, using the ISI Unique Article Identifier (no duplicate records found) and (b) clean and standardize the analysis fields Author Affiliations (Organization and City and Country) and Cited References, using the List Cleanup tool in addition to manual cleaning. Data regarding scientific publication over time and the rankings of journals, countries, research areas, organizations and cited references were exported to Microsoft Excel for graphical visualization. Finally, the networks of countries, research areas and organizations were generated using the VantagePoint's Aduna cluster map tool.

3. Results and discussion

Fig. 1 displays the annual evolution of scientific publications from 1990, the first recorded occurrence of a specific Environmental Metalloproteomics publication, until September 2016, with four published articles. The highest amount of publications occurred in 2014, with 12 publications. Taken together, the data point to a growing trend

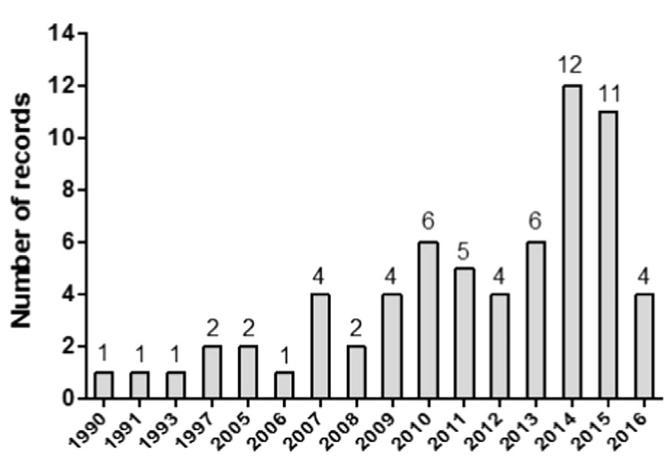

Fig. 1. Number of publications in Environmental Metalloproteomics between 1990 and 2016 (September).

of publications over time, reflecting the interest of the scientific community in Environmental Metalloproteomics, although the number of publications is still lower when compared to Clinical Metalloproteomics, for example.

Several scientific journals published the articles found in the bibliometric evaluation conducted herein. The top journals with over 2 records of scientific papers published on this topic are displayed in Fig. 2. The most noteworthy journals regarding number of publications were, not surprisingly, *Metallomics*, with 8 publications, followed by *Analytical and Bioanalytical Chemistry* and *Journal of Analytical Atomic Spectrometry*, both with 4 publications. Together, these journals correspond to 24.2% of total publications.

All impact factors are from 2015. Of the journals that make up the observed ranking, *Talanta* has the highest impact factor (4.035), followed by *Journal of Proteomics* (3.867), *Chemosphere* (3.698), *Aquatic Toxicology* and *Metallomics* (3.540). The other journals showed impact factors ranging from 1.096 to approximately 3.5.

It is interesting, however, to note that, according to its web-site, *Talanta*'s scope deals in "all branches of pure and applied analytical chemistry" and not specifically with the subject of metallomics. *Journal*

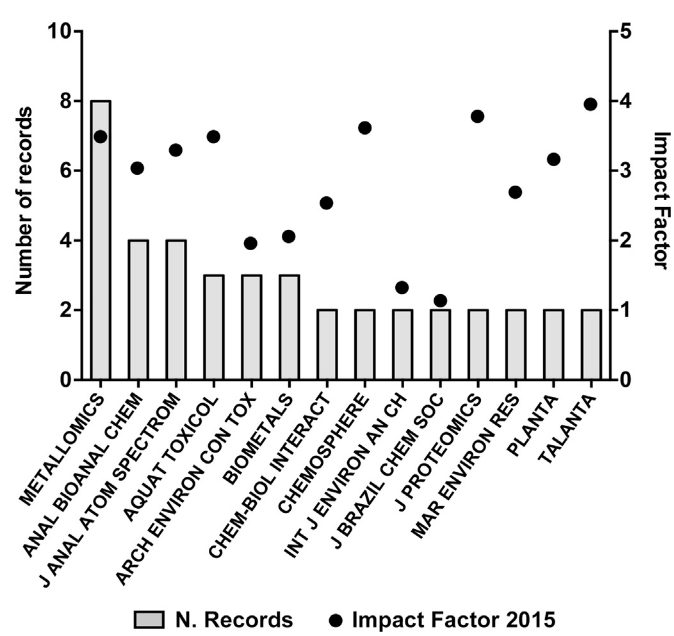

Fig. 2. Top journals with over 2 records of scientific articles on Environmental Metalloproteomics, with their respective impact factors (2015) (•).

