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1 Linking genes to microbial biogeochemical cycling: lessons from arsenic

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20

21 **Abstract**

22 The biotransformation of arsenic is highly relevant to the arsenic biogeochemical
23 cycle. Identification of the molecular details of microbial pathways of arsenic
24 biotransformation coupled with analyses of microbial communities by meta-omics can
25 provide insights into detailed aspects of the complexities of this biocycle. Arsenic
26 transformations couple to other biogeochemical cycles, and to the fate of both
27 nutrients and other toxic environmental contaminants. Microbial redox metabolism of
28 iron, carbon, sulfur and nitrogen affects the redox and bioavailability of arsenic
29 species. In this critical review we illustrate the biogeochemical processes and genes
30 involved in arsenic biotransformations. We discuss how current and future
31 metagenomic-, metatranscriptomic-, metaproteomic-, and metabolomic-based
32 methods will help to decipher individual microbial arsenic transformation processes,
33 and their connections to other biogeochemical cycle. These insights will allow future
34 use of microbial metabolic capabilities for new biotechnological solutions to
35 environmental problems. To understand the complex nature of inorganic and organic
36 arsenic species and the fate of environmental arsenic will require integrating
37 systematic approaches with biogeochemical modeling. Finally, from the lessons
38 learned from these studies of arsenic biogeochemistry, we will be able to predict how
39 the environment changes arsenic, and, in response, how arsenic biotransformations
40 change the environment.

41

42 **1. Introduction**

43 Biogeochemical cycles are interconnected through redox reactions and other
44 biotransformations. ¹ Biogeochemical processes such as the cycling of a particular
45 element are likely to be mediated by multiple microbes and are often linked to other
46 biogeochemical processes. For example, redox changes of arsenic are mediated by
47 diverse arsenate (As(V))-reducing and arsenite (As(III))-oxidizing microbes. Arsenic
48 biogeochemical cycling is often coupled to the cycling of iron (Fe), ² carbon (C) ³ and
49 nitrogen (N), ⁴ and to the dynamics of elements/ions associated with the arsenic redox
50 cycle, such as sulfur (S). ⁵ Coupling of biogeochemical cycles has recently received
51 attention. The study of coupled biogeochemical cycles offers a scientific basis for
52 major current environmental problems. ⁶

53 The proteins catalyzing physiological processes in living organisms are
54 influenced by geological, physical and chemical forces and therefore continuously
55 evolve and redistribute chemical species involved in biogeochemical cycles. Genetic
56 analysis is the key to understand the arsenic biogeochemical cycle. Once the genes
57 associated with the reactions and the environmental signals that affect gene expression
58 are understood, we will be able to predict how microbial metabolism influences
59 arsenic biogeochemical cycling. In this review, we focus on the known genes
60 involved in arsenic biotransformations and the effect of other elements on arsenic
61 biogeochemistry. We highlight the effects of other elements on arsenic metabolism
62 and the current state of meta-omics research in microbial arsenic metabolism. Finally,
63 we discuss how integration of meta-omics information into biogeochemical models
64 can allow us to predict the possible biotransformation of other elements.

65

66 **2. Arsenic metabolism: from genes to biogeochemical processes**

67 Organisms have evolved various strategies to transform arsenic for detoxification or
68 energy metabolism. ⁷ An overview about the enzymatic pathways for arsenic
69 biotransformations is presented in Figure 1, and related microbial genes are
70 summarized in Table 1.

71 **2.1 The arsenic redox cycle**

72 The earliest microorganisms evolved in an anoxic environment, where the
73 predominant arsenic species was most probably reduced As(III), with little oxidized
74 As(V). The physiological activities of the earliest microorganisms were, therefore,
75 largely driven by anaerobic metabolic processes, ⁸ and we propose that As(III)
76 bioavailability was a driving force for the evolution or acquisition of genes encoding
77 anaerobic respiratory pathways. ³³ For example, the photosynthetic purple sulfur
78 bacterium *Ectothiorhodospira* PHS-1 carries out anoxygenic photosynthesis using
79 As(III) as an electron donor in the light ^{34, 35, 36} and uses As(V) as an electron acceptor
80 in the dark. ³⁷ The chemolithoautotrophic As(III)-oxidizer *Alkalilimnicola ehrlichii*
81 MLHE-1 utilizes As(III) as an electron donor and nitrate as an electron acceptor in
82 energy-generating respiratory chains. ³⁸ Microorganisms with similar metabolic
83 versatility probably evolved quite early. These microbes could cope with extreme
84 growth conditions, such as high concentrations of As(III) or low oxygen, similar to
85 those that existed in an primordial anoxic biosphere.

