The role of sulfate-reducing prokaryotes in the coupling of element biogeochemical cycling

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Linking genes to biogeochemical cycling: lessons from arsenic

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Abstract

The biotransformation of arsenic is of particular relevance to biogeochemical processes. Identification of the molecular details of microbial pathways of arsenic biotransformation coupled with analyses of microbial communities by meta-omics can provide insights into specific aspects of the complexities of the biogeochemical arsenic cycle. Arsenic transformation couples to other biogeochemical cycles, and to the fate of both nutrients and other toxic environmental contaminants. In some cases, microbial metabolisms associated with redox of other elements (e.g. iron, carbon and nitrogen) affect arsenic species, occurrence state, and bioavailability. The arsenic biogeochemical cycle can be understood through the combination of microbial geochemical activity analyses with biogeochemical models. In this critical review we discuss how metagenomic-, metatranscriptomic-, metaproteomic-, and metabolomic-based methods now and in the future will help to decipher individual microbial arsenic transformation processes, their links to other biogeochemical cycles, and allow us to use the metabolic capabilities of the microbes involved for biotechnological purposes. Integrating biogeochemical model and meta-omics data will offer novel insights into the evaluation and prediction of arsenic biotransformation processes in the environment. It is believed that lessons learnt from arsenic biogeochemistry can potentially be applied to other biogeochemical processes.

1. Introduction

Many biogeochemical cycles are inter-connected based on redox reactions of the transformations within each biogeochemical cycle.¹ Any biogeochemical process, such as the cycling of a particular element, is likely to be mediated by more than one (micro)organism and is often linked to other biogeochemical processes. For example, the redox changes of arsenic are mediated by diverse arsenate (As(V))-reducing and arsenite (As(III))-oxidizing microbes. Arsenic biogeochemical cycling is often coupled to the cycling of iron,² carbon³ and nitrogen,⁴ and to the dynamics of elements/ions associated with the arsenic redox cycle, such as sulfur.⁵ Coupling of biogeochemical cycles is receiving increasing attention in recent years since the study of coupled biogeochemical cycles will offer the scientific basis for some major environmental problems that we are facing today.⁶

The proteins catalyzing physiological processes in living organisms are influenced by geological, physical and chemical forces and therefore continuously evolve and redistribute between various chemical species involved in biogeochemical cycles. Genetic analysis is the key to understanding arsenic biogeochemical cycle. Once the genes associated with arsenic relevant reactions and the conditions that affect gene expression are understood, how organism metabolisms influence arsenic biogeochemical cycles will be predicted. This review focuses on an account of known functional genes involved in arsenic biotransformation and the effect of many other elements on arsenic biogeochemistry. Our article highlights the current state of meta-omics research in arsenic

metabolizing microbes. It also attempts to discuss the integration of meta-omics information into biogeochemical models, with the aim of predicting elemental biogeochemistry in a given environment.

2. Arsenic metabolism: from genes to biogeochemical processes

Organisms have evolved various strategies to transform arsenic for detoxification or energy metabolism. An overview about the pathways for arsenic redox reactions and synthesis of novel organoarsenicals is presented in Figure 1. Each step of the reaction network is catalyzed by proteins encoded by genes. Genes involved in arsenic metabolism that have been identified are summarized in Table S1.

2.1 The arsenic redox cycle

The earliest microorganisms on Earth have evolved in an anoxic environment, where the relevant arsenic redox species was most probably the reduced As(III) rather than the oxidized As(V). The physiological activities of the earliest microorganisms were, therefore, largely driven by anaerobic metabolic processes,⁷ and As(III) bioavailability may have been a driving force for the evolution or acquisition of genes encoding proteins involved in anaerobic respiratory pathways.⁸ Microbes, such as *Oscillatoria*-like cyanobacteria that used As(III) as the sole photosynthetic electron donor to grow as a photoautotroph,⁹ or chemoautotrophic As(III)-oxidizers that could utilize As(III) as an electron donor and nitrate as an electron acceptor in energy-generating respiratory chains,¹⁰ probably evolved quite early. These microorganisms could cope with extreme growth conditions, such as high

concentrations of As(III) or low oxygen, similar to those that existed in an primordial anoxic biosphere.