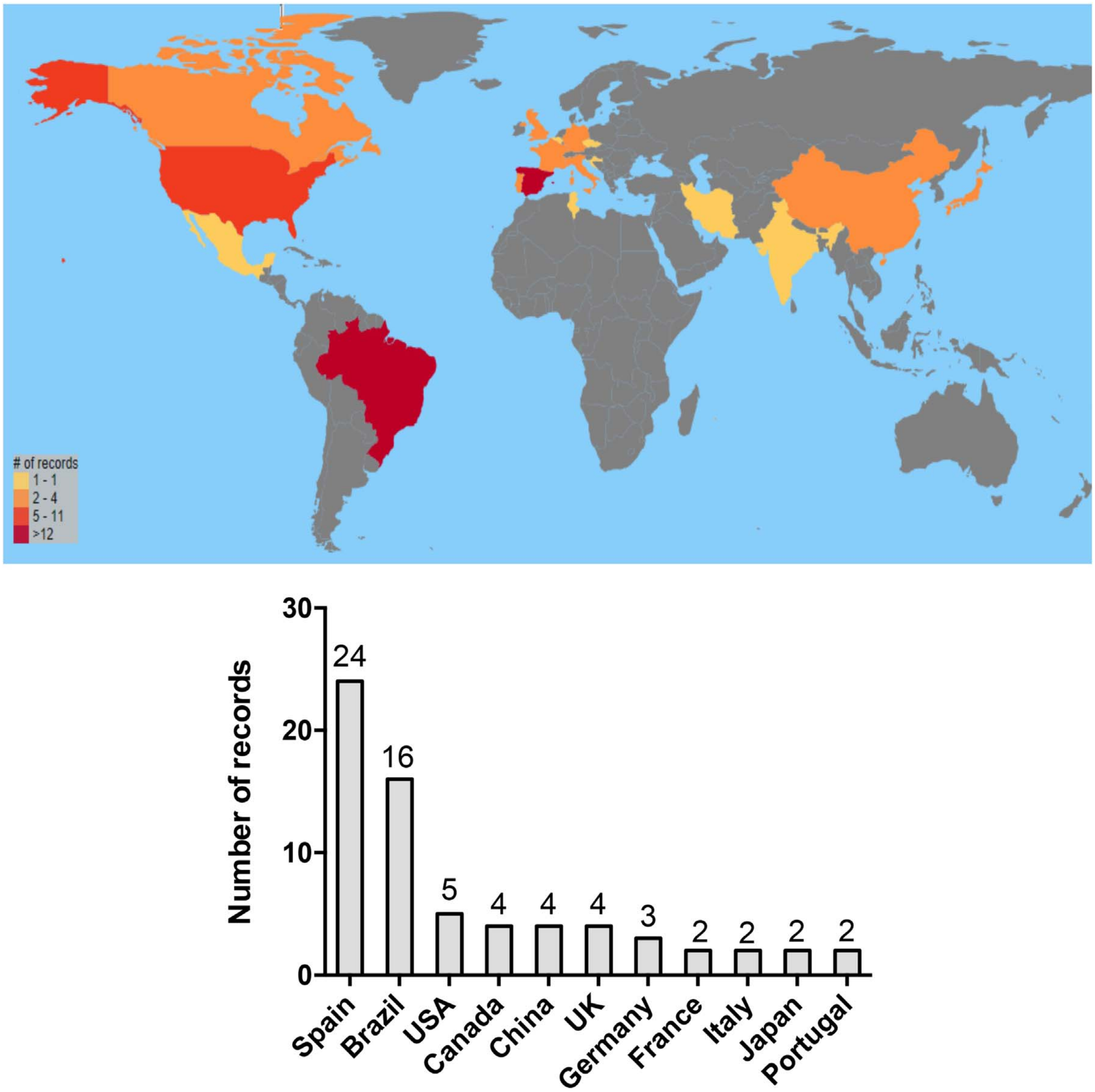

Fig. 3. Number of publications in Environmental Metalloproteomics per country.

of Proteomics, on the other hand, is more specific in this regard, although citing only proteomics in general, which would include metalloproteomics studies. Of the top publishing journals, the only one dealing specifically with metalloproteins, as a subarea of metallomic analyses is, in fact, *Metallomics*. Nevertheless, other journals such as *Journal of Analytical Atomic Spectrometry* and *Analytical and Bioanalytical Chemistry* are journals with tradition in novel analytical research in instrumentation, method development, and applications, including mass spectrometry and atomic spectroscopy, chromatographic separations and hyphenated techniques within all fields of application, which makes them adequate vehicles for publications on metalloproteomic studies and applications.

It also important to note than many journals are only recently beginning to accept papers on "omic" technologies and their applications, since these were usually viewed as specific to "omic" journals, such as *Journal of Proteomics*. Certain journals of specific areas, such as, for example, *Marine Pollution Bulletin* and *Aquatic Toxicology*, which focus on marine research and ecotoxicology, now accept papers applying 'omic technologies if they offer 'mechanistic insights into the toxic effects of environmental pollutants on organisms, such as adaptations to environmental perturbations, including the evolution of toxicant responses, biochemical and physiological responses, interactions between pollutants and functional responses, and interactions between natural and toxicant-induced environmental changes', which also take into account metalloproteomic approaches and discoveries.

Fig. 3 displays the number of publications in Environmental Metalloproteomics per country, in which Spain was ranked first, with 24 publications, probably due to being the first country to delve in Environmental Metalloproteomics, followed by Brazil, with 16 publications, showing increased production in 2015, while other countries ranged from 2 to 5 publications. Only those with 2 or more published records are displayed. The major regions that have published papers in Environmental Metalloproteomics are North America, South America (Brazil), Europe and Asia, with some countries in the Middle East also participating.