86 Since As(III) was probably the primary bioavailable arsenic species on the early
87 anoxic Earth, it was the inevitable choice for organisms to utilize As(III) as an
88 electron donor to produce energy. ³⁹ As(III) oxidation is catalyzed by the enzyme
89 As(III) oxidase, which is composed of two different subunits, a large subunit (α)
90 having molybdopterin and a [3Fe-4S] cluster (AioA) and a smaller subunit (β)

91 incorporating a Rieske-type [2Fe-2S] cluster (AioB).⁴⁰ The cluster of *aioA* and *aioB*
92 genes (*aio* operon) usually consists of *aioS* and *aioR* genes, encoding for a
93 two-component signal transduction pair, AioS (sensor histidine kinase)/AioR
94 (transcriptional regulator), which regulates expression of *aio* genes via recognizing
95 As(III).⁹ The operon sometimes has an *aioX* gene that encodes an As(III)-binding
96 protein involved in As(III)-based signaling and regulation of As(III) oxidation,¹² a
97 *cytC* gene encoding a cytochrome c that is required for efficient As(III) oxidation in
98 *Ochrobactrum tritici* SCII24,⁴¹ or a *moeA* gene encoding MoeA protein that
99 synthesizes the molybdenum cofactor of AioAB oxidase.⁹ Recently, a new type of
100 As(III) oxidase, ArxA that exhibited both As(V) reductase and As(III) oxidase
101 activities *in vitro*,¹⁰ was identified in *A. ehrlichii* MLHE-1.⁴² In *Ectothiorhodospira*
102 sp. PHS-1 these genes code for As(III) oxidation coupled to photosynthesis.^{35, 11} In
103 addition to *arxA*, the MLHE-1 and PHS-1 *arx* operons, contain four other genes *arxB2*,
104 *arxB*, *arxC*, and *arxD*, that encode two proteins with [4Fe-4S] centers, a membrane
105 anchoring and quinol oxidoreductase subunit and a TorD-like molybdoenzyme
106 chaperone respectively.¹¹ An adjacent and divergent gene cluster, *arxXSR*, encodes
107 putative regulatory proteins, a periplasmic substrate-binding protein specific for
108 phosphate (ArxX), a two-component histidine kinase sensor (ArxS), and a response
109 regulator (ArxR).¹¹ ArxA has higher sequence similarity to the ArrA subunit than to
110 AioA, and fills the phylogenetic gap between As(III) oxidases and As(V) reductases.
111^{42, 11}

112 Note that As(III) oxidation by anaerobes would have produced As(V) in the
113 absence of an oxygen-containing atmosphere, which opened a niche for
114 As(V)-respiring microbes prior to the Great Oxidation Event (GOE).³³ Dissimilatory
115 As(V)-respiring prokaryotes (DARPs) evolved pathways to take advantage of the

116 appearance of As(V) as a terminal electron acceptor. This new energy-generating
117 respiratory chain utilized the respiratory As(V) reductase, ArrAB, that reduce the less
118 toxic As(V) to the more toxic and potentially more mobile As(III).^{40, 43, 44} ArrAB is a
119 heterodimer consisting of a large catalytic subunit (ArrA) and a small subunit (ArrB).
120^{15, 16} The *arr* operon also includes *arrC*, *arrD*, *arrS*, and *arrR*. Their gene products are
121 ArrC, a membrane-bound As(V) reductase subunit, ArrD, a As(V) reductase chaperon,
122 ArrS, a sensor histidine kinase and ArrR, a transcriptional regulator respectively.¹⁷ A
123 phylogenetic analysis was conducted to search for molybdenum-bis (pyranopterin
124 guanine dinucleotide)-containing catalytic subunits of representative enzymes. This
125 complex iron sulfur molybdoenzyme family includes Arr, Aio, Arx, polysulfide
126 reductase, and nitrate reductase. The results indicate that Arr clusters most likely
127 evolved from polysulfide reductases.¹⁷

