MINIREVIEW

Archaeal transformation of metals in the environment

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Abstract

We are becoming increasingly aware of the role played by archaea in the biogeochemical cycling of the elements. Metabolism of metals is linked to fundamental metabolic functions, including nitrogen fixation, energy production, and cellular processes based on oxidoreductions. Comparative genomic analyses have shown that genes for metabolism, resistance, and detoxification of metals are widespread throughout the archaeal domain. Archaea share with other organisms strategies allowing them to utilize essential metals and maintain metal ions within a physiological range, although comparative proteomics show, in a few cases, preferences for specific genetic traits related to metals. A more in-depth understanding of the physiology of acidophilic archaea might lead to the development of new strategies for the bioremediation of metal-polluted sites and other applications, such as biomining.

Introduction

The cycling of metallic elements on Earth is mediated by geological and biological processes, and microorganisms, including archaea, have a considerable impact on the latter. Since Woese's demonstration of the existence of a third domain of life based on clustering of 16S rRNA gene sequences (Woese *et al.*, 1990), archaea were thought to colonize mostly, if not exclusively, extreme environments. Although archaea are actually prevalent in environments characterized by extremes of salinity, temperature, pH, or pressure, in the past years, we have become more and more aware of their widespread presence in all types of environments due to new methods of analysis, improved techniques of cultivation, and advanced sequencing technologies, which have led to the discovery of novel archaeal species and new niches colonized by these microorganisms. (DeLong *et al.*, 1994; Murray *et al.*, 1998; Galand *et al.*, 2009a; Manganelli *et al.*, 2009) As a consequence of this shifted focus toward their study and enhanced interest in their activities, archaea have been discovered to play important roles in the biogeochemical cycles of carbon and nitrogen (Konneke *et al.*, 2005; Hallam *et al.*, 2006). In the past few years, it has been proposed that archaea are the largest group in marine deep subsurface sediments (Biddle *et al.*, 2006, 2008; Teske & Sorensen, 2008), and although some data disagree with this view (Schippers *et al.*, 2005; Fry *et al.*, 2008), the prevalence of archaea in marine subsurface sediments has been supported by metagenomic data (Biddle *et al.*, 2008), which should better reflect the composition of microbial communities. Marine subsurface sediments are estimated to host 60–90% of the Earth's prokaryotes (Whitman *et al.*, 1998). If these approximations are correct, the impact of archaea on the cycling of elements becomes even more relevant. Furthermore, in diverse environments, such as terrestrial and aquatic mesophilic environments (Galand *et al.*, 2009b; van der Wielen *et al.*, 2009), hydrothermal vents (Wang *et al.*, 2009), and hot springs (Zhang *et al.*, 2008a), archaea have only recently been observed to play a major role in the nitrogen cycle through their activity of ammonia oxidation (Zhang *et al.*, 2008a), carried out by metal-dependent ammonia monooxygenases.

Many prokaryotes, including archaea, are capable of transforming the oxidation state of metals in processes leading to either their solubilization or biomineralization. Although these phenomena have been observed in the environment and studied in cultures, there is still much to be learned about the genetic determinants of these metal transformations. This review will attempt to provide the basis for investigations that aim to correlate the cycling of

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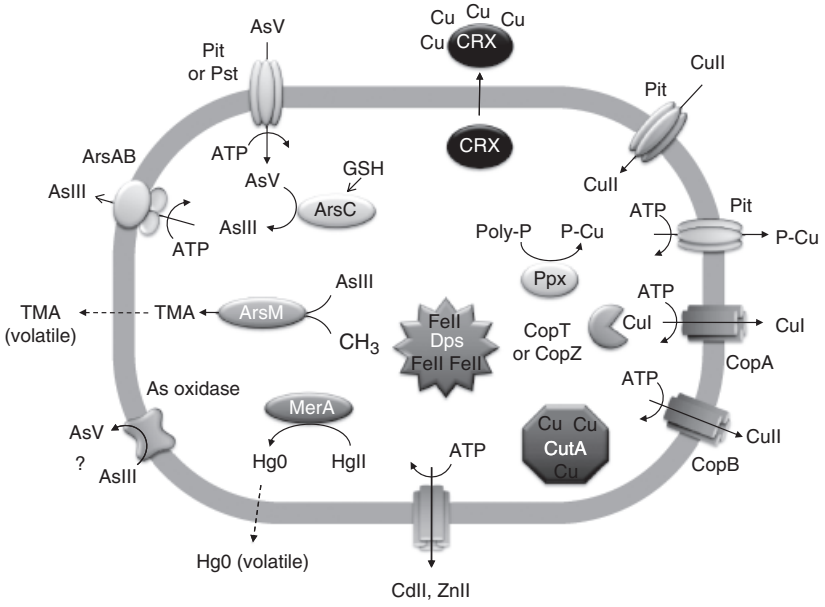

Fig. 1. Mechanisms of metal resistance and detoxification taking place in archaea. Microorganisms where these processes were demonstrated to occur are listed in Table 1. The question mark by the arsenite oxidation indicates that the biochemical details of the process are not known, but the activity was found to be associated with the membrane. As for the arsenate reduction, the entire set of enzymes involved are represented in the diagram, although many archaea do not possess an ArsC homolog.

metals in the environment with the activity of archaea. Hence, the distribution of metal-dependent enzymes and genetic traits for the utilization of metals in archaea are reviewed, and current knowledge of archaeal 'metallomes' as a whole is assessed. The following two sections summarize specific metal requirements in metabolic processes, such as respiration, energy production, and other processes based on oxidoreductions, the mechanisms of metal resistance evolved by archaea (Fig. 1), and how knowledge of these processes can support our understanding of metal transformations in the environment. The final section surveys the archaeal species that, due to their ability to carry out specific metal transformation, have applications or have potential application in bioremediation and biomining.

Archaeal metallomes

A metallome or metalloproteome is constituted by the metalloproteins encoded by the genome of an organism, that is, all those proteins and enzymes requiring a metal cofactor for structural stability or to carry out their function. Additionally, the enzymes and proteins required for the utilization and metabolism of a certain metal, when possible, are considered in this survey of archaeal metallomes. The availability of archaeal genomes and databases of structural domains and motifs, including PDB (http://www.rcsb.org/pdb/home/home.do) and Pfam (Finn *et al.*, 2008), combined with the development of bioinformatic tools, has enabled the analyses of the distribution of metal-binding proteins in archaea, and bioinformatic methods designed to identify metal-binding sites were reviewed by Andreini *et al.* (2009). While traditional genetic and biochemical methods are fundamental to the functional characterization of metal-requiring enzymes and proteins, more recently, global studies of the metalloproteome of an organism have allowed the discovery of new proteins with metal-binding properties, and comparisons among metalloproteomes may represent a new way to formulate hypotheses on the evolutionary history of the species under study.

Highly represented metal-binding domains (MBDs)

Dupont and colleagues, through the analysis of proteomes of the three domains of life, have determined the frequencies of Fe-, Mn-, Co-, and Zn-binding structural domains, which were the most frequent MBDs, while Cu-, Mo-, and Ni-binding domains were found to represent $< 0.3\%$ of the average proteome, considering all the archaeal, bacterial, and eukaryotic species included in the study (Dupont *et al.*, 2006). In archaea, as in the other two kingdoms, the presence of MBDs was correlated to the proteome size. However, the relative size of each metallome varied between kingdoms. Particularly interesting was the discovery that archaea, as well as bacteria, had a lower abundance of Zn-binding domains compared with the eukaryotic proteomes. However, archaea shared with eukaryotes a substantial fraction of the Zn-binding domains belonging to the so-called 'small protein' class, which included Zn finger motifs and RING (Really Interesting New Gene) domains. As for the iron-binding sites, archaea, together with bacteria, were shown to be characterized by a higher fraction of Fe–S-containing proteins than eukaryotes, which instead contain a higher proportion of heme proteins (Andreini

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et al., 2006; Dupont *et al.*, 2006). The fact that Fe-binding domains in archaea and bacteria tended to be functionally different from the ones in eukaryotes was also interpreted as further evidence indicating that prokaryotes and eukaryotes evolved independently in anoxic and oxic environments (Dupont *et al.*, 2006). Further bioinformatic analysis by Andreini *et al.* (2007) focused on the distribution of the nonheme iron proteins in 12 archaeal genomes, which were selected by considering one organism per order. The report showed that, although there were large variations in the proportion of iron proteins in each species, archaeal proteomes contained between 4% and 10% of iron proteins, with an average of 7.1%. For comparison, the bacterial and eukaryotic proteomes contained an average of 3.9% and 1.1% of iron proteins, respectively. The majority (more than half) of these proteins were shared among the three domains, while only 10% of the iron proteins in individual proteomes were specific to only one domain. As for their function, the most frequent iron-binding domains in archaea and bacteria were Fe_4S_4-ferredoxin and a second domain involved in the cleavage of *S*-adenosylmethionine and containing a specific type of Fe_4S_4 cluster (Andreini *et al.*, 2007).

Rarely represented MBDs

The presence and distribution of sequences related to the utilization of Ni and Co in archaea were also assessed using *in silico* analyses (Rodionov *et al.*, 2006; Zhang *et al.*, 2009). Nickel is an essential cofactor for Ni–Fe hydrogenases, carbon monoxide dehydrogenase, methyl CoM reductase, and urease, among others. Cobalt is found mainly in coenzyme B12. At least six systems for Ni/Co uptake are known (Rodionov *et al.*, 2006). Such systems are required for the high-affinity uptake of nickel or cobalt because their environmental concentration is usually below the required levels. Of these families of Ni/Co transporters, only three were found in archaea, one of which was Nik/CbiMNQO, which is also the most common system for the uptake of Ni and Co in bacteria (Zhang *et al.*, 2009). These systems possess a protein belonging to the ABC family of transporters, CbiO or NikO. Metal accumulation assays showed that the activity of the CbiMN component confirmed its hypothesized function of cobalt transporter (Rodionov *et al.*, 2006). A second type of Ni/Co transporter found in archaea is the NikABCDE multicomponent permeases, a family of ABC transporters initially characterized in *Escherichia coli* (Navarro *et al.*, 1993). The NikA component of the permease is also thought to be involved in Ni sequestration when Ni is in excess (Eitinger & Mandrand-Berthelot, 2000). Using sequence similarity and additional criteria, including proximity to nickel- or cobalt-requiring enzymes and Ni regulatory elements, transporters belonging to the NikABCDE family of permeases were discovered in the genomes of *Methanosarcina acetivorans*, *Methanosarcina barkeri*, and *Methanosarcina mazei* (Rodionov *et al.*, 2006; Zhang *et al.*, 2009). Similar criteria were applied to search for homologs of NiCoT, a family of metal permeases with preferential affinity for nickel or cobalt, in archaeal genomes. Homologs were only present in *Sulfolobus solfataricus* and *Thermoplasma acidophilum* (Rodionov *et al.*, 2006) and in one species of the *Methanomicrobiales* (Zhang *et al.*, 2009). NiCoT is the most common Ni/Co eukaryotic transporter. Sequences similar to the secondary bacterial transporters for nickel and cobalt, HupE/UreJ and UreH/SodT, were not found in archaea (Zhang *et al.*, 2009).

The most frequent Ni-dependent enzymes were searched in the archaeal genomes. These enzymes were urease and three families of Ni–Fe hydrogenase. In contrast with bacteria, only a few archaeal genomes encoded urease genes, which were found in two *Sulfolobales* and three *Halobacteriales* sp., while Ni–Fe hydrogenases, carbon monoxide dehydrogenases (Ni–CODH), and acetyl-coenzyme A decarbonylase/synthases (CODH/ACS) were identified in 33, 9, and 15 species, corresponding to 70%, 19%, and 32% of the archaeal species considered, respectively. In addition, all methanogen genomes encoded MCR, a Ni-binding enzyme that is archaeal specific and involved in the biosynthesis of methane (Zhang *et al.*, 2009). The fact that nickel is an important cofactor of many enzymes in methanogens has led to a new proposition by Konhauser *et al.* (2009) that a reduced availability of nickel approximately 2.7 Gyr ago might have been responsible for the decreased levels of atmospheric methane that occurred before the establishment of an oxidative atmosphere (Konhauser *et al.*, 2009). This proposition contrasts with the view that instead, the decline of methane was a consequence of the accumulation of sulfate and the rise of sulfate-reducing microorganisms.

Genes for the B12 biosynthetic pathway were present in 75% of the archaea, and 45 of 47 genomes encoded genes for the utilization of B12, specifically the B12-binding enzyme RNR II. In particular, *Methanosarcina* sp. encoded up to 15 B12-dependent methyltransferases. However, many families of B12-dependent proteins were not found in archaea; these families included MetH, 5,6-LAM, DDH, EAL, and CprA. Taken together, these results showed that Ni and Co utilization was widespread in prokaryotes, especially in archaea, in which, of the 47 genomes analyzed, 45 contained genes for the utilization of Co, 39 contained Ni-related genes, and 38 used both metals (Zhang *et al.*, 2009).

A comparative genomic analysis by Andreini *et al.* (2008) of the distribution of copper-binding proteins showed that only a minimal percentage of the proteome is represented by copper proteins, with small differences between the three domains of life. In fact, this percentage represented, on average, 0.3% in bacteria and eukaryotes and 0.4% in archaea. Large variations were observed between individual

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species; some microorganisms, including the archaeon *Nanoarchaeon equitans*, did not encode copper proteins at all, a characteristic probably due to their symbiotic lifestyle. On the other hand, *Halobacterium* sp. had the highest content of copper proteins within archaea, which belonged mostly to the plastocyanin/azurin family. From the distribution of Cu proteins, it was found that archaea share 30% of their Cu proteins with bacteria. Additionally, this fraction of proteins belongs mostly to two families of proteins, the largest of which is characterized by the presence of the NosD domain, described initially in a periplasmic protein of *Rhizobium* and having the role of delivering copper to the N_2O reductase (Holloway *et al.*, 1996).

The occurrence of molybdenum-dependent enzymes and genes for the utilization of molybdenum was assessed by Zhang & Gladyshev (2008). The researchers determined that utilization of Mo was widespread across the three domains, although eukaryotes contained fewer molybdoenzymes than prokaryotes. With a few exceptions, they also found a general co-occurrence of molybdoenzymes with Mo transporters and genetic traits for the synthesis of molybdopterin (Moco) (Zhang & Gladyshev, 2008). Moco biosynthesis genes were widespread in bacteria and especially frequent in the archaeal genomes analyzed (95%), suggesting an ancient origin for Mo utilization. Within the archaea, only *Methanosphaera stadtmanae* and *N. equitans* lacked genes for Mo utilization (Zhang & Gladyshev, 2008). The *wtp* system, for the uptake of tungstate and molybdate, is widespread in archaea. WtpA homologs are present in the proteomes of several archaea. In all cases, adjacent to genes encoding WtpA, sequences encoding the permease component WtpB and the ATPase component WtpC of the ABC transporter were also identified (Bevers *et al.*, 2006). In a comparative genomic analysis, WtpABC sequences were found to be more represented in archaea (63.95%) than in bacteria (only 10 out of 294 genomes), suggesting that WtpABC has an archaeal origin (Zhang & Gladyshev, 2008) and that the bacteria encoding a *wtp* system might have acquired it through horizontal gene transfer. Transporters specific for either Mo (MoABC) or W (TupABC) were also present in archaea. Of particular interest was the finding of a novel ModABC-like system in the hyperthermophilic archaeon *Pyrobaculum*. The fact that homolog sequences of the system were only present in *Pyrobaculum* sp. suggests that ModABC-like systems originated from the ModABC and quickly underwent divergent evolution only in *Pyrobaculum*. As for the Mo-dependent enzymes, dimethylsulfoxide reductase (DMSOR) and aldehyde ferredoxin reductase (AOR) were only present in prokaryotes. In particular, the DMSOR family was present in all the Mo-utilizing archaea, and the AOR family was present in a large proportion (69.4% of the Mo-utilizing species) in contrast with bacteria, in which it had a limited representation (Zhang & Gladyshev, 2008). These metal-binding proteins are involved in a variety of cell functions: from dissimilatory processes in which metals are utilized as terminal electron acceptors for energy production, to assimilatory reactions in which they bind metal ions and use them as cofactors; metal-binding proteins may also play a role in the homeostasis and detoxification of specific metals. These aspects will be examined in the following two sections.

Requirement for metals in archaea

Metabolism of metals is linked to a wide range of fundamental metabolic processes, such as nitrogen fixation, respiration, and other processes relying on oxidoreduction reactions or transport of electrons for energy production, because the enzymes of all these pathways contain metal cofactors, or in the case of anaerobic respiration, the metal itself is used as the terminal electron acceptor. Similar to bacteria, many archaeal species have the ability to derive energy from the reduction of a variety of metals. *Archaeoglobus fulgidus* and *Pyrococcus furiosus* are capable of reducing Fe(III), and two *Pyrobaculum* sp. can effectively grow respiring Fe(III) (Vargas *et al.*, 1998; Feinberg *et al.*, 2008; Kashefi *et al.*, 2008a). At least one archaeal species, *Pyrobaculum arsenaticum*, can use arsenate as a terminal electron acceptor for growth (Oremland & Stolz, 2003).

Methanogenic archaea and bacteria share determinants of nitrogen fixation (Fani *et al.*, 2000; Leigh, 2000). Nitrogenases are highly conserved across these domains, and for this reason, either an early origin or a horizontal transfer of these sequences has been hypothesized. Nitrogenases are complex enzymes made of two components, including multiple subunits: one component contains iron, and the second carries molybdenum and in some cases, vanadium (Rubio & Ludden, 2005). Because of the importance of nitrogenases in the biogeochemical cycling of nitrogen, there are extensive studies on the activities of microbial communities based on nitrogenases (Zehr *et al.*, 2003). While the presence of nitrogenases in methanogens has also been confirmed by genomic analysis, archaeal enzymes and their functions and metal requirements are yet to be characterized. Nickel is another important requirement for methanogens: it is required for methanogenesis in *Methanobacterium* strains (Hartzell & Wolfe, 1986) and in the methanogenic archaea *Methanobrevibacter smithii* and *M. barkeri* for incorporation into cofactor F430, a yellow chromophore found in the methylreductase of *Methanobacterium* (Diekert *et al.*, 1981; Ellefson *et al.*, 1982).

Tungsten and molybdenum have similar chemical properties. Molybdenum is a trace metal required by virtually every species, and tungsten can replace molybdenum in some instances (Kletzin & Adams, 1996). In most enzymes, both metals are found to be associated with an organic

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component called molybdopterin, often containing dinucleotides (Johnson *et al.*, 1993). Early studies of tungsten-requiring enzymes in hyperthermophilic archaea have led to the discovery that tungsten has a biological role. In fact, tungsten is an essential trace metal for some archaea. The hyperthermophile *P. furiosus* possesses at least three enzymes, AOR, formaldehyde ferredoxin oxidoreductase (FOR), and glyceraldehyde-3-phosphate oxidoreductase (GAPOR), that specifically require tungsten for their activity, as well as for the synthesis of the enzymes (Mukund & Adams, 1996). Two additional enzymes containing tungsten in *Pyrococcus*, the aldehyde oxidoreductases WOR4 and WOR5, were then characterized (Roy & Adams, 2002; Bevers *et al.*, 2005). The AOR of *Thermococcus* strain ES-1 was purified and shown to contain tungsten, in addition to Fe and Mg (Heider *et al.*, 1995). *Thermococcus litoralis* uses another tungsten-containing enzyme, FOR (Dhawan *et al.*, 2000).

Two types of systems for tungsten and molybdenum uptake have been identified in archaea: these are the *wtp* and *mod* systems, both belonging to the ABC family of transporters. *Pyrococcus furiosus* has been reported to use the tungsten-binding protein WtpA for the selective uptake of molybdenum and tungsten (Bevers *et al.*, 2006), and a similar system has also been characterized in *M. acetivorans* (Gerber *et al.*, 2008). WtpA belongs to the ABC family of transporters. In addition to the WtpABC system for tungsten and molybdenum, the uptake of molybdate in some archaea, similar to bacteria, has also been accomplished via ABC-type uptake systems using the metal-binding protein ModA, the membrane protein ModB, and the ATPase ModC (Self *et al.*, 2001). The structure of the *Archaeoglobus* molybdate importer ModBC, with its binding protein ModA, was solved by X-ray crystallography, providing insights into the mechanisms of molybdenum import in *Archaeoglobus* (Hollenstein *et al.*, 2007). The transporter is composed of two transmembrane ModB subunits forming an inward-facing gate in the closed conformation, and two ATP-hydrolyzing ModC subunits on the cytoplasmic side. Binding of ATP would result in an outward-facing open conformation. Because only ModA binds molybdenum specifically, its association with ModB on the external side of the membrane ensures unidirectional transport (Hollenstein *et al.*, 2007). Additional work focused on the distribution of Mo-dependent proteins is described in the metalloproteome section.

Energy can be generated either by oxidation or reduction of specific arsenic oxyanions. Arsenite oxidases, enzymes that convert As(III) to As(V), have been characterized in bacteria (Muller *et al.*, 2003), and the structure of the *Alcaligenes faecalis* enzyme has been determined (Ellis *et al.*, 2001). Several bacterial species, including strains of *Pseudomonas*, *Chloroflexus*, *Thiobacillus*, *Alcaligenes*, and *Thermus*, can oxidize arsenite for energy metabolism. Operons encoding putative arsenite oxidase have been found in the genomes of *Aeropyrum pernix* and *Sulfolobus tokodaii* (Lebrun *et al.*, 2003; Silver & Phung, 2005), and a phylogenetic analysis of these sequences suggests a common origin before the separation between archaea and bacteria (Lebrun *et al.*, 2003; Duval *et al.*, 2008). It is not surprising that most sequences retrieved were from thermophilic archaea and bacteria from hydrothermal environments, where arsenic compounds are prevalent (Lebrun *et al.*, 2003).

Two types of arsenate reductases are known, which have different structures and functions, and belong to distinct families. These are the Arr respiratory reductases, discussed in this section, and ArsC-type reductases used for detoxification, which will be considered later. Respiratory reductases have been characterized in a limited number of arsenate-respiring bacteria, although homologs of *arr* genes are present in a wide diversity of microorganisms. These enzymes have been described in bacteria as heterodimers composed of two subunits. The ArraA subunit is characterized by the presence of a molybdopterin cofactor, and a [4Fe-4S] cluster, while the ArrB subunit is a smaller iron–sulfur protein, predicted to bind four iron–sulfur clusters (Krafft & Macy, 1998; Afkar *et al.*, 2003). ArrA sequences form a distinct clade within the DMSOR family, which also include nitrate reductase, selenate reductase, arsenite oxidase, and formate dehydrogenase sequences (Silver & Phung, 2005; Duval *et al.*, 2008). Although the genetic determinants of arsenate respiration are yet to be characterized in archaea, the conserved molybdopterin dinucleotide-binding domain characteristic of the ArrA subunit is present in the genomes of the archaea *Hyperthermus butylicus* (BisC), *Pyrobaculum islandicum*, *Pyrobaculum aerophilum*, *P. arsenaticum*, and *A. fulgidus*. The presence of Arr-type sequences may indicate the ability to grow using arsenate as an alternate electron acceptor. This ability to reduce arsenate for energy production was confirmed in *P. aerophilum* and *P. arsenaticum* (Huber *et al.*, 2000). *Pyrobaculum aerophilum* is characterized by respiratory flexibility, being able to use a variety of electron acceptors, including oxygen, nitrate, nitrite, arsenate, selenite, selenate, and iron. Through the analysis of the genome-wide expression in the presence of different terminal electron acceptors, a few genes were found to be specifically induced by As(V) in this archaeon. Three genes were strongly upregulated and included a molybdopterin oxidoreductase (PAE1265) with low similarity to characterized Arr genes, a putative iron–sulfur protein (PAE1263), and a putative membrane protein (PAE1264), indicating the presence of a pathway for arsenate respiration in *P. aerophilum* (Cozen *et al.*, 2009).

Oxyanions of selenium can be reduced by prokaryotes for energy conservation. Developments in studies of arsenic and selenium metabolism in bacteria and archaea have been reviewed by Stolz *et al.* (2006). Two archaea, *P. arsenaticum*

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and *P. aerophilum*, can respire selenate, which is reduced to selenite and elemental selenium (Huber *et al.*, 2000). Selenium also plays an important role as a nutrient, being a component of the amino acid selenocysteine (Sec), through which it is incorporated in enzymes requiring this metal as cofactor. Sec insertion (SECIS) elements have been detected in archaeal genomes and form secondary structures in the 3′ untranslated region of genes requiring the recoding of the UGA codon with selenocysteine. SECIS sequences are highly conserved among *Methanococcus* sp. (Wilting *et al.*, 1997). The proteins SelA, SelB, SelC, and SelD are involved in Sec incorporation. While many archaea have the genes for two pathways of selenate utilization, Sec and SeU, a few species only carry the gene encoding SelD, a selenophosphate synthetase. This suggested an alternative pathway for Se utilization in some bacteria and in the archaeon *Haloarcula marismortui* where the gene was found to be plasmid encoded (Zhang *et al.*, 2008b). A selenium-binding protein with a possible function in the transport of selenium was isolated from *Methanococcus vannielii*. The recombinant protein formed tetramers upon binding of selenium (Self *et al.*, 2004; Patteson *et al.*, 2005).

The iron rivets of *Ferroplasma*

Not only are metals required for energy conservation or used as cofactors in enzymatic reactions but they can also have unique roles. In one instance, iron has been shown to be essential in stabilizing the proteome of one archaeal species. *Ferroplasma acidiphilum*, which thrives in extremely acidic environments containing high levels of iron, such as acid mine drainage (AMD), is a remarkable organism, in that the majority of its proteins (approximately 86%) contain iron, as shown by a study conducted by Ferrer *et al.* (2007). The same analysis performed on the close relative *Picrophilus torridus*, and the unrelated bacterial species *Acidithiobacillus ferrooxidans* that shares similar habitats, demonstrated that both microorganisms were equipped with a complement of typical iron proteins. Interestingly, most of the homologs of the *Ferroplasma* iron-containing protein are not metalloproteins in other microorganisms. One characterized example is the enzyme ligase, that in *F. acidiphilum* is stabilized by iron and has no requirements for other ions (Mg^{2+} or K^{+}), differentiating this enzyme from all other ligases (Ferrer *et al.*, 2008). This special function of iron has been referred to as 'iron rivet', but it is not clear as to what would be the advantages offered by it. One proposal is that this function evolved early in a iron-rich environment, and it has been retained only in the *Ferroplasma* lineage (Ferrer *et al.*, 2007).

Metal resistance

Excessive exposure to any metal can cause considerable damage to cellular components and impair cell functions. Strategies used by archaeal microorganisms are essentially the same as those observed for bacteria and include mostly efflux by ATP-driven transporters and enzymatic detoxification and, to a lesser extent, exclusion and metal sequestration (Fig. 1). Toxic metals obviously have no uptake systems and enter the cells using channels designed for useful ions and organic molecules. For example, arsenic enters the cell using transport systems Pit or Pst designed for phosphate uptake in both archaea and bacteria. Known systems of defense rely on the use of more specific uptake systems for essential nutrients so that the toxic metals can be excluded (Cervantes *et al.*, 1994). Another strategy, described in bacteria, is the repression of permeases for the specific uptake of nickel and cobalt (Chivers & Sauer, 2000). It is worth mentioning that the exposure to toxic metals may elicit general stress responses, resulting in the expression of proteins that are not metal specific, but nonetheless contribute to metal resistance. The analysis of the *Ferroplasma acidarmanus*' proteome, an archaeon that grows in metal-rich environments, revealed sets of proteins that were overexpressed during arsenate (Baker-Austin *et al.*, 2007) or copper (Baker-Austin *et al.*, 2005) exposure. Components of the thermosome group II HSP60 chaperonin family and a DnaK-like heat shock protein were upregulated. Antioxidant enzymes, including a peroxiredoxin and a thioredoxin, were also induced (Baker-Austin *et al.*, 2007). The expression of chaperone proteins and enzymes involved in DNA and protein repair was also observed in the proteome of *Ferroplasma* exposed to high levels of copper (Baker-Austin *et al.*, 2005). Furthermore, in a transcriptomic study of the crenarchaeote *S. solfataricus*, after long-term exposure to copper, we observed that transposases were the category of genes mostly affected by the metal (data not shown), which is typical of a general stress response.

Metal sequestration

Sulfolobus metallicus, a species capable of growing in concentrations of copper up to 200 mM, uses a mechanism of resistance based on sequestration by organic phosphate (Remonsellez *et al.*, 2006), which is presumably followed by an active efflux of the metal–phosphate complex. This is similar to what is observed in *E. coli*, *Acinetobacter johnsonii*, and *Acidithiobacillus ferroxidans* (Alvarez & Jerez, 2004) that also use the inorganic phosphate transport system (Pit) for the transport of metal–phosphate complexes (Fig. 1). *Sulfolobus metallicus*, but not *Sulfolobus acidocaldarius* or *S. solfataricus*, synthesizes and accumulates large amounts of organic polyphosphate (polyP), which is rapidly hydrolyzed by an exopolyphosphatase in the presence of copper (Remonsellez *et al.*, 2006). *Metallosphaera sedula*, which also displays a high copper resistance, possesses ORFs with similarities to a polyphosphate/NAD kinase and Ppx, but

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no sequences were found with similarities to the components of the Pit system. However, sequences with low similarity to a phosphate transport regulation protein and a putative phosphate uptake regulator were identified using similarity searches (Auernik *et al.*, 2008). Sequestration of metal ions by metal-binding proteins is a strategy to cope with an excess of toxic metals. An important class of metal-binding proteins is represented by metallothioneins. However, metallothioneins are not represented in archaeal genomes. Members of the CutA family of metal-binding proteins are found in archaea (Fig. 1), bacteria, and eukaryotes. The crystal structure of the *Pyrococcus horikoshii* CutA has been determined with and without copper (Tanaka *et al.*, 2004), contributing to the clarification of the protein's function. In fact, binding of heavy metals induced the reversible multimerization of CutA. Thus, a role has been proposed for CutA in the capture and precipitation of metal ions. Interestingly, while the metal-binding site of the *E. coli* homolog contains Cys and His residues, these amino acids are absent in the *Pyrococcus* protein. Therefore, the archaeal protein might represent a new model of metal-responsive multimerization. Multimeric proteins that protect cells from oxidative stress by sequestering intracellular iron were identified and described in *Halobacterium salinarum*, *S. solfataricus*, and *P. furiosus* (Reindel *et al.*, 2002; Wiedenheft *et al.*, 2005; Ramsay *et al.*, 2006); in particular, the *Sulfolobus* and the *Halobacterium* antioxidant DNA-binding protein from nutrient-starved cells (DPS)-like proteins resulted from the assembly of 12 units (Reindel *et al.*, 2002; Gauss *et al.*, 2006).

An example of extracellular sequestration of metal is represented by *Methanobacterium bryantii*, a highly copper-resistant methanogen species isolated from a copper mine in Michigan. Kim and colleagues discovered that in the presence of high external copper, *M. bryantii* excreted at least three copper response extracellular (CRX) proteins into the medium (Kim *et al.*, 1995); the transcripts encoding CRX proteins increased with copper exposure, indicating the existence of a copper-responsive system. It was proposed that these proteins, by acting as copper chelators, would significantly decrease the copper concentration surrounding the cell (Fig. 1).

Active efflux systems

The most widely used mechanism of metal resistance is based on active efflux. The simplest example is provided by the type P1B subfamily of ATPases. These are single-unit membrane proteins that transport ions of transition metals, such as zinc, lead, cadmium, cobalt, copper, and silver. Catalytic mechanisms and structural characteristics of the functional domains in this class of ATPases in prokaryotes and eukaryotes were reviewed by Arguello *et al.* (2007). Copper-transporting ATPases belong to this subfamily and are important components of systems controlling copper homeostasis in prokaryotes and eukaryotes. Although no structure has been solved for a P1B-type ATPase, extensive structural and functional studies of individual domains of a copper-transporting ATPase were performed on the *Archaeoglobus* protein CopA (Sazinsky *et al.*, 2006a, b). The presence of six conserved amino acids located within the sixth, seventh, and eighth transmembrane helices was demonstrated. These residues determine the ion specificity and they are responsible for Cu(I) transport (Arguello *et al.*, 2007; Gonzalez-Guerrero *et al.*, 2008). The mechanisms of Cu(I) transfer to CopA were elucidated, showing that a copper chaperone CopZ is involved in the process. CopZ delivers Cu(I) to the two terminal MBDs and to the transmembrane-binding domain (TM-MBS) of the CopA transporter. However, only the Cu(I) transferred from CopZ to the TM-MBS activates CopA, leading to metal translocation (Gonzalez-Guerrero & Arguello, 2008; Gonzalez-Guerrero *et al.*, 2009).

Metal-transporting ATPases have quite conserved sequences and are widespread throughout the three domains of life. A survey of the archaeal genomes has shown the presence of P-type ATPase sequences, a superfamily of cation-transporting ATPases that includes the P1B-type subset of metal transporters. Metal-transporting ATPases were present in all the genomes considered, with a few exceptions (*Cenarchaeum symbiosum*, *Halorubrum lacusprofundi*, *N. equitans*, *Methanopyrus kandleri*, and *P. horikoshii*). A phylogenetic analysis of archaeal P1B-type ATPases showed a separation into two distinct groups representing Cu ATPases and Cd/Zn ATPases. Furthermore, Cu ATPases could be divided into Cu(I) and Cu(II) transporters (Bini, 2008).

Systems for copper efflux

Copper is the cofactor of important enzymes responsible for redox reactions, including superoxide dismutases, cytochrome *c* oxidases, and enzymes for iron metabolism, among many others. Because it is highly toxic in concentrations outside the physiological range, all microorganisms possess systems for controlling its homeostasis by regulating influx and efflux and producing copper-binding proteins that readily complex the free copper.

In archaea, similar to bacteria and yeast, genes for copper-transporting ATPases are often associated with genes encoding copper-binding proteins and a transcriptional regulator controlling the expression of the operons. *Sulfolobus solfataricus* possesses two P-type ATPases encoded by Sso2651 and Sso8962 (She *et al.*, 2001). The entire *copRTA* operon, encoding a copper regulator (CopR), a copper-binding protein (CopT), and a Cu-transporting ATPase (CopA), is constitutively expressed as a single transcript in the absence of copper (Villafane *et al.*, 2009), while treatment with $CuCl_2$ causes a transient increase of *copTA* transcription (Villafane *et al.*, 2009). Sso2651, encoding CopA, is specifically induced

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by exposure to copper and the product of Sso2652 binds the region upstream of copA, suggesting a role as a regulator of transcription (Ettema *et al.*, 2006). A knockout of the putative regulator CopR resulted in a loss of *copA* induction, indicating a positive regulatory function for CopR (unpublished results). A second locus, unlinked from the *copRTA* operon, includes the sequences Sso8967, Sso8968, and Sso11415, encoding CopB, a putative transcriptional regulator and a copper-binding protein, respectively. CopB might play the role of a Cu(II) transporter, complementing the function of Cu(I) detoxification by CopA. In fact, the catalytic ATP-binding/phosphorylation domain of the *S. solfataricus* ATPase CopB was capable of hydrolyzing ATP, and its activity was stimulated by Cu(II), but not by Cu(I) (Deigweiher *et al.*, 2004). In *M. sedula*, a species related to *Sulfolobus*, genes encoding a copper-binding protein and a Cu-transporting ATPase were also identified. A regulator of transcription was also present upstream of the two genes and encoded in the opposite direction (Auernik *et al.*, 2008). Two copper-transporting ATPases, CopA and CopB, were isolated and characterized in the hyperthermophilic *A. fulgidus* and shown to be preferentially activated by Cu(I) and Cu(II), respectively (Mana-Capelli *et al.*, 2003; Mandal & Arguello, 2003). Moreover, the extreme acidophile *F. acidarmanus* possesses a *cop* operon for copper resistance, including genes encoding the transcriptional regulator CopY, the copper-binding protein CopZ, and the putative copper-transporting ATPase CopB. Cotranscription of *copZ* and *copB* was shown to increase in response to copper, indicating a role in copper efflux (Baker-Austin *et al.*, 2005).

Systems for arsenic efflux

Genetic determinants of bacterial resistance to arsenic have been reviewed elsewhere (Mukhopadhyay *et al.*, 2002). Arsenic resistance operons can be either chromosomally or plasmid encoded, and carry genes encoding the arsenic-responsive regulator *arsR*, the As(III) transporter *arsB*, and the arsenate reductase *arsC*. Arsenate must be converted to arsenite to be actively removed from the cells. The arsenate reductase ArsC is the enzyme that carries out this transformation. ArsC possesses a conserved motif also shared by glutaredoxins and thioredoxins, and requires glutaredoxin as the source of reducing equivalents for arsenate reduction. The arsenate reductase converts arsenate As(V) into arsenite As(III), which is actively transported outside the cell. Two additional genes encoding an As(III)-translocating ATPase, ArsA, and ArsD, an arsenic chaperone that transfers As(III) to ArsA, can be found on separate operons or plasmids, both in archaea and in bacteria (Xu *et al.*, 1998; Dopson *et al.*, 2003; Lin *et al.*, 2006). The ATPase ArsA supplements the activity of the transporter ArsB, acting as a catalytic subunit (Dey & Rosen, 1995). Table 1 summarizes the activities related to metal metabolism and resistance presence in archaeal species. Homologs of ArsC, the bacterial detoxifying arsenate reductase, are annotated in several archaeal genomes (*P. furiosus*, *M. mazei*, *M. acetivorans*, *Methanothermobacter thermautothrophicus*, *A. fulgidus*, *Candidatus nitrosopumilus*, *Haloquadratum walsbyi*, *Natronomonas pharaonis*, *Thermococcus kodakarensis*, and *H. marismortui*). Surprisingly, the *arsC* gene is missing in some archaeal genomes encoding other components of the *ars* operon, or in species known to be resistant to arsenate. In fact, *T. acidophilum* possesses only homologs of the *arsRB* operon and of a partial *arsA* gene at two distant loci (Dopson *et al.*, 2003). *Sulfolobus solfataricus* and its relative *M. sedula* encode a stand-alone arsenite transporter ArsB (Auernik *et al.*, 2008). The acidophilic archaeon *F. acidarmanus* can grow in high concentrations of arsenate (up to 133 mM) without an effect on growth rate (Baker-Austin *et al.*, 2007). Interestingly, although *Ferroplasma* is capable of growth in such high levels of arsenate, it does not encode an arsenate reductase, *arsC*, or a phosphate transporter system, Pst. The absence of arsenate reduction was confirmed by biochemical analysis. Hence, the authors speculated that additional genes for arsenate resistance should be present. The *Ferroplasma* chromosome possesses an operon homologous to *arsRB*, which is inducible by arsenite, but not by arsenate (Gihring *et al.*, 2003; Baker-Austin *et al.*, 2007). At a separate locus, a sequence similar to *arsA* was also identified on the *Ferroplasma* chromosome (Gihring *et al.*, 2003); however, this sequence might be a pseudogene in that it lacks an N-terminal domain and promoter (Baker-Austin *et al.*, 2007). In a transcriptomic analysis of *P. aerophilum*, a homolog of *arsR* (PAE1592) was found to be upregulated during growth using arsenate as the terminal electron acceptor. Surprisingly, genes with similarity to an As-transporter and arsenite permease were not affected by the presence of As(III) resulting from the respiration of As(V) by *P. aerophilum*, suggesting, according to the authors, that other pathways might be in place for arsenite detoxification in this microorganism (Cozen *et al.*, 2009).

A study of arsenic resistance in *Halobacterium* was conducted by the DasSharma and Rensing laboratories (Wang *et al.*, 2004). Homologs of arsenic resistance genes were identified on the chromosome and on one of the two megaplasmids of *Halobacterium* sp. NRC-1. The megaplasmid pNRC100 encodes the gene clusters *arsADRC* and *arsR2M*. Deletion of *arsADRC* produced arsenite and antimonite sensitivity, but not sensitivity to arsenate, indicating the presence of an export system specific for As(III) and Sb(III). Knockout of *arsB*, chromosomally encoded, did not affect the cell sensitivity to arsenic oxyanions, although *arsB* was shown to be inducible by arsenite and antimonite (Wang *et al.*, 2004). It is possible that some species use alternative strategies for arsenic resistance. For example,

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Table 1. Cellular processes involving metals carried out in archaea

Process	Microorganism	References
Energy conservation		
As(V) reduction	*Pyrobaculum arsenaticum*	Huber *et al*. (2000)
	Pyrobaculum aerophilum	Huber *et al*. (2000), Cozen *et al*. (2009)
Au(III) reduction	*Pyrobaculum islandicum*	Kashefi *et al*. (2001)
	Pyrococcus furiosus	Kashefi *et al*. (2001)
Fe(II) oxidation	*Ferroplasma thermophilum*	Zhou *et al*. (2008)
	Ferroplasma cupricumulans	Hawkes *et al*. (2006)
	Ferroplasma acidiphilum	Johnson & Hallberg (2003)
	Ferroplasma acidarmanus	Edwards *et al*. (2000)
	Sulfolobus metallicus	Bathe & Norris (2007)
	Sulfolobus tokodaii	Bathe & Norris (2007)
	Acidianus brierleyi	Larsson *et al*. (1990)
	Metallosphaera spp.	Huber (1989), Kozubal *et al*. (2008)
Fe(III) reduction	Euryarchaeota DHVE2	Reysenbach *et al*. (2006)
	Archaeoglobus fulgidus	Vargas *et al*. (1998)
	Pyrococcus furiosus	Kashefi *et al*. (2001)
	Pyrobaculum islandicum	Feinberg *et al*. (2008), Kashefi *et al*. (2008a)
	Pyrobaculum aerophilum	Feinberg & Holden (2006)
Se(VI), Se(IV) reduction	*Pyrobaculum aerophilum*	Huber *et al*. (2000)
Co(III), Cr(VI), Mn(IV), Tc(VII), U(VI) reduction	*Pyrobaculum islandicum*	Kashefi & Lovley (2000), Kashefi *et al*. (2008a, b)
Metal assimilation		
W, Mo uptake	*Pyrococcus furiosus*, *M. acetivorans*	Bevers *et al*. (2006), Gerber *et al*. (2008)
Mo uptake	*Archaeoglobus fulgidus*	Self *et al*. (2001), Hollenstein *et al*. (2007)
Se incorporation in Sec	*Methanococcus sp.*	Wilting *et al*. (1997)
	Haloarcula marismortui	Zhang *et al*. (2008b)
Metal detoxification		
As(V)*	*Thermoplasma acidophilum*	Dopson *et al*. (2003)
As(III) export*	*Ferroplasma acidarmanus*	Baker-Austin *et al*. (2007)
As(III), Sb(III) export	*Halobacterium* sp. NRC-1	Wang *et al*. (2004)
As(III) oxidation	*Sulfolobus metallicus* (form. *S. acidocaldarius* BC)	Sehlin & Lindstrom (1992)
Cu sequestration and export	*Sulfolobus metallicus*	Remonsellez *et al*. (2006)
Cu sequestration	*Pyrococcus horikoshii*	Tanaka *et al*. (2004)
Cu external sequestration	*Methanobacterium bryantii*	Kim *et al*. (1995)
Cu(I) export	*Sulfolobus solfataricus*	Ettema *et al*. (2006), Villafane *et al*. (2009)
	Archaeoglobus fulgidus	Mandal & Arguello (2003)
	Ferroplasma acidarmanus	Baker-Austin *et al*. (2005)
Cu(II) export	*Archaeoglobus fulgidus*	Mana-Capelli *et al*. (2003)
Fe(II) oxidation and sequestration	*Halobacterium salinarum*	Reindel *et al*. (2002)
	Sulfolobus solfataricus	Wiedenheft *et al*. (2005)
	Pyrococcus furiosus	Ramsay *et al*. (2006)
Hg(II) reduction	*Sulfolobus solfataricus*	Schelert *et al*. (2004)

*Resistant to high As(V), although no ArsC homolog has been identified in the species.

S. acidocaldarius strain BC (renamed *S. metallicus*), an archaeon of interest for bioleaching, oxidizes arsenite to the less toxic arsenate using an As(III) oxidase located in the membrane (Sehlin & Lindstrom, 1992) (Fig. 1).

Detoxification by volatilization

A mechanism of detoxification involves the methylation of inorganic forms of arsenic to volatile arsines and nonvolatile species. Arsenic methylation has been studied in microbial communities (Islam *et al*., 2005) and in pure cultures both of archaea and bacteria. The process was first discovered by McBride and Wolfe in *Methanobacterium* that was reported to produce dimethylarsine (McBride & Wolfe, 1971). The methanogenic archaea *M. bryantii*, *Methanobacterium formicicum*, and *M. barkeri* were reported to produce volatile forms of methylated arsenic (Michalke *et al*., 2000). Although methylation of arsenic has been described in

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eukaryotes, the mechanism is still unclear in microorganisms. ArsM is a bacterial homolog of the rat methyltransferase and catalyzes the formation of trimethylarsine from arsenite (Qin *et al.*, 2006). A knockout of the gene encoding ArsM in the archaeon *Halobacterium* resulted in sensitivity to arsenite, confirming its role as a detoxifying enzyme (Wang *et al.*, 2004). ArsM has also been identified in 16 archaeal species, including three *Methanosarcina* sp. and *H. salinarum* (Qin *et al.*, 2006). In addition to arsenic methylation, archaea isolated from the human gut, including the two species *M. stadtmanae* and *M. smithii*, were shown to be able to derivatize a greater variety of metals and metalloids into volatile compounds and with higher efficiency than gut bacteria (Meyer *et al.*, 2008).

Microbial mercury transformations affect the biogeochemical cycle of this toxic metal, and its impact on the environment. Two different processes result in mercury volatilization. In the case of mercury methylation, the transformation occurs anaerobically and it is coupled to dissimilatory reduction of different electron acceptors, mostly sulfate, in bacteria (King *et al.*, 2000). Very little is known about Hg methylation in archaea, although some methanogens are capable of Hg(II) methylation, as shown in *Methanococcus maripaludis* cocultured with the sulfidogen *Desulfovibrio desulfuricans* (Pak & Bartha, 1998).

In another strategy of detoxification, resistance is mediated by the Hg-reductase MerA, which catalyzes the conversion of Hg(II) into the volatile Hg(0) (Fig. 1). The molecular analysis of a naturally mercury-rich hot spring showed the presence of both archaeal and bacterial mercury reductase sequences (Simbahan *et al.*, 2005). A mercury detoxification system has been described in the crenarchaeote *Sulfolobus*. The *merRAHI* operon of *Sulfolobus* represents the most detailed study of mercury resistance in archaea. Studies using target gene disruption have shown that the *S. solfataricus* homolog of the bacterial mercury reductase MerA confers a low but measurable level of mercury resistance. The *Sulfolobus* MerR acts as a negative regulator (Schelert *et al.*, 2004). However, similar to bacterial MerR factors, but presumably using different mechanisms, the archaeal MerR also induces transcription without leaving the *merA* promoter by producing conformational changes of the promoter itself in the presence of mercury (Schelert *et al.*, 2006). Two additional genes, named *merH* and *merI* and located up- and downstream of *merA*, respectively, were cotranscribed with *merA* and induced by mercury. MerH contains the conserved MBD TRASH; for this reason, it has been proposed to function as a chaperone for mercury mobilization, while the role of MerI is still unclear (Schelert *et al.*, 2006). BLAST searches have identified homologs of MerA in 17 out of 135 archaeal genomes and in some uncultured archaea at the time of writing.

Metal transformations in the environment

Archaea play important ecological roles in a variety of environments. Members of the archaeal domain exert their impact on the mobility of metals in the environment either directly, by the oxidation or reduction of elements with the purpose of energy conservation or detoxification, or indirectly, by altering the pH or redox conditions of their environment, which in turn affects metal precipitation or solubilization. Selected examples of characterized metal transformations carried out by archaeal microorganisms are summarized in Table 1.

Biomineralization

Some archaeal species are able to transform metals into their insoluble forms in biomineralization processes, leading to the formation of mineral deposits of the corresponding metal ores. In fact, the accumulation of mineral deposits can be used as an indication of dissimilatory microbial activities. The presence of magnetite and uraninite in hyperthermophilic habitats has been proposed to be due to the activity of *P. islandicum*. Cell cultures of *P. islandicum* were capable of both Fe(III) oxide and U(VI) mineral reduction, leading to the formation of ultrafine magnetite and UO_2, respectively (Kashefi *et al.*, 2008a, b). Other metals, including Tc(VII), Cr(VI), Co(III), Mn(IV) (Kashefi & Lovley, 2000), and Au(III) (Kashefi *et al.*, 2001), were also reduced by *P. islandicum* in the presence of hydrogen as the electron donor, whereas arsenate and selenate were not (Kashefi & Lovley, 2000). *Pyrococcus furiosus* and the archaeal strain 234 were also able to reduce gold, as well as Fe(III), in the presence of H_2 (Kashefi *et al.*, 2001). The presence of Au(III) as the sole electron acceptor was not sufficient to sustain cell growth in these strains (Kashefi *et al.*, 2001). Metal transformations leading to the formation of insoluble precipitates may also result from metabolic processes. For example, anaerobic oxidation of methane (AOM) can be carried out using different electron acceptors, including the metals manganese or iron (Beal *et al.*, 2009). However, it should be noted that under such conditions, AOM proceeds at significantly slower rates than those observed for sulfate-dependent AOM (Beal *et al.*, 2009). Archaea capable of AOM include the anaerobic methanotroph groups ANME-1, ANME-2, and ANME-3, but the manganese-dependent AOM could not be definitely assigned to a specific ANME or bacterial group (Beal *et al.*, 2009).

Biomining

For the purpose of bioleaching, prokaryotic thermophilic species capable of mobilizing metals are probably the most attractive systems. Essentially, the process of bioleaching is

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based on the oxidation of sulfide minerals constituting and leads to the release of sulfate and metals. Such a process is especially advantageous for the extraction of metals from low-grade ores. Although chemical oxidation occurs naturally, its rate can be increased substantially by the presence of sulfur- and iron-oxidizing microorganisms, including archaea (Edwards *et al*., 2000). Various bacterial species are involved in bioleaching; the most widely recognized are the mesophilic iron and sulfur oxidizer *A. ferrooxidans* (Rawlings, 2002), the moderately thermophilic *Acidithiobacillus caldus* and *Leptospirillum* spp. (Johnson & Hallberg, 2003), for the extraction of metals from sulfide ores. In general, microorganisms with a potential in biomining are those naturally found in AMD or isolated from metal-rich habitats, and because sulfuric acid results from the oxidation of sulfide minerals and sulfur, these microorganisms are obligate acidophiles. In acidic environments, the microbial oxidation of Fe(II) plays an important role because it proceeds at a much faster rate than chemical oxidation. Such environments are often predominantly colonized by archaeal species. For example, the hydrous ferric oxide microbial mats of Norris Geyser Basin in Yellowstone are composed of a mixed microbial community, including, among others, the archaeal species *Metallosphaera prunae*, *S. solfataricus*, *P. islandicum*, and *Vulcanisaeta distributa*, though the contribution of each species to Fe(II) oxidation is not clear (Kozubal *et al*., 2008). *Ferroplasma* sp., reviewed by Golyshina & Timmis (2005), are important contributors to the cycling of sulfide metals in extremely acidic environments. Members of the species have been isolated from AMD (Edwards *et al*., 2000), natural acidic ecosystems like the Rio Tinto (Gonzalez-Toril *et al*., 2003), and a chalcocite heap from a Myanmar copper company (Hawkes *et al*., 2006). 16S rRNA gene analyses of metal-rich acidic sites have demonstrated the prevalence of *Ferroplasma* sequences. Thus, members of these archaeal genera are able to mobilize metals from mineral ores and can be valuable in the biomining industry. *Ferroplasma acidophilum* and *F. acidarmanus* are mesophilic and live in environments with low pH and high levels of sulfide ores, and they oxidize ferrous iron. Some members of the *Sulfolobales* that are capable of sulfur and/or iron oxidation have potential in biomining. *Sulfolobus metallicus* can oxidize ferrous iron, reduced inorganic sulfur compounds, sulfide ores, arsenopyrite, and chalcopyrite (Bathe & Norris, 2007). Additionally, *S. tokodaii* can oxidize iron, while *S. solfataricus* and *S. acidocaldarius* cannot, an observation that is consistent with a lack of the *fox* genes responsible for iron oxidation in the genomes of these last two species (Bathe & Norris, 2007). The genome of *M. sedula*, another member of the *Sulfolobales*, was found to encode genes for iron and sulfur oxidation, including the *fox* cluster (Auernik *et al*., 2008). Global transcription analyses also confirmed the utilization of iron and sulfur oxidation pathways (Auernik & Kelly, 2008), demonstrating the potential of *Metallosphaera* in biomining.

Bioremediation

Industrial and mining activities and combustion of fossil fuels have released a substantial amount of metal compounds into the environment. Those same microorganisms that can be used in biomining because of their high resistance to high concentrations of metals and toxic metals might also have important applications in bioremediation. Sites contaminated with high levels of metals and sulfur compounds are usually found in mines in which the activity of microbial communities leads to the generation of AMD. Several AMD environments have been studied with respect to their physical and chemical features and the structure of the microbial communities responsible for the metal transformations occurring at those sites. The Richmond Mine at the Iron Mountain site in California is rich in iron and sulfur, which sustains a microbial community composed of species belonging to the *Thermoplasmatales* among the archaea (Druschel *et al*., 2004). *Thermoplasmatales* include *Ferroplasma*, *Thermoplasma*, and the five groups Aplasma, Bplasma, Cplasma, Dplasma, and Eplasma (so-called 'alphabet plasmas') (Baker & Banfield, 2003) and colonize a variety of environments characterized by low pH, high ferrous iron concentrations, and other metals. Therefore, they often dominate the archaeal species colonizing AMD sites at pyrite mines (Tan *et al*., 2009) and Pb/Zn mines (Tan *et al*., 2008). Further insights into the microorganism–metal interactions occurring at the Richmond Mine were provided by the sequencing of the metagenome from a biofilm growing on the AMD. The dominance of few species in the biofilm made possible the assembly of near-complete genomes of the *Leptospirillum* and *Ferroplasma*, and the partial sequencing of three other genomes (Tyson *et al*., 2004). These data, combined with a proteomic study of the same microbial community, allowed to match expression data to corresponding microorganisms (Ram *et al*., 2005). Such an approach revealed the metabolic potential of the AMD biofilm, and helped to assign cell processes to individual species. In addition to protein involved in fundamental cell functions, antioxidants and enzymes with roles in protein refolding were present in abundance, an observation that agrees with proteomic studies of pure *F. acidarmanus* cultures challenged with metals (Baker-Austin *et al*., 2005, 2007).

Members of the *Thermoplasmatales* order were also isolated from bioleaching pilot plants (Golyshina *et al*., 2000) and found in shallow submarine and continental solfataras, including the ones at Vulcano Island (Italy), where most of the cultured species were initially isolated (Golyshina *et al*., 2009). In the field of bioremediation, Fe(III)-reducing microorganisms have been proposed to have significant potential in removing toxic metals from contaminated water

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through reduction and immobilization in insoluble precipitates. Archaeal iron reducers have been isolated in diverse geographical locations and environments, mostly from geothermal marine environments for strains belonging to Crenarchaeota and Euryarchaeota (Kashefi *et al.*, 2008a, b) including the sulfur- and iron-reducer '*Aciduliprofundum boonei*', T469 a member of the hitherto uncultured Euryarchaeote DHVE2 group (Reysenbach *et al.*, 2006).

Final remarks

In the past years, it has become clear that archaea are widespread and found in every environment that has been explored (Elshahed *et al.*, 2004; Konneke *et al.*, 2005). Particularly in extreme environments, archaea often represent the majority of the microbial community (i.e. in highly saline environments). Thus, archaea have a considerable impact on the biogeochemistry of the elements in the environment, and to better understand these processes at a global level, in-depth investigations are required to elucidate the mechanisms of metal transformation and resistance in archaea, in which they have not been as extensively studied as in bacteria. New and improved methods of gene analysis and expression will facilitate the elucidation of these processes. In particular, advances in sequencing technology and the application of deep sequencing will prove to be extremely useful in the acquisition of genome data from entire communities of unculturable microorganisms. Next-generation sequencing technologies will be especially powerful when applied to extreme environments with limited microbial diversity. The availability of a growing number of new genome sequences generated this way will provide insights into novel pathways of metal metabolism and resistance. Additionally, it will be essential to correlate these activities of metal transformations as they occur in nature with the species and microbial communities responsible for such transformations, and efforts are needed to clarify the transformations carried out by synthropic communities of archaea and bacteria. High-throughput sequencing applied to the monitoring of metatranscriptomes from environmental samples will enable the elucidation of the pathways of metal metabolism and utilization that are active under specific conditions within a microbial community. From a more applied point of view, elucidating the physiology of acidophilic microorganisms, including archaea, in relation to their ability to mobilize metals and the underlying molecular processes will be critical for developing strategies aimed to remediate AMD habitats and to applications, such as bioleaching.

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