Separating data per year, the countries that published the most number of scientific papers related to Environmental Metalloproteomics between 1990 and 2016 (September) are displayed in Fig. 4. Greater amounts of publication clusters are clearly observed from the late 2000's onwards. This is certainly related to the increasing technological advances in the area, such as the development of techniques combining atomic spectroscopy and biochemical or proteo-

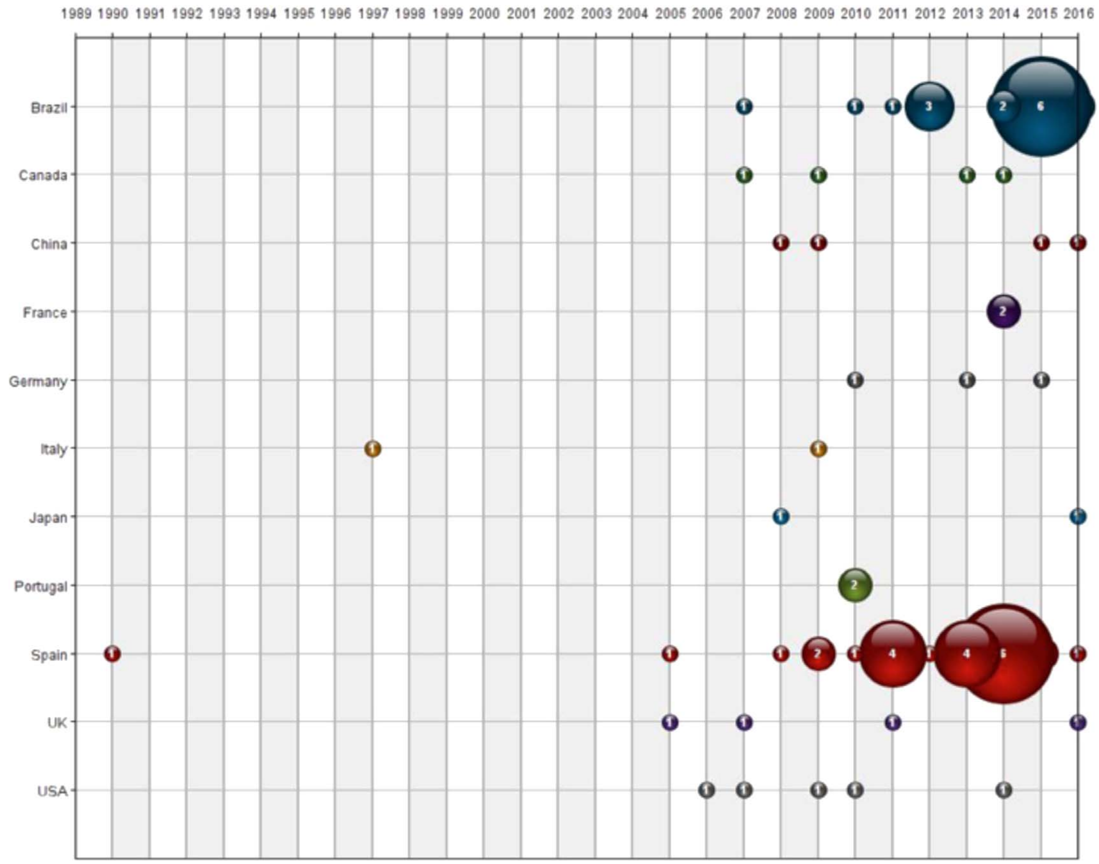

Fig. 4. Countries that published the most number of scientific papers related to Environmental Metalloproteomics between 1990 and 2016 (September).

mic techniques such as gel electrophoresis, capillary chromatography or multidimensional nanoflows, as well as the development of strategies for the additional elemental applications and techniques in molecule detection, such as mass spectrometry approaches like inductively coupled plasma (ICP-MS) and electrospray (ESI-MS) (Prange and Profrock, 2005).

Not surprisingly, the data displayed in Fig. 5 indicates major collaborations between European countries, extending towards North and Central America, as well as collaborations between Asian countries. The other listed countries show no interconnected collaborative networks in Environmental Metalloproteomics, with isolated networks only.

The cluster map of the most frequently publishing organizations (Fig. 6) indicates two main collaborative networks considering the number of papers published in collaboration, one composed only of Brazilian research centres, while the other is composed of organizations from Spain, Portugal and Canada. In the Brazilian cluster, the State University of Campinas published 9 papers in total, three published in collaboration with other institutes, namely with UNIRIO, UNESP and USP, of 1 paper each. Huelva, on the other hand, shows 18 published papers in total, with 5 published in collaboration with the University of Córdoba and 1 with the University of Calgary.

These results suggest the need for the other clustered institutes to begin collaborative efforts with other countries to further investigations in Environmental Metalloproteomics, since this type of action always creates further information exchange and developments in the chosen field of knowledge and the success of knowledge management initiatives depends on knowledge sharing (Wang and Noe, 2010). As currently stands, the research interactions in this field are still country- and organization-specific.