128 After the GOE, As(III) in oceans mostly oxidized to As(V), a new environmental
129 toxin. As(V) enters the cells of most organisms adventitiously via phosphate uptake
130 systems.⁴⁵ As a consequence, early life had to evolve novel strategies for coping with
131 new (potentially toxic) arsenic species. As described in more detail below, nearly
132 every extant microbe has ArsB or Acr3 efflux permeases for As(III) detoxification, so
133 it is reasonable to assume that organisms that arose before the GOE already had an
134 As(III) efflux system. When As(V) became the predominant soluble species, all cells
135 had to do was to reduce As(V) to As(III), the substrate of ArsB or Acr3, and they
136 would become resistant to As(V). A number of independently-evolved As(V)
137 reductases arose in a variety of organisms using a small molecular mass protein As(V)
138 reductases (one of several types of ArsC or Acr2 reductases). The ArsC system
139 conferred by the *ars* operon is the most well studied mechanism of arsenic
140 detoxification and resistance (for details see the previous review).¹⁸ Most recently, a

141 glutathione S-transferase B (GstB) was found to mediate an alternate pathway which
142 conferred As(V) resistance to *E. coli* mutant cells lacking *arsC* by directly reducing
143 As(V) to As(III).²¹ These enzymes all use small molecule proteins such as
144 glutaredoxin (Grx) or reduced glutathione (GSH) coupled to thioredoxin (Trx) as
145 electron donor. The Acr2 reductases evolved from proteins that incorporated the
146 phosphate binding loop of phosphorprotein tyrosine phosphatases related to the cell
147 phosphatase CDC25.⁴⁶ These phosphatase can be converted into As(V) reductases by
148 just a few mutations,⁴⁷ indicating a facile evolutionary path.

149 **2.2 The arsenic methylation cycle**

150 In addition to oxidation and reduction of inorganic arsenic species, pathways for
151 biotransformation of arsenic, including methylation and demethylation,
152 organoarsenical degradation, evolved in early organisms. Interest in arsenic
153 biomethylation began in 1800's with the observation that inorganic arsenic
154 compounds used as wallpaper pigments were converted into Gosio gas
155 (trimethylarsine) by fungi. More recent reports of methylated arsenical showed that
156 arsenic methylation was widespread in the environment and detected in bacteria,⁴⁸
157 cyanobacteria,⁴⁹ algae,²³ protozoa.⁵⁰ Arsenic methylation is a common stratagem to
158 detoxify arsenic. The highly toxic trivalent products are rapidly oxidized
159 nonenzymatically in air to the less toxic pentavalent methylated arsenic species. Also,
160 gaseous end-products such as trimethylarsine will emit to air, thus removing the
161 product. Methylation is catalyzed by the enzyme As(III) S-adenosylmethionine (SAM)
162 methyltransferase (EC 2.1.1.137), designated as AS3MT in animals and as ArsM in
163 microorganisms. Expression of typical prokaryotic and archaeal *arsM* genes are
164 regulated by the As(III)-responsive transcriptional repressor ArsR,²⁰ consistent with
165 arsenic methylation being a detoxification pathway in the microbes. Expression of

166 *arsM* in some cyanobacteria appears to be constitutive,⁵¹ indicating that alternate
167 detoxification pathways are used by microorganisms in which the expression of *arsM*
168 is not regulated.⁵²

169 The degradation of environmental organoarsenicals has been documented for
170 some time,^{53, 54} while few molecular mechanisms for these reactions have been
171 demonstrated. Recently, a two-step pathway of MSMA reduction and demethylation
172 was elucidated.⁵⁵ Although no reductases of pentavalent organoarsenicals have been
173 identified as yet, the enzyme, ArsI, which catalyzes demethylation of trivalent
174 organoarsenicals, was identified and characterized from the environmental isolate
175 bacterium *Bacillus* sp. MD1²⁴ and from the cyanobacterium *Nostoc* sp. 7120.⁵⁶ ArsI,
176 a non-heme iron-dependent dioxygenase with C-As lyase activity, cleaves the C-As
177 bond in MAs(III), trivalent roxarsone, and other trivalent aromatic arsenicals. Putative
178 ArsI orthologs were found only in bacterial species, suggesting that alternate
179 pathways of organoarsenical demethylation might exist in other organisms.²⁴

180 **2.3 The organoarsenical cycle**

181 The arsenic concentration in seawater is around 1 to 2 µg per liter, mainly inorganic
182 arsenic that is usually transformed into complex organoarsenical compounds by
183 marine organisms.⁵⁷ Arsenosugars, first identified in 1981,⁵⁸ are commonly detected
184 water-soluble arsenic species present in marine algae; arsenobetaine is the most
185 abundant arsenic species in the majority of marine animals.⁵⁷ More complex
186 organoarsenicals have been identified with the improvement of analytical techniques
187 in recent years. Since the structure of an arsenosugar phospholipid (AsPL) from a
188 brown alga *Undaria pinnatifida* was first identified,⁵⁹ AsPL has been found in algae
189⁶⁰ and cyanobacteria.⁶¹ Arsenic-containing fatty acids (AsFA) that were first
190 identified in cod liver oil⁶² have now been found in algae⁶³ and various fish species.