Since As(III) was probably the primary bioavailable arsenic species on the early anoxic Earth, it may be an inevitable choice for organisms to utilize As(III) as an electron donor to produce energy.¹¹ As(III) oxidation is catalyzed by the enzyme As(III) oxidase, which contains two heterologous subunits, a large subunit (α) having molybdopterin and a [3Fe-4S] cluster (AioA) and a smaller subunit (β) incorporating a Rieske-type [2Fe-2S] cluster (AioB).¹² The cluster of *aioA* and *aioB* genes (*aio* operon) usually consists of *aioS* and *aioR* genes, encoding for a two-component signal transduction pair, AioS (sensor histidine kinase)/AioR (transcriptional regulator), which regulates expression of *aio* genes via recognizing As(III).¹³ The operon sometimes has an *aioX* gene that encodes an As(III)-binding protein involved in As(III)-based signaling and regulation of As(III) oxidation¹⁴, a *cytC* gene encoding a cytochrome c that is required for efficient As(III) oxidation in *Ochrobactrum tritici* SCII24,¹⁵ or a *moeA* gene that encodes the MoeA protein that synthesizes the molybdenum cofactor of AioAB oxidase.¹³ More recently, a new type of As(III) oxidase, ArxA, was identified in the chemolithoautotrophic *Alkalilimnicola ehrlichii* strain MLHE-1, which couples As(III) oxidation to NO₃⁻ reduction.¹⁶ ArxA was found to catalyze As(III) oxidation coupled to photosynthesis in the purple-sulfur bacterium *Ectothiorhodospira* sp. strain PHS-1.¹⁷ Moreover, ArxA has greater homology to ArrA subunit than to AioA, and fills the phylogenetic gap between As(III) oxidases and As(V) reductases.^{16,17}

When the atmosphere became oxidizing with the rise of oxygenic photosynthetic microorganisms during the great oxidation event ca. 2.3-2.5 Ga, the majority of aqueous As(III) would have been oxidized to As(V). This presented both an opportunity and a challenge to the organisms of that time. The opportunity was that this new oxidized species could be used for energy generation by serving as a terminal electron acceptor. The challenge was that organisms were now exposed to a new environmental toxin, As(V), for which they had not developed any defenses.

To take advantage of the appearance of As(V) as a new potential terminal electron acceptor for the respiratory chain, dissimilatory As(V)-respiring prokaryotes (DARPs) evolved pathways that a new energy-generating respiratory chain utilizing the respiratory As(V) reductase, ArrAB, that reduce the less toxic As(V) to the more toxic and potentially more mobile As(III).^{12, 18} The reductase encoded by *arr* is a heterodimer consisting of a large catalytic subunit (ArrA) and a small subunit (ArrB).

¹⁹

The rise of oxidized As(V) in oceans created a new environmental toxin. As(V) enters the cells of most organisms adventitiously via phosphate uptake systems. As a consequence, early life had to evolve novel strategies for coping with new (potentially toxic) arsenic species. As described in more detail below, nearly every extant microbe has ArsB or Acr3 efflux permeases for As(III) detoxification, so it is reasonable to assume that organisms that arose before the GOE already had an As(III) efflux system. When As(V) became the predominant soluble species, all cells had to do was to reduce As(V) to As(III), the substrate of ArsB or Acr3, and they would

become resistant to As(V). A number of independently-evolved As(V) reductases arose in a variety of organisms using a small molecular mass protein As(V) reductases (one of several types of ArsC or Acr2 reductases). The ArsC system conferred by the *ars* operon is the most well studied mechanism of arsenic detoxification and resistance (for details see the previous review).²⁰ These enzymes all use small molecule proteins such as glutaredoxin (Grx) or reduced glutathione (GSH) coupled to thioredoxin (Trx) as electron donor. The Acr2 reductases evolved from proteins that incorporated the phosphate binding loop of phosphorprotein tyrosine phosphatases related to the cell phosphatase CDC25.²¹ These phosphatase can be converted into As(V) reductases by just a few mutations,²² indicating a facile evolutionary path.