Brazil shows publications from 6 different organizations, while Spain, the top publishing country, shows three publishing organizations: Huelva University (18 records), followed by the Universities of Córdoba (6) and Barcelona (2). This suggests that more Brazilian institutions are delving in Environmental Metalloproteomics compared to other countries with higher number of publications, although it is important to note that the present study only reports institutions that show 2 or more publications in this area, and that there might be other institutions that present ongoing research in the field that were not observed when refining the results discussed herein. However, as can be noted by these results, the field of Environmental Metalloproteomics is still in its infancy and much remains to be investigated.

It is clear that the field of Environmental Metalloproteomics is interdisciplinary and shows applications in several areas of research and knowledge, since research in this topic is often indexed or occurs at the same time with a variety of research areas. The areas of research with the most records are Biochemistry & Molecular Biology (24 records), Chemistry (20 records), Environmental Sciences and Ecology (19) and Toxicology (14), followed by other areas with 6 or less publications (Table 2). The fields of Biochemistry & Molecular Biology, Environmental Sciences and Ecology and Toxicology report mostly applied metalloproteomics studies, aiming at investigating, characterizing and elucidating the metalloproteome in several contexts, while the field of Chemistry, on the other hand, may also include the development of novel metallomic techniques, and, in fact, reports many studies in this context.

The cluster map of research areas displayed in Fig. 7 clearly indicates that the major interconnected areas are Environmental Sciences, Biochemistry & Molecular Biology and Chemistry, while specific areas with less amounts of publications are likely to apply metalloproteomic techniques to specific problems, such as in Agricultural Sciences, for example, which are not as likely to be connected to

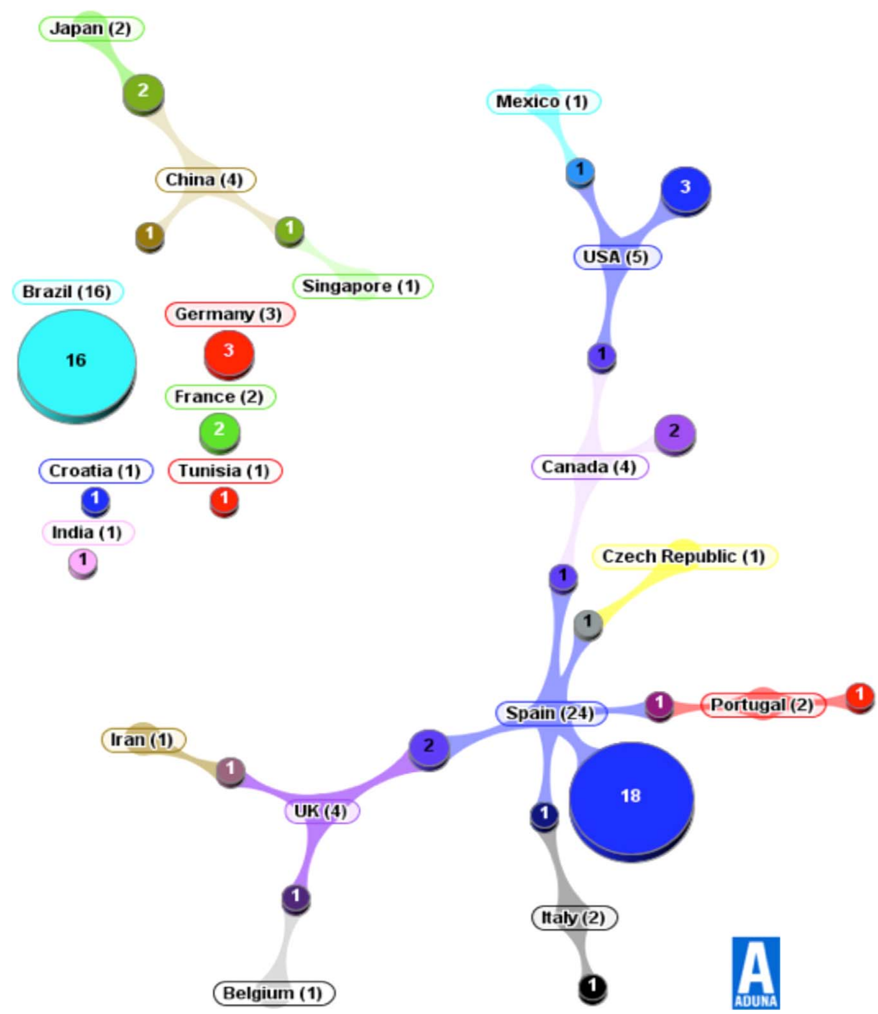

Fig. 5. Collaborative networks between countries that have published over two records in the field of Environmental Metalloproteomics.