191 ^{64, 65} AsHC that were first reported in capelin ⁶⁶ have been detected in fish ^{64, 65} and
192 algae. ⁶⁰ A new class of arsenolipids, trimethylarsenio fatty alcohols (TMAsFOH),
193 was reported in Capelin oil. ⁶⁷ Two new groups of arsenolipids, arsenic-containing
194 phosphatidylcholines (AsPC) and arsenic-containing phosphatidylethanolamine
195 (AsPE) from herring caviar, were characterized. ⁶⁸ In total, more than 20 arsenosugars
196 and 70 arsenolipids have been identified in marine organisms that live in low
197 phosphate and high salt environments. These organoarsenicals are not toxic for the
198 marine plants and animals, but their function in these marine organisms is not known.
199 Phytoplankton can substitute sulfur- and nitrogen-containing membrane lipids for
200 membrane phospholipids, ⁶⁹ arsenolipids might be used in membranes in place of
201 phospholipids due to the more similarity of As(V), than sulfate and nitrate, to
202 inorganic phosphate. Thus As(V) could be used as a phosphate-sparing substitute in
203 phosphate-limiting environments. A recent study on *Ectocarpus siliculosus* that was
204 found to produce more arsenosugar phospholipids under low-phosphate than under
205 normal phosphate conditions ⁷⁰ supports this hypothesis.

206 These organoarsenicals may be toxic to organisms that cannot biosynthesize
207 them. *In vitro* toxicological characterization of three arsenic-containing hydrocarbons
208 showed that cytotoxicity of the arsenic-containing hydrocarbons was comparable to
209 that of As(III) for cultured human bladder and liver cells, ⁷¹ and arsenolipids were
210 metabolized by humans to dimethylated arsenical species (DMAs) and other small
211 molecular arsenic compounds, then excreted in the urine. ^{72, 73}

212 Although several potential pathways have been proposed for the synthesis of
213 complex organoarsenicals, ⁸ few genes involved in these biotransformation have been
214 identified. Even less is known about the degradation of these organoarsenicals, and
215 more studies are needed on this front.

216 **2.4 The arsenic thiolation cycle**

217 Thioarsenates ($\text{H}_3\text{AsS}_n\text{O}_{4-n}$) are the dominant arsenic species in alkaline, arsenic-rich,
218 sulfidic environments. These play a significant role in the arsenic biochemical cycle in
219 sulfidic geothermal environments.^{74, 75, 76} Thioarsenates are transformed to As(V)
220 and/or As(III) via exposing to oxidizing agents or increased pH,⁷⁷ by biological
221 conversion by sulfur-oxidizing bacteria,^{75, 78} or by abiotic decomposition
222 (desulfidation) with subsequent biological oxidation.^{77, 79} Thioarsenates contain
223 reduced S^{2-} and oxidized As(V). They can serve both as electron donors and electron
224 acceptors. For example, monothioarsenate can be used as an electron donor by
225 *Thermocrinis ruber* OC 14/7/2,⁸⁰ and for anoxygenic photosynthesis by phototrophic
226 purple sulfur bacteria growing in an alkaline environment.⁸¹ Recently, the
227 haloalkaliphilic bacterium MLMS-1 can grow chemolithotrophically by oxidizing the
228 S^{2-} of monothioarsenate to S^0 or SO_4^{2-} , while concurrently reducing As(V) to As(III).
229 ⁷⁸ In summary, various microbes have evolved to utilize thioarsenates that are
230 widespread in sulfidic environments.