In addition to the Arr and ArsC As(V) reductases, there are several other enzymes that have the potential to reduce As(V) to As(III). Most recently, a glutathione S-transferase B (GstB) was found to mediate an alternate pathway which conferred As(V) resistance to *E. coli* mutant cells lacking *arsC* by directly reducing As(V) to As(III) with reduced GSH as the electron donor.²³ A new As(V) reductase High Arsenic Content 1 (HAC1)²⁴ and inositol transporters (AtINT2 and AtINT4)²⁵ were identified to be required for As(V) reduction and As(III) loading into the phloem in *Arabidopsis thaliana*, respectively. There are other As(V) reductases related to the CDC25 phosphatases from rice, named as OsACR2.1 and OsACR2.2.²⁶ More and more arsenic reductases and trivalent arsenic-specific transporters

identified show that arsenic reduction plays an important role in arsenic biogeochemical cycling.

2.2 The arsenic methylation cycle

In addition to oxidation and reduction of inorganic arsenic species, pathways for biotransformation of arsenic, including methylation and demethylation, organoarsenical degradation, evolved in early organisms. Interest in arsenic biomethylation began in 1800's with the observation that inorganic arsenic compounds used as wallpaper pigments were converted into Gosio gas (trimethylarsine) by fungi. More recent reports of methylated arsenical showed that arsenic methylation was widespread in the environment and detected in bacteria,²⁷ cyanobacteria,²⁸ algae,²⁹ protozoan,³⁰ et al. Arsenic methylation is always considered as a common means to detoxify arsenic because the products are less toxic pentavalent methylated arsenic species and the more toxic trivalent species are only intermediates, and because the gaseous end-products escape from cells/environments, leading to detoxification. The process is catalyzed by As(III) S-adenosylmethionine (SAM) methyltransferases, designated as AS3MT in animals and as ArsM in microorganisms. Expression of typical prokaryotic and archaeal *arsM* genes are regulated by ArsR,³¹ suggesting that arsenic methylation is a detoxification pathway in the microbes. Expression of *arsM* in some cyanobacteria appears to be constitutive,³² indicating that alternate detoxification pathways are used by microorganisms in which the expression of *arsM* is not regulated.³³

The degradation of environmental organoarsenicals has been documented for some time,^{34, 35} while few molecular mechanisms for these reactions have been demonstrated. Recently, a two-step pathway of MSMA reduction and demethylation was elucidated.³⁶ Although no reductases of pentavalent organoarsenicals have been identified as yet, the enzyme, ArsI, which catalyzes demethylation of trivalent organoarsenicals, was identified and characterized from the environmental isolate bacterium *Bacillus* sp. MD1³⁷ and from the cyanobacterium *Nostoc* sp. 7120.³⁸ ArsI, a non-heme iron-dependent dioxygenase with C-As lyase activity, cleaves the C-As bond in MAs(III), trivalent roxarsone, and other trivalent aromatic arsenicals. Putative ArsI orthologs were found only in bacterial species, suggesting that alternate pathways of organoarsenical demethylation might exist in other organisms.

³⁷

2.3 The organoarsenical cycle

The arsenic concentration in seawater is around 1 to 2 µg per liter, mainly inorganic arsenic that is usually transformed into complex organoarsenical compounds by marine organisms.³⁹ Arsenosugars, first identified in 1981,⁴⁰ are commonly detected water-soluble arsenic species present in marine algae; arsenobetaine is the most abundant arsenical in the majority of marine animals.³⁹ More complex organoarsenicals have been identified with the improvement of analytical techniques in recent years. Since the structure of an arsenosugar phospholipid (AsPL) from a brown alga *undaria pinnatifida* was first identified,⁴¹ AsPL has been found in algae⁴² and cyanobacteria.⁴³ Arsenic-containing fatty acids (AsFA) that were first

identified in cod liver oil ⁴⁴ have now been found in algae ⁴⁵ and various fish species.
^{46, 47} AsHC that were first reported in capelin ⁴⁸ have been detected in fish ^{46, 47} and
algae. ⁴² A new class of arsenolipids, trimethylarsenio fatty alcohols (TMAsFOH),
was recently reported in Capelin oil. ⁴⁹ Recently, two new groups of arsenolipids,
arsenic-containing phosphatidylcholines (AsPC) and arsenic-containing
phosphatidylethanolamine (AsPE) from herring caviar, were characterized. ⁵⁰ In total,
more than 20 arsenosugars and 70 arsenolipids have been identified, and most were
identified in marine organisms that live in low phosphate and high salt environments.
These organoarsenicals are not toxic for the marine plants and animals, but their
function in these marine organisms is not known. Phytoplankton can substitute
sulfur- and nitrogen-containing membrane lipids for membrane phospholipids, ⁵¹
arsenolipids might be used in membranes in place of phospholipids due to the more
similarity of As(V), than sulfate and nitrate, to inorganic phosphate. Thus As(V)
could be used as a phosphate-sparing substitute in phosphate-limiting environments.
A recent study on *Ectocarpus siliculosus* that was found to produce more
arsenosugar phospholipids under low-phosphate than under normal phosphate
conditions ⁵² supports this hypothesis.