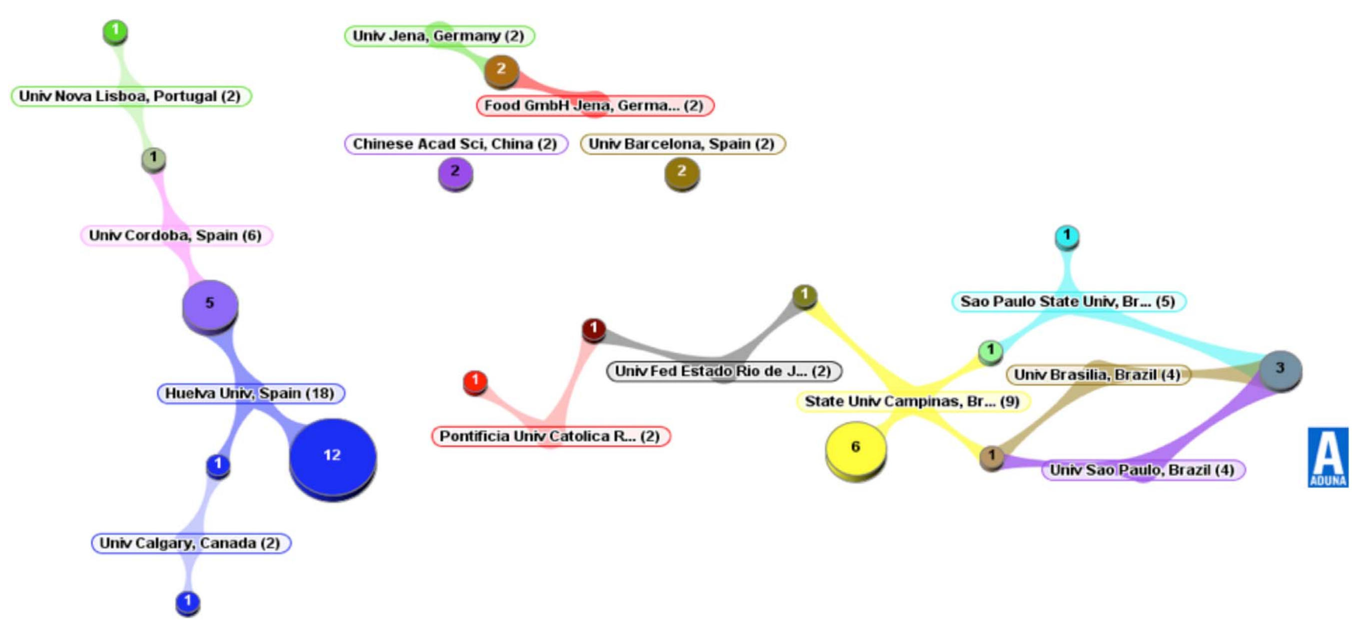

Fig. 6. Cluster map of organizations that have published over two records in the field of Environmental Metalloproteomics.

other, broader, areas.

The fields of Chemistry, Biochemistry & Molecular Biology, Toxicology and Environmental Sciences are at the core of the research area clusters that have published on Environmental Metalloproteomics, interconnected with other specific areas such as Marine & Freshwater Biology and Plant Sciences, for example. It is interesting to note that

Table 2
Ranking of research areas that have published on Environmental Metalloproteomics (2 > records).

Research Field	Number of records
Biochemistry and molecular biology	24
Chemistry	20
Environmental science & ecology	19
Toxicology	14
Marine & freshwater biology	6
Plant sciences	5
Spectroscopy	4
Agriculture	3
Endocrinology and metabolism	2
Pharmacology & pharmacy	2
Public, environmental & occupational health	2

Fisheries shows one record of Environmental Metalloproteomics only, not interconnected to other research areas, although this is most likely caused by too specific index words, since it is clear that this area is almost certainly linked to the area of Marine & Freshwater Biology. Thus, it is important to choose adequate key words in order for the paper to be indexed in as broad an area as possible, however still maintaining specificity regarding the area of research.

Table 3 lists the ranking of the first authors that were most cited by the 66 papers we selected on Environmental Metalloproteomics, with their addressed topics. These articles and authors can, thus, be considered important for the construction of knowledge in the field of Environmental Metalloproteomics, although some are very basic. These include the 3rd paper, describing the classic protein quantification method by Bradford and the 23rd paper, citing the classic electrophoresis gel method. The fact that these papers were cited by the 66 studies we selected on Environmental Metalloproteomics indicate their importance to some degree in this field, albeit with regard to prior steps for sample preparation. The 19th paper, on a proteomics study in soy, was cited by the same group regarding sample preparation methods.

The references displayed in Table 3 indicate that, although many reviews are available with regard to the field of metalloproteomics, most deal mainly with the analytical aspect of this field, discussing techniques and recent advances to the field, cited by the papers discussed in this study. One can also note that, although purely "applied" studies to Environmental Metalloproteomics are available, all deal with mice, an organism with its entire genome already sequenced, making it easier to identify metalloproteins in cases of altered expression, for example, when comparing two or more differentially contaminated areas. This has been noted as a limitation of proteomic techniques, that they have, in fact, benefitted, primarily, research on well-characterized species, such as humans, mice and yeast, which, unfortunately, may be inappropriate from and environmental and ecotoxicological point of view (Hogstrand et al., 2002), which is also true regarding metalloproteomic techniques. Thus, the recent advances in genomic, proteomic and metallomic areas, have allowed for further applications in Environmental Metalloproteomics in non-model organisms, as the number of increasing publications verified and discussed herein in this context indicate, as well as in complex field studies.