231 **2.5 Arsenic efflux pathways**

232 The best way to deal with toxic arsenicals in cells is acquisition of an efficient efflux
233 system. As(III) efflux systems have been intensively studied in both microbes and
234 higher organisms.^{82, 83} As(III) efflux in most bacteria is mediated by ArsB in an
235 energy-dependent process, driven in *Staphylococcus aureus* by the membrane
236 potential⁸⁴ and in *E. coli* by ATP hydrolysis that ArsA binds to ArsB to an
237 ATP-driven arsenic-specific pump.²⁶ In the legume symbiont *S. meliloti*, an
238 aquaglyceroporin (AqpS), instead of ArsB, has been identified to extrude As(III) from
239 cells.²⁷ Acr3 has been shown to be an As(III)-efflux transporter in both bacteria and
240 yeast, and provides a pathway for As(III) extrusion from cells.¹⁹ In fact, genes for

241 Acr3 are more wide-spread in bacteria and archaea than are *arsB* genes. The cytosolic
242 As(III)/glutathione complex sequestered into vacuoles by an ABC-type transporter,
243 Ycflp (yeast cadmium factor protein), is the second pathway for As(III)
244 detoxification in yeast *S. cerevisiae*.²⁸

245 Moreover, a novel mechanism for As(V) resistance was identified in a variety of
246 microbes including *Pseudomonas aeruginosa*.²⁹ In these bacteria there are two genes
247 that always go together, one encoding a typical glyceraldehyde-3-phosphate
248 dehydrogenase (GAPDH) and the second one, called *arsJ*, that encodes an
249 organoarsenical efflux permease (ArsJ). GAPDH uses As(V) and glyceraldehyde
250 3-phosphate to form the extremely unstable organoarsenical
251 1-arsenol-3-phosphoglycerate, which is extruded from cells by ArsJ and immediately
252 breaks down into As(V) and 3-phosphoglycerate. The net reaction is effectively As(V)
253 extrusion, and the coupled reaction confers As(V) resistance to these microbes, the
254 only known efflux pathway for As(V). Meanwhile the bacterial permease, ArsP, from
255 *Campylobacter jejuni*, was demonstrated to be an efflux system specific for trivalent
256 organoarsenicals.³⁰ It is more selective for the ancient organoarsenical MAs(III) than
257 for the recently anthropogenically-developed antimicrobial aromatic arsenical growth
258 promoters such as trivalent roxarsone. More and more arsenic reductases and trivalent
259 arsenic-specific transporters identified show that arsenic reduction and efflux play an
260 important role in arsenic biogeochemical cycling.

261

262 **3. Coupling of arsenic biogeochemical cycling to other elements**

263 Any biogeochemical process, such as the cycling of a particular element, is likely to
264 be mediated by more than one organism, and often linked to other fundamental
265 biogeochemical processes. Arsenic biotransformations are often coupled to the

266 cycling of C, Fe, S and N. ^{85, 2, 86} The effect of turnover of these elements on microbes
267 involved in arsenic biogeochemical cycling is summarized in Figure 2 which contains
268 data based on previous studies ^{8, 87, 88, 89} and as described below.

269 **3.1 The effects of iron on arsenic biogeochemical cycling**

270 The chemical speciation of arsenic and arsenic mobility in natural environments are
271 strongly dependent on redox potential and pH. Under oxic conditions, As(V) is the
272 predominated arsenic species, present mainly as H_2AsO_4^- at acid pH or HAsO_4^{2-} at
273 alkaline pH. In anoxic environments, arsenic occurs primarily as reduced As(III)
274 ($\text{As}(\text{OH})_3$ at neutral pH or H_2AsO_3^- at alkaline pH), and more mobile than As(V). ⁹⁰
275 Moreover, pH will impact arsenic interactions with Fe, the sorption of As(V) onto
276 amorphous iron oxide and goethite is higher than that of As(III) below pH 5-6, As(V)
277 and As(III) sorption onto iron oxide are both relatively high at neutral pH, As(III) is
278 more easily adsorbed to iron oxide than As(V) above pH 7-8. ⁹¹

279 Transformation of arsenic-bearing Fe mineral phases strongly affects the
280 bioavailability of arsenic within soils and aquifers due to direct and indirect
281 interactions between the arsenic and Fe cycles including mineral formation,
282 transformation, dissolution and redox reactions. ^{89, 92, 93, 94} Previous studies from our
283 laboratory showed that Fe plaque consisting of Fe(III) (oxyhydr)oxides, which was
284 induced artificially through adding ferrous iron in solution to paddy soils, has high
285 affinity for As(V), and reduced arsenic uptake by rice. ^{95, 96, 97}

