



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



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ARTICLE INFO

Keywords:

Environmental Metalloproteomics
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 Metalloproteomics is still very low compared to other metallomic areas. In this context, the evolution of Environmental Metalloproteomics 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 Metalloproteomics, 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 Metalloproteomics in non-model organisms. The results reported herein indicate that Environmental Metalloproteomics 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

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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 (Koppelaar 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 (García 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 (García-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

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