4. Conclusions

The use of bibliometric techniques allowed for evaluation of number of publications in this field regarding the identification of main authors, published articles, institutions, countries and collaborative networks involved in academic research on this subject. Results indicate that, although the number of Environmental Metalloproteomics publications is still very low compared to other metallomic areas, publications have increased rapidly in number and complexity over the last years, including applications of Environmental Metalloproteomics in non-model organisms. This is clearly a result of increasing technological advances in the area, although research interactions in this field are still country- and organization-specific. Despite this, the results reported herein indicate that the field of Environmental Metalloproteomics seems to be reaching a more mature stage, in which analytical techniques are now well established and can be routinely applied in environmental scenarios, benefitting researchers and allowing for further insights into this fascinating field.

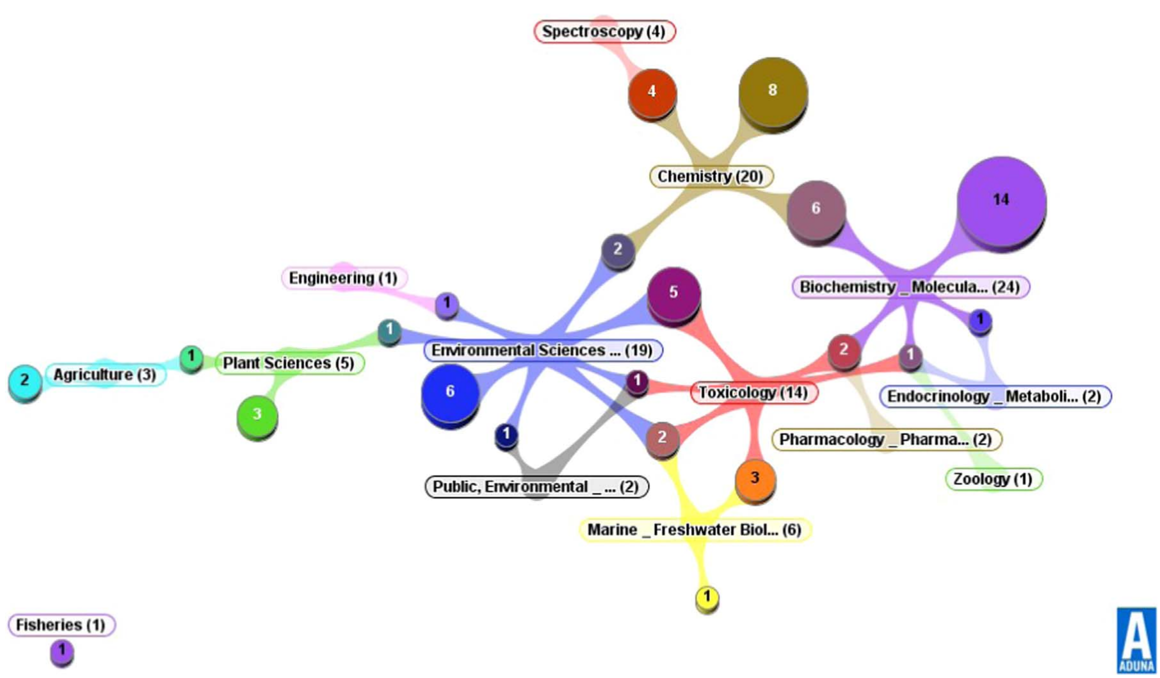

Fig. 7. Cluster map of research areas that have published on Environmental Metalloproteomics.

Table 3
Most cited references with over 5 records by the base papers obtained in the bibliometric analysis in the present study.