286 Fe(III)-reducing bacteria modulate arsenic mobility in the rhizosphere. ^{98, 99, 100}
287 Dissimilatory reduction of Fe(III) (oxyhydr)oxides to Fe(II) by dissimilatory
288 iron-reducing bacteria (DIRB) can result either in the release of As(V) from poorly
289 crystalline or more crystalline ferric minerals as well as from sorption sites within
290 sediments, ¹⁰¹ or in the binding of arsenic to the formed Fe(II) minerals. ^{102, 103, 104, 105,}

291 ¹⁰⁶ DIRB are commonly present in rice paddy soil, and mediate dissimilatory
292 reduction of Fe(III) on the rice root-plaque. ¹⁰⁷ A study on the role of DIRB in arsenic
293 release under a range of biogeochemical regimes indicated that Fe(III) reduction was
294 stimulated by addition of acetate as a potential electron donor that resulted in a
295 marked increase in the number of DIRB, reduction of As(V) to As(III), and arsenic
296 release after Fe(III) reduction. ¹⁰⁰ If DARPs were used as Fe(III)-reducers, *Shewanella*
297 sp. ANA-3 ¹⁰⁸ or *Sulfurospirillum barnesii* ¹⁰⁹ could release both As(III) and Fe(II)
298 from ferrihydrite containing As(V) by reducing solid-phase As(V) and Fe(III).
299 Eventually, most of the ferrihydrite matrix was liberated as Fe(II) and As(III) if
300 sufficient organic electron donor was present. ¹¹⁰ There is more aluminum in the crust
301 than iron. However, *S. barnesii* does not reductively dissolve the As(V)-aluminum
302 hydroxide precipitate, ¹¹¹ so we did not include a detailed description of the effect of
303 aluminum on arsenic biogeochemical cycling.

304 In addition to Fe(III) reduction that has the potential to mobilize or immobilize
305 arsenic depending on geochemical conditions that lead to the formation of either
306 dissolved Fe²⁺ or Fe(II) minerals, the formation of Fe(III) minerals under
307 Fe(II)-oxidizing conditions has the potential to significantly immobilize arsenic and
308 thus to lower its bioavailability. ^{112, 113} In particular for nitrate-reducing
309 Fe(II)-oxidizing bacteria it has been shown that they form poorly soluble Fe(III)
310 minerals and efficiently co-precipitate arsenic (Figure 2). ^{112, 113, 114} Besides
311 nitrate-dependent Fe(II) oxidation, also microaerophilic Fe(II) oxidation has the
312 potential to influence arsenic mobility and could even be used in biotechnical
313 applications for arsenic removal, e.g. in drinking water filters ¹¹⁵ although it has been
314 shown that in commercial drinking water filters the formation of iron biominerals by
315 Fe(II)-oxidizing bacteria lowers arsenic removal from the water. ¹¹⁶ Moreover, a

316 thermo-acidophilic iron-oxidizing archaeon *Acidianus brierleyi*, has been used to
317 immobilize As(III) in the copper refinery process by producing thermodynamically
318 stable crystalline scorodite ($\text{FeAsO}_4 \cdot 2\text{H}_2\text{O}$).¹¹⁷

319 **3.2 The effects of sulfur on arsenic biogeochemical cycling**

320 More than 200 different arsenic-containing minerals have been found in the Earth's
321 crust, and 20% are sulfides and sulfosalts.¹¹⁸ The behavior of arsenic is affected by
322 abiotic or biological redox of sulfur, which can either release or immobilize arsenic.
323^{114, 119} Abiotic sulfide, a strong reductant under sulfate-reduced conditions, plays a
324 critical role in arsenic solubility by forming pyrite (FeS_2), realgar (AsS), orpiment
325 (As_2S_3),¹²⁰ arsenopyrite (FeAsS),¹²¹ or by reducing As(V).¹²²

326 In addition to abiotic factors, sulfate-reducing bacteria (SRB) also cause dramatic
327 changes in Fe, sulfide and arsenic species by generating hydrogen sulfide¹²³ or
328 elemental sulfur from sulfate,⁵ or by localized reprecipitation of released arsenic as
329 As_2S_3 ¹²⁴ or FeAsS , which have low solubility.¹²⁵ Sulfur-oxidizing bacteria have the
330 potential to immobilize arsenic by using free or arsenic-bound sulfur as an electron
331 donor to directly or indirectly transform As(III) and thioarsenates to As(V),⁷⁵ or
332 reduce As(V)^{126, 127} In brief, transformations involving sulfur have the potential to
333 significantly impact the fate of environmental arsenic.