However, these organoarsenicals may be toxic to organisms that cannot
biosynthesize them. *In vitro* toxicological characterization of three
arsenic-containing hydrocarbons showed that cytotoxicity of the arsenic-containing
hydrocarbons was comparable to that of As(III) for cultured human bladder and liver

cells,⁵³ and arsenolipids were metabolized by humans to DMA(V) and other small molecular arsenic compounds, then excreted in the urine.^{54, 55}

Although several potential pathways have been proposed for the synthesis of complex organoarsenicals,⁷ few genes involved in these biotransformation have been identified. Even less is known about the degradation of these organoarsenicals, and more studies are needed on this front.

2.4 Arsenic efflux pathways

The best way to deal with toxic arsenicals in cells is acquisition of an efficient efflux system. As(III) efflux systems have been intensively studied in both microbes and higher organisms.^{56, 57} As(III) efflux in most bacteria was mediated by ArsB in an energy-dependent process, driven in *Staphylococcus aureus* by the membrane potential⁵⁸ and in *E. coli* by ATP hydrolysis that ArsA binds to ArsB to an ATP-driven arsenic-specific pump.⁵⁹ In the legume symbiont *S. meliloti*, an aquaglyceroporin (AqpS), instead of ArsB, has been identified to extrude As(III) from cells.⁶⁰ Acr3 has been shown to be an As(III)-efflux transporter in both bacteria and yeast, and provides a pathway for As(III) extrusion from cells.⁶¹ In fact, genes for Acr3 are more wide-spread in bacteria and archaea than are *arsB* genes. The cytosolic As(III)/glutathione complex sequestered into vacuoles by an ABC-type transporter, Ycf1p (yeast cadmium factor protein), is the second pathway for As(III) detoxification in yeast *Saccharomyces cerevisiae*.⁶²

Recently, a novel mechanism for As(V) resistance was identified in a variety of microbes including *Pseudomonas aeruginosa*.⁶³ In these bacteria there are two

genes that always go together, one encoding a typical glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and the second one, called *arsJ*, that encodes an organoarsenical efflux permease (ArsJ). GAPDH uses As(V) and glyceraldehyde 3-phosphate to form the extremely unstable organoarsenical 1-arseno-3-phosphoglycerate, which is extruded from cells by ArsJ and immediately breaks down into As(V) and 3-phosphoglycerate. The net reaction is effectively As(V) extrusion, and the coupled reaction confers As(V) resistance to these microbes, the only known efflux pathway for As(V).

At the same time, the bacterial permease, ArsP, from *Campylobacter jejuni*, was demonstrated to be an efflux system specific for trivalent organoarsenicals.⁶⁴ It is more selective for the ancient organoarsenical MAs(III) than for the recently anthropogenically-developed antimicrobial aromatic arsenical growth promoters such as trivalent roxarsone. This suggests that the earliest organisms may have had the capability of methylating arsenic, and not to use arsenic methylation as arsenic detoxification pathway instead of generating more toxic methylated arsenic compounds and extruding them as antibiotics.⁶⁵ Arsenic methylation slowly became an arsenic detoxification pathway for organisms with increasing oxygen concentration in the atmosphere.⁶⁵

3. Coupling of arsenic biogeochemical cycling to other elements

Any biogeochemical process, such as the cycling of a particular element, is likely to be mediated by more than one organism, and often linked to other fundamental

biogeochemical processes. Arsenic transformation is often coupled to the cycling of carbon, iron and nitrogen.^{66, 2} The effect of Fe, N, and natural organic matter (NOM) turnover on arsenic biogeochemical cycling is summarized in Figure 2 based on previous studies.^{7, 67, 68, 69} The importance of these three biogeochemical cycles (Fe, N, C) for the environmental behavior of arsenic is described below.