Citation records	Cited reference	Main focus
18	Gomez-Ariza JL, 2004, ANAL CHIM ACTA, V524, P15, DOI 10.1016/j.aca.2004.01.061	Applications of mass spectrometry techniques for metalloprotein characterization
13	Bettmer J, 2009, J PROTEOMICS, V72, P989, DOI 10.1016/j.jprot.2009.05.003	The emerging role of ICP-MS in proteomic analysis
12	BRADFORD MM, 1976, ANAL BIOCHEM, V72, P248, DOI 10.1006/abio.1976.9999	Protein quantitation method description
12	Garcia-Sevillano MA, 2012, ANAL BIOANAL CHEM, V404, P1967, DOI 10.1007/s00216–012–6274–2	Application of SEC-ICP-MS to environmental contamination assessments (mice)
12	Mounicou S, 2009, CHEM SOC REV, V38, P1119, DOI 10.1039/b713633c	A general review on some techniques for metallomic analysis
11	Szpunar J, 2004, ANAL BIOANAL CHEM, V378, P54, DOI 10.1007/s00216–003–2333-z	A general review on some techniques for metallomic analysis
9	Garcia JS, 2006, TALANTA, V69, P1, DOI 10.1016/j.talanta.2005.08.041	A general review on some techniques for metallomic analysis
9	Gonzalez-Fernandez M, 2011, J ANAL ATOM SPECTROM, V26, P141, DOI 10.1039/c0ja00127a	Application of SEC-ICP-MS to environmental contamination assessments (mice)
9	Montes-Nieto R, 2007, PROTEOMICS, V7, P4376, DOI 10.1002/pmic.200700409	Application of proteomics to environmental contamination assessments (mice)
9	Szpunar J, 2005, ANALYST, V130, P442, DOI 10.1039/b418265k	A general review on some techniques for metallomic analysis
8	Bonilla-Valverde D, 2004, TOXICOLOGY, V197, P123, DOI 10.1016/j.tox.2003.12.010	Application of biochemical biomarkers in environmental contamination assessments
8	Ruiz-Laguna J, 2006, ENVIRON SCI TECHNOL, V40, P3646, DOI 10.1021/es0600056e	Metal biomonitoring using absolute transcript expression signatures
7	Garcia-Sevillano MA, 2013, BIOMETALS, V26, P651, DOI 10.1007/s10534–013–9642–2	Application of SEC-ICP-MS to environmental contamination assessments (mice)
7	Gonzalez-Fernandez M, 2008, ANAL BIOANAL CHEM, V390, P17, DOI 10.1007/s00216–007–1690–4	Application of SEC-ICP-MS in the investigation of the mouse metalloproteome (laboratory mice)
6	Haraguchi H, 2004, J ANAL ATOM SPECTROM, V19, P5, DOI 10.1039/b308213j	Proposal of the metallomics field as a new scientific field in symbiosis with genomics and proteomics
6	Lopez-Barea J, 2006, PROTEOMICS, V6, pS51, DOI 10.1002/pmic.200500374	A review on the emerging field of environmental metalloproteomics and proteomics
6	Mataveli LRV, 2010, METALLOMICS, V2, P800, DOI 10.1039/c0mt00040j	Application of SEC-ICP-MS for the comparison of transgenic and non-transgenic soybean seeds
6	Sanz-Medel A, 2005, ANAL BIOANAL CHEM, V381, P1, DOI 10.1007/s00216–004–2907–4	A general review on some techniques for metallomic analysis
5	Brandao AR, 2010, J PROTEOMICS, V73, P1433, DOI 10.1016/j.jprot.2010.01.009	Proteomic applications for the comparison of transgenic and non-transgenic soybean seeds
5	Garcia-Sevillano MA, 2013, METALLOMICS, V5, P1644, DOI 10.1039/c3mt00186e	Integrated "omics" approaches to investigate laboratory metal exposure in mice
5	Grimalt JO, 1999, SCI TOTAL ENVIRON, V242, P3, DOI 10.1016/S0048–9697(99)00372–1	Description of an environmental accident in Spain - spillage of acidic waters and mud containing toxic metals
5	HAMER DH, 1986, ANNU REV BIOCHEM, V55, P913, DOI 10.1146/annurev.biochem.55.1.913	Review on metallothionein
5	LAEMMLI UK, 1970, NATURE, V227, P680, DOI 10.1038/227680a0	Cleavage of structural proteins during the assembly of the head of bacteriophage T4
5	Papp LV, 2007, ANTIOXID REDOX SIGN, V9, P775, DOI 10.1089/ars.2007.1528	A review on selenium and selenoproteins and their role in human health.
5	ROESIJADI G, 1992, AQUAT TOXICOL, V22, P81, DOI 10.1016/0166–445X(92)90026-J	A review on metallothioneins in metal regulation and toxicity in aquatic animals.
5	Romero-Ruiz A, 2006, PROTEOMICS, V6, pS245, DOI 10.1002/pmic.200500444	Application of proteomics to assess pollutant response in clams
5	Santos FA, 2011, MICROCHIM ACTA, V173, P43, DOI 10.1007/s00604–010–0522-y	Proteomic and metalloproteomic techniques for the study of Nile tilapia plasma
5	Sussulini A, 2007, MICROCHIM ACTA, V158, P173, DOI 10.1007/s00604–006–0678–7	Evaluation of soybean seed protein extraction focusing on metalloprotein analysis
5	Zalups RK, 2000, J PHARMACOL EXP THER, V295, P74	Transcription of metallothionein genes in response to treatment with inorganic mercury in rats

Acknowledgements

The authors would like to thank the Vice-Presidency for Research and Reference Laboratories and the Center of Strategic Studies at the Fundação Oswaldo Cruz for institutional support.

References

Andreini, C., et al., 2009. Metalloproteomes: a bioinformatic approach. Acc. Chem. Res. 42, 1471–1479.
Arruda, S.C.C., et al., 2011. Two-dimensional difference gel electrophoresis applied for analytical proteomics: fundamentals and applications to the study of plant proteomics. Analyst 136, 4119–4126.
Cherfi, A., et al., 2016. Risk assessment of heavy metals via consumption of vegetables collected from different supermarkets in La Rochelle, France. Environ. Monit. Assess. 188, 136.
De Battisti, F., Salini, S., 2013. Robust analysis of bibliometric data. Stat. Methods Appl. 22, 269–283.
De Pinho, L.A., et al., 2015. Mapping knowledge produced on problem-based learning between 1945 and 2014: a bibliometric analysis. Creat. Educ. 6, 576–584.
Garcia, J.S., et al., 2006. Metal contamination effects on sunflower (Helianthus annuus L.) growth and protein expression in leaves during development. J. Agric. Food Chem. 54, 8623–8630.
Garcia-Sevillano, M.A., et al., 2012. Biological response of free-living mouse Mus spretus from Doana National Park under environmental stress based on assessment of metal-binding biomolecules by SEC-ICP-MS. Anal. Bioanal. Chem. 404, 1967–1981.
Ge, R.G., Sun, H.Z., 2009. Metallomics: an integrated biometal science. Sci. China Ser. B-Chem. 52, 2055–2070.
Gomez-Ariza, J.L., et al., 2004. Use of mass spectrometry techniques for the characterization of metal bound to proteins (metallomics) in biological systems. Anal. Chim. Acta 524, 15–22.
Gómez-Ariza, J.L., et al., 2004. Use of mass spectrometry techniques for the characterization of metal bound to proteins (metallomics) in biological systems. Anal.