334 **3.3 The effects of N on arsenic biogeochemical cycling**

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

341 oxidation bacterium *A. ehrlichii* strain MLHE-1 was found to be capable of coupling
342 As(III) oxidation with partial denitrification of nitrate to nitrite.^{38, 128} Two other
343 anoxic chemolithoautotrophic strains, *Azoarcus* strain DAO1 and *Sinorhizobium*
344 strain DAO10, were able to oxidize As(III) and fix CO₂ via complete denitrification of
345 nitrate to dinitrogen gas.¹²⁹ Biological nitrate-dependent As(III) oxidation is
346 widespread in the environment, and potentially plays a significant role in arsenic
347 biogeochemical cycling.¹³⁰

348 As mentioned above, nitrate also influences the bioavailability and mobility of
349 arsenic indirectly by linking nitrate reduction to Fe(II) oxidation. Previous studies
350 showed tight coupling between N, Fe, and arsenic in paddy soil.⁸⁵ Addition of nitrate
351 reduced arsenic uptake by rice probably because i) the nitrate inhibited/reduced Fe(III)
352 reduction leading to less arsenic mobilization and ii) nitrate-dependent
353 Fe(II)-oxidizing bacteria stimulated Fe(II) oxidation, which led to arsenic
354 co-precipitation with Fe(III) minerals in soil. Nitrate strongly affects arsenic cycling
355 under anoxic conditions in nitrate-rich Upper Mystic Lake by microbially catalyzing
356 As(III) to more particle-reactive As(V) and oxidizing Fe(II) to arsenic-sorbing
357 particulate ferric oxides.⁴ Microbial nitrate-dependent Fe(II) oxidation in
358 groundwater,¹³¹ freshwater sediments¹³² and marine sediments¹³³ has the potential to
359 contribute to the reduction of arsenic mobility in various ecosystems.

360 **3.4 The effects of organic matter on arsenic biogeochemical cycling**

361 Natural organic matter (NOM) is widely distributed in the environment. NOM
362 consists of heterogeneous mixtures of organic compounds with various structural and
363 functional properties,¹³⁴ that influence the fate of arsenic by competitive adsorption
364 and redox reactions,^{135, 136, 137} and by formation of arsenic-bearing
365 organic-metal-complexes and mineral colloids.^{138, 139} NOM molecules have

366 combinations of carboxylic, amino, sulfhydryl, hydroxyl, esteric, phenolic, nitroso,
367 and other functional groups.¹⁴⁰ They are considered to be an efficient geochemical
368 trap for arsenic both under oxic and reducing conditions. Whereas As(V) is
369 immobilized by binding to protonated amino groups of NOM³ or a nucleophile
370 substitution reaction between As(V) and phenolic OH groups of NOM,¹⁴¹ As(III) is
371 associated with NOM via phenolic OH or carboxyl groups of NOM by H-bonding,
372 hydrophobic As(III)-NOM interactions,¹⁴¹ or via ternary As(III)-Fe(III)-NOM
373 complexes that form bridges between Fe(III), arsenic oxyanions and the functional
374 entities of NOM.¹⁴² In contrast, under sulfate-reducing conditions, the formation of a
375 trigonal-pyramidal complex between As(III) and sulfhydryl groups of NOM could
376 potentially be a sequestration mechanism for arsenic.¹⁴³

377 Organic matter could also change the fate of arsenic by influencing microbial
378 communities or activities.^{144, 145, 146} NOM is thought to drive the reductive dissolution
379 of Fe(III) (oxyhydr)oxides, thereby causing redox transformations of As(V) to As(III)
380 and facilitate arsenic release.¹⁴⁷ In addition to the reductive dissolution of
381 arsenic-bearing Fe(III) (oxyhydr)oxide phases, studies have revealed that addition of
382 organic matter to paddy soil significantly increased arsenic methylation and
383 volatilization.¹⁴⁸ Application of rice straw into soil increased arsenic accumulation in
384 rice by influencing microbial processes involved in arsenic redox.¹⁴⁹

385 Humic acids, which are forms of NOM, can reduce As(V).^{150, 151, 152} Small
386 organic molecules, including lactate, pyruvate, fumarate, malate, succinate, butyrate,
387 citrate, acetate, glycerol, ethanol, and formate, can be used as an electron donor by
388 DARPs for As(V) reduction.^{153, 154, 155, 156} *Desulfosporosinus* sp. Y5 has been found
389 to couple even complex aromatic substrates such as phenol, syringic acid, benzoate,
390 ferulic acid, and toluene, to As(V) reduction.¹⁵⁷ In fact, some DARPs can also respire

391 sulfate, selenite, Fe(III), thiosulfate, nitrate, or nitrite. ^{153, 154} This diversity of electron
392 donors and acceptors may be of benefit to microbes grown in environments where Fe,
393 N, S, or C coexist with arsenic.

394 Apart from iron oxides and organic materials, silicon significantly decreased
395 As(III) concentration, but increased the concentration of DMAs in both the vegetative
396 and reproductive tissues of rice. ¹⁵⁸ In brief, in addition to biological transformations,
397 other inorganic elements, compounds/minerals and physico-chemical properties
398 interact with arsenic in the environment. Coupling of arsenic with other elements
399 makes it necessary to consider genes involved in cycling of other elements, such as Fe,
400 N, S, and C when studying the arsenic biogeochemical cycling. ^{2, 87, 88}

401 Known genes involved in arsenic biotransformation are readily determined in
402 pure cultures. However, in the field, these genes cannot easily be quantified in
403 bacterial communities with a limited number of primers, even though As(V)-reducing
404 and As(III)-oxidizing bacteria are widely distributed in the environment. ^{159, 160, 161} In
405 addition, the speciation, fate and biogeochemical transformation processes of arsenic
406 in the environment are much more complex than under laboratory conditions. ^{162, 163} It
407 is therefore necessary to apply more systematic and more comprehensive approaches
408 such as metagenomics, metatranscriptomics, metaproteomics, and metabolomics to
409 understand interactions between environmental microbes. These approaches will take
410 into account local geochemical surroundings and neighboring organisms by analyzing
411 DNA, RNA, proteins, and metabolites extracted directly from environmental samples.

412

413 **4 Understanding biogeochemical arsenic cycling by application of “omics”** 414 **methods and integrated modeling**

415 **4.1 Metagenomics**

416 Metagenomics provides an inestimable window into the microbial world by
417 characterizing microorganisms involved in difficult-to-elucidate but important
418 biochemical pathways, as the overwhelming majority of microbes in the environment
419 cannot be cultured in the laboratory. From a metagenomic library two
420 arsenic-resistant bacteria and one novel As(V) resistance gene (*arsN*), which encodes
421 a protein similar to acetyltransferases, were identified.²² Xiao et al applied
422 metagenomic techniques to analyze genes associated with arsenic transformation.
423 They analyzed five low-arsenic paddy soils using high-throughput sequencing and
424 constructed a protein database of arsenic metabolizing genes. Their analysis shows
425 that arsenic metabolism genes are ubiquitous and abundant, even in low-arsenic
426 environments.¹⁶⁴ Metagenomics was also used to unravel the correlations between the
427 microbes and arsenic transformation in different niches.^{165, 166, 167, 168, 169} Although
428 metagenomics provides taxonomic and functional profiles of a microbial community,
429 it does not demonstrate the levels of expression of the genes nor their physiological
430 activity.¹⁷⁰ Therefore, metatranscriptomics is needed to delineate the active functional
431 genes and communities.

432 **4.2 Metatranscriptomics**

433 Metatranscriptomics offers novel insights into the expression of functional genes and
434 microbial activities of complex microbial communities at a specific moment or under
435 specific environmental conditions by sequencing the total mRNAs extracted from
436 natural microbial communities. Functional metatranscriptomics has potential for
437 isolation and characterization of novel genes involved in heavy metal transformation.
438¹⁷¹ Metatranscriptomics enhances our understanding of microbial responses to their
439 environment¹⁷² and the functional profile of a microbial community.¹⁷³ Recently, a
440 transcriptomics meta-analysis was used to unravel the effect of As(III) on the

441 symbiotic interaction between the model legume *Medicago truncatula* and its
442 symbiont *Ensifer* (syn. *Sinorhizobium*) *medicae* MA11.¹⁷⁴ This study identified the
443 adaptive responses of the bacterial symbiont to arsenic exposure. This
444 metatranscriptomic approach will be useful to study how microbes regulate their
445 genes to adapt to the changes in environmental conditions, particularly arsenic
446 concentrations.¹⁷⁵ The correlation between mRNA and protein inventories in
447 environmental microbial communities is low when environmental conditions change
448 rapidly. mRNA inventories respond rapidly and sensitively to the shift, while changes
449 in protein inventories are slow