3.1 The effects of iron on arsenic biogeochemical cycling

The chemical speciation of arsenic in natural environments and arsenic mobility are strongly dependent on redox potential and pH. Arsenic in solution occurs primarily as oxidized As(V) at oxidizing redox conditions (500-200 mV), while arsenic is present mainly as As(III) at alkaline pH or upon reduction to -200 mV. Arsenic is often adsorbed onto Fe(III) (oxyhydr)oxides in the form of As(V) under moderately reducing conditions (0-100 mV),⁷⁰ As(III) appears to be more mobile. Below pH 5-6 the sorption of As(V) onto amorphous iron oxide and goethite is higher than that of As(III), at neutral pH As(V) and As(III) sorption onto iron oxide is both relatively high, whereas above pH 7-8, As(III) is more easily adsorbed to iron oxide than As(V).⁷¹

Transformation of arsenic-bearing Fe mineral phases strongly affects the bioavailability of arsenic within soils and aquifers due to direct and indirect interactions between the arsenic and Fe cycles including mineral formation, transformation, dissolution and redox reactions.^{69, 72, 73} Previous studies from our laboratory showed that Fe plaque consisting of Fe(III) (oxyhydr)oxides, which was

induced artificially through adding ferrous iron in solution to paddy soils, has high affinity for As(V), and reduced arsenic uptake by rice.^{74, 75, 76}

Fe(III)-reducing bacteria modulate arsenic mobility in the rhizosphere. Dissimilatory reduction of Fe(III) (oxyhydr)oxides to Fe(II) by dissimilatory iron-reducing bacteria (DIRB) can result either in the release of As(V) from poorly crystalline or more crystalline ferric minerals as well as from sorption sites within sediments,⁷⁷ or in the binding of arsenic to the formed Fe(II) minerals.^{78, 79, 80} DIRB are commonly present in rice paddy soil, and mediate dissimilatory reduction of Fe(III) on the rice root-plaque.⁸¹ A study on the role of DIRB in arsenic release under a range of biogeochemical regimes indicated that Fe(III) reduction was stimulated by addition of acetate as a potential electron donor that resulted in a marked increase in the number of DIRB, reduction of As(V) to As(III), and arsenic release after Fe(III) reduction.⁸² If DARPs were used as Fe(III)-reducers, *Shewanella* sp. ANA-3⁸³ or *S. Barnesii*⁸⁴ could release both As(III) and Fe(II) from ferrihydrite containing As(V) by reducing solid-phase As(V) and Fe(III). Eventually, most of the ferrihydrite matrix was liberated as Fe(II) and As(III) if sufficient organic electron donor was present.⁸⁵

The release of arsenic by Fe(III) reduction (by DIRB) could be affected partly by the metabolic activities of sulfate-reducing bacteria (SRB) that are integral parts of microbial communities. SRB cause dramatic changes in Fe, sulfide and arsenic species by generating hydrogen sulfide⁸⁶ or elemental sulfur from sulfate.⁵ SRB produce sulfide using SO_4^{2-} and result in localized reprecipitation of released arsenic

as poorly soluble sulfides such as arsenic trisulfide⁸⁷ or Fe-As-sulfide.⁸⁸ These transformations have the potential to significantly impact the fate of environmental arsenic.

In addition to Fe(III) reduction that has the potential to mobilize or immobilize arsenic depending on geochemical conditions that lead to the formation of either dissolved Fe²⁺ or Fe(II) minerals, the formation of Fe(III) minerals under Fe(II)-oxidizing conditions has the potential to significantly immobilize arsenic and thus to lower its bioavailability.^{89, 90} In particular for nitrate-reducing Fe(II)-oxidizing bacteria it has been shown that they form poorly soluble Fe(III) minerals and efficiently co-precipitate arsenic (Figure 2).^{89, 90} Besides nitrate-dependent Fe(II) oxidation, also microaerophilic Fe(II) oxidation has the potential to influence arsenic mobility and could even be used in biotechnical applications for arsenic removal, e.g. in drinking water filters⁹¹ although it has been shown that in commercial drinking water filters the formation of iron biominerals by Fe(II)-oxidizing bacteria lowers arsenic removal from the water.⁹²

3.2 The effects of N on arsenic biogeochemical cycling

Nitrate is an ecologically significant oxidant that can support microbial oxidation of As(III) in the absence of oxygen. The first evidence that microbes are capable of linking anoxic As(III) oxidation to denitrification came from a field study in anoxic lake water columns.⁴ The absence or presence of nitrate affected the redox state of arsenic. As(III) was present where nitrate was depleted, but As(V) was the dominant species during anoxic nitrate-rich periods. Subsequently, a nitrate-dependent As(III)

oxidation bacterium *A. ehrlichii* strain MLHE-1 was found to be capable of coupling As(III) oxidation with partial denitrification of nitrate to nitrite.^{10, 93} Two other anoxic chemolithoautotrophic strains, *Azoarcus* strain DAO1 and *Sinorhizobium* strain DAO10, were able to oxidize As(III) and fix CO₂ via complete denitrification of nitrate to dinitrogen gas.⁹⁴ Biological nitrate-dependent As(III) oxidation is widespread in the environment, and potentially plays a significant role in arsenic biogeochemical cycling.⁹⁵

As mentioned above, nitrate also influences the bioavailability and mobility of arsenic indirectly by linking nitrate reduction to Fe(II) oxidation. Previous studies showed tight coupling between N, Fe, and arsenic in paddy soil.⁶⁶ Addition of nitrate reduced arsenic uptake by rice probably because i) the nitrate inhibited/reduced Fe(III) reduction leading to less arsenic mobilization and ii) nitrate-dependent Fe(II)-oxidizing bacteria stimulated Fe(II) oxidation, which led to arsenic co-precipitation with Fe(III) minerals in soil. Nitrate strongly affects arsenic cycling under anoxic conditions in nitrate-rich Upper Mystic Lake by microbially catalyzing As(III) to more particle-reactive As(V) and oxidizing Fe(II) to arsenic-sorbing particulate ferric oxides.⁴ Microbial nitrate-dependent Fe(II) oxidation in groundwater,⁹⁶ freshwater sediments⁹⁷ and marine sediments⁹⁸ has the potential to contribute to the reduction of arsenic mobility in various ecosystems.

3.3 The effects of organic matter on arsenic biogeochemical cycling

Organic matter affects the fate of arsenic by competitive adsorption and redox reactions,^{99, 100, 101} and formation of arsenic-bearing organic-metal-complexes and

mineral colloids.^{102, 103} NOM is considered to be an efficient geochemical trap for arsenic both under oxic and reducing conditions. Whereas As(V) is immobilized by binding to protonated amino groups of NOM³ or a nucleophile substitution reaction between As(V) and phenolic OH groups of NOM,¹⁰⁴ As(III) is associated with NOM via phenolic OH or carboxyl groups of NOM by H-bonding, hydrophobic As(III)-NOM interactions,¹⁰⁴ or via ternary As(III)-Fe(III)-NOM complexes that form bridges between Fe(III), arsenic oxyanions and the functional entities of NOM.^{105, 106} In contrast, under sulfate-reducing conditions, the formation of a trigonal-pyramidal complex between As(III) and sulfhydryl groups of NOM could potentially be a sequestration mechanism for arsenic.¹⁰⁷

Organic matter could also change the fate of arsenic by influencing microbial communities. NOM is thought to drive the reductive dissolution of Fe(III) (oxyhydr)oxides, thereby causing redox transformations of As(V) to As(III) and facilitate arsenic release.¹⁰⁷ In addition to the reductive dissolution of arsenic-bearing Fe(III) (oxyhydr)oxide phases, our studies revealed that addition of organic matter to paddy soil significantly increased arsenic methylation and volatilization.¹⁰⁸ Application of rice straw into soil increased arsenic accumulation in rice by influencing microbial processes involved in arsenic redox.¹⁰⁹

Apart from iron oxides and organic materials, silicon significantly decreased As(III) concentration, but increased the concentration of DMAs in both the vegetative and reproductive tissues of rice.¹¹⁰ In brief, in addition to biological transformations, other inorganic elements, compounds/minerals and

physico-chemical properties interact with arsenic in the environment. Coupling of arsenic with other elements makes it necessary to consider genes involved in cycling of other elements, such as Fe, N, S, and carbon when studying the arsenic biogeochemical cycling.

4 Understanding biogeochemical arsenic cycling by application of “omics” methods and integrated modeling

Microbes are ubiquitous in nature and so govern critical processes of arsenic biotransformation and influence arsenic redox speciation and bioavailability in soils, sediments and bodies of water.¹¹¹ Currently, attention is being paid to functional groups and functional genes in the environment, and their linkage with biogeochemical processes. Genes associated with arsenic biotransformation are widely distributed in paddy soils, and the variation in gene distribution and abundances were driven by soil properties, such as pH, total C and N content, Fe, etc.^{112, 113} Microbes involved in arsenic transformation were found to be ubiquitously distributed in paddy soils, resulting in various concentrations and percentage of inorganic and methylated arsenic species among different rice plants.^{114, 115, 116} Since higher plants appear not to methylate arsenic,¹¹⁷ microbial mediated methylation is probably the primary source of methylated arsenic in plants, which is expected to occur in soil prior to plant uptake.

Although some genes involved in arsenic biotransformation have been well characterized and easily quantified in laboratory studies with pure cultures of

microorganisms, the speciation, fate and biogeochemical transformation processes of arsenic in the environment are much more complex to determine due to the fact that arsenic biogeochemical cycling is driven by various arsenic metabolism genes and genes involved in other element cycles or related to arsenic bioavailability. It is therefore necessary to apply more systematic and more comprehensive approaches, such as metagenomics, metatranscriptomics, metaproteomics, and metabolomics to understand the interactions between environmental microbes, their geochemical surrounding, and neighboring organisms by analyzing DNA, RNA, proteins, and metabolites extracted directly from environmental samples.

4.1 Metagenomics

Metagenomics provides an inestimable window into the microbial world by characterizing microorganisms involved in difficult-to-elucidate but important biochemical pathways, as the overwhelming majority of microbes in the environment can not be cultured in the laboratory. Chauhan et al constructed a metagenomic library, identified two arsenic-resistant bacteria and one novel As(V) resistance gene (*arsN*) which encodes a protein similar to acetyltransferases.¹¹⁸ Metagenomics was also used to unravel the correlations between the microbes and arsenic transformation in different niches.^{119, 120, 121} Although metagenomics provides us the taxonomic and functional profiles of a microbial community but does not tell us the expression levels of the genes nor their physiological activity.¹²² Therefore, metatranscriptomics is needed to delineate the active functional genes and communities.

4.2 Metatranscriptomics

Metatranscriptomics offers novel insights into the expression of functional genes and microbial activities of complex microbial communities at a specific moment or under specific environmental conditions by sequencing the total mRNAs extracted from natural microbial communities.¹²³ Functional metatranscriptomics has potential for isolation and characterization of novel genes involved in heavy metal transformation.¹²⁴ Metatranscriptomics enhances our understanding of microbial responses to their environment¹²⁵ and the functional profile of a microbial community.¹²⁶ Recently, a transcriptomics meta-analysis was used to unravel the effect of As(III) on the symbiotic interaction between *Medicago–Ensifer*¹²⁷ and adaptive responses of bacteria to arsenic exposure.¹²⁸ The metatranscriptomic approach will be useful to study how microbes regulate their genes to adapt to the changes in environmental conditions, particularly arsenic concentrations.

4.3 Metaproteomics and metabolomics

Metaproteomics and metabolomics are the comprehensive methods by which proteins produced by microbes and metabolites released by microorganisms into the environment are characterized and quantified using a combination of liquid or gas chromatography-based separations and mass spectrometry-based identification techniques.^{129, 130} The study of microbial proteome and metabolome can provide valuable information about the function of microbial communities and the interactions of the microbial communities with the environment.^{131, 132} When the diversity of arsenic-adapted prokaryotic communities in mildly arsenic-contaminated

sediments was analyzed using meta-proteomic and 16S rDNA amplification, the results indicated that the data sizes provided by metaproteomics are less than those provided by metagenomics and metatranscriptomics.¹³³ So far, metabolomics has been used mainly to analyze low molecular mass metabolites within a tissue, biofluid, a cell or cell compartment of an organism including plants, animals, bacteria, and human exposed to environmental stressor.¹³² High-throughput metabolomics has been applied to the analysis of metabolites in the liver of mice when co-exposed to high fat and cholesterol diets and arsenic-contaminated drinking water.¹³⁴ However, application of metaproteomic and metabolomic techniques to real environment is limited due to difficulties with amplification and the low quantities of extractable proteins and metabolites because of the interferences with many components present in complex environmental systems, such as soil.^{132, 135}

4.4 Integrating meta-omic techniques

From the above, meta-omics are key techniques in elucidating the dynamic and complex interactions between microbial communities and the environment. Integrating multiple meta-omic datasets will provide a complete exhibition from genes to biogeochemical cycles. Metatranscriptomic and metagenomic techniques were combined to detect large numbers of novel genes from complex marine microbial communities.¹²⁶ Datasets of meta-genomics were integrated with metabolomics to reveal how a microbial community interacts with the environment and responds to environmental parameters.¹³⁶ Taken together, meta-omic technologies offer an unprecedented opportunity to elucidate the functions of

microbes that are not readily cultured under normal laboratory conditions in biogeochemical cycles.

Recently, "Arsenomomics" was termed as an approach to focusing on the analysis of alterations in transcriptome, proteome and metabolome occurring in microbes exposed to arsenic.^{137, 138} With the application of meta-omics to environmental science, we believe that Arsenomomics will evolve to include the analysis of metagenomic, metatranscriptomic, metaproteomic, and metabolomic changes in microbial communities from the real environment where they are exposed to arsenic.

4.5 Integrating environmental meta-omics into biogeochemical models for arsenic

Microbes are ubiquitous in diverse environmental niches including soil, oceans, sediments, freshwater environments, and inside the body of animals or plants, and exert great influence on biogeochemical cycles in these habitats. Characterization of genes involved in arsenic biotransformation and application of multiple meta-omics in environment analysis will lead to insights into the microbial world, as limited information on functional genes cannot predict the status of arsenic in the environment. In addition, arsenic biogeochemistry is also controlled by other environmental factors. The information of field/*in situ* characterization of functional genes/functional microbial communities and biogeochemical fluxes should be integrated into biogeochemical models to complete the transition from lab to the field, from biochemistry to biogeochemistry, and from genes-genomics to microbial communities. This integration will help to predict the dynamics of arsenic in the

environment, and to improve the effectiveness of mitigation technologies. Many strategies have been developed to model low complexity environments. For example, recent work integrating environmental genomics and qPCR in biogeochemical models explored the nexus between microbial community and geochemistry in the Arabian Sea oxygen minimum zone.¹³⁹ Recently, metabolic processes coupling carbon, nitrogen, and sulfur transformations in the Saanich Inlet oxygen-starved zone were integrated using a biogeochemical model that integrates multi-omic information and geochemistry.¹⁴⁰ These studies indicated that such integrated modeling approaches can provide a novel insight into microbial metabolic networks in water bodies, and pave a road for prediction of elemental cycling.

5 Perspectives

In summary, as arsenic biotransformations are catalyzed by a suite of enzymes from diverse environmental organisms, and these are coupled to biogeochemical cycles of other elements such as Fe, S, and N. As more and more genomes are being sequenced, more genes directly or indirectly involved in arsenic metabolism will be discovered and characterized. With the development of new technologies, we anticipate rapid advances in analytical chemistry, microbiology and genomics that will improve our understanding of how microbial metabolic pathways contribute to and govern complex environmental processes. In the future, integrating meta-omic datasets into biogeochemical models will improve the ability of prediction and offer a deeper insight into arsenic biogeochemical processes in diverse niches.

In future studies, it will be necessary to perform the phylogenetic analyses of the genes involved in arsenic metabolism and analyze the interaction between organisms and the environment using additional meta-omics approaches at different spatio-temporal scales. Geochemical analyses in combination with genetic analyses will provide insights into the specific roles of the complex biochemical pathways in the global arsenic biogeochemical cycle. More importantly, integrating modeling approaches linking arsenic biogeochemical cycle with meta-omics data should be developed to predict the dynamic of arsenic species in water, sediments and soils and provide our society and authorities with the tools necessary for limiting arsenic pollution, improving remediation and providing safe drinking water and food.

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Legends

Fig. 1. Pathways for arsenic redox reactions and synthesis of novel organoarsenicals.

Fig. 2. The model of effect of Fe, N, S and natural organic matter (NOM) on arsenic biogeochemical cycling highlights proteins encoded by genes associated with elemental metabolisms.

Associated content

Supporting Information: The genes involved in arsenic metabolisms (Table S1).