Chim. Acta 524, 15–22.
González-Fernández, M., et al., 2008. Metal-binding molecules in the organs of Mus musculus by size-exclusion chromatography coupled with UV spectroscopy and ICP-MS. Anal. Bioanal. Chem. 390, 17–28.
Gonzalez-Fernandez, M., et al., 2011. Size characterization of metal species in liver and brain from free-living (Mus spretus) and laboratory (*Mus musculus*) mice by SEC-ICP-MS: application to environmental contamination assessment. J. Anal. At. Spectrosc. 26.
Guedes, T.S., et al., 2014. Mercury and selenium in tropical marine plankton and their trophic successors. Chemosphere 111, 32–39.
Haraguchi, H., 2004. Metallomics as integrated biometal science. J. Anal. At. Spectrosc. 19, 5–14.
Hauser-Davis, R.A., et al., 2012. A novel report of metallothioneins in fish bile: SDS-PAGE analysis, spectrophotometry quantification and metal speciation characterization by liquid chromatography coupled to ICP-MS. Aquat. Toxicol. 116–117, 54–60.
Hogstrand, C., et al., 2002. Application of genomics and proteomics for study of the integrated response to zinc exposure in a non-model fish species, the rainbow trout. Comp. Biochem. Physiol. B-Biochem. Mol. Biol. 133, 523–535.
Kehrig, H.A., et al., 2016. mercury species, selenium, metallothioneins and glutathione in two dolphins from the southeastern Brazilian coast: mercury detoxification and physiological differences in diving capacity. Environ. Pollut. 213, 785–792.
Khoei, J.K., Bastami, A.A., 2013. Mercury concentrations in tissues of blue swimming crab Portunus pelagicus and sediments from Khark Island. World Appl. Sci. J. 21, 1391–1397.
Kira, A., et al., 2011. Publications as an indicator of increased tobacco control research productivity (quantity and quality) in New Zealand. Nicotine Tob. Res. 13, 474–478.
Koppenaal, D.W., Hieftje, G.M., 2007. Metallomics—the future of atomic spectroscopy? J. Anal. At. Spectrosc. 22.
Lavradas, R.T., et al., 2016. Investigation of thermostable metalloproteins in Perna perna mussels from differentially contaminated areas in Southeastern Brazil by bioanalytical techniques. J. Trace Elem. Med. Biol. 34, 70–78.
López-Barea, J., Gómez-Ariza, J.L., 2006. Environmental proteomics and metallomics. Proteomics 6, S51–S62.
Lothian, A., et al., 2013. Metalloproteomics: principles, challenges and applications to neurodegeneration. Front. Aging Neurosci. 5, 1–7.
Michalke, B., 2016. Metallomics: Analytical Techniques and Speciation Methods. Wiley.
Mounicou, S., et al., 2009. Metallomics: the concept and methodology. Chem. Soc. Rev. 38, 1119–1138.
Prange, A., Profrock, D., 2005. Application of CE-ICP-MS and CE-ESI-MS in metalloproteomics: challenges, developments, and limitations. Anal. Bioanal. Chem. 383, 372–388.
Reichmuth, J.M., et al., 2010. Bioaccumulation and depuration of metals in blue crabs (*Callinectes sapidus* Rathbun) from a contaminated and clean estuary. Environ. Pollut. 158, 361–368.
Scott, S.D.E.A., 2010. Mapping The Knowledge Utilization Field in Nursing from 1945 to 2004: A Bibliometric Analysis Worldviews on Evidence-Based Nursing. 7.
Shi, W., Chance, M.R., 2008. Metallomics and metalloproteomics. Cell. Mol. Life Sci. 65, 3040–3048.
Shi, W.X., Chance, M.R., 2011. Metalloproteomics: forward and reverse approaches in metalloprotein structural and functional characterization. Curr. Opin. Chem. Biol. 15, 144–148.
Sun, H., Chai, Z.F., 2010. Metallomics: an integrated science for metals in biology and medicine. Annu. Rep. Prog. Chem. Sect. A Inorg. Chem. 106, 20–38.
Szpunar, J., et al., 2003. Hyphenated techniques for elemental speciation in biological systems. Appl. Spectrosc. 57, 102A.
Tess, B.H., et al., 2009. Assessing the scientific research productivity of a Brazilian healthcare institution: a case study at the heart Institute of Sao Paulo, Brazil. Clinics 64, 571–576.
Vasconcellos, A.G.M., C.M., 2012. Enabling policy planning and innovation management through Patent Information and Co-Autorship network analyses: a study of tuberculosis in Brazil. Plos One 7.
Wang, S., Noe, R.A., 2010. Knowledge sharing: a review and directions for future research. Hum. Resour. Manag. Rev. 20, 115–131.
Williams, R.J.P., 2001. Chemical selection of elements by cells. Coord. Chem. Rev. 216–217, 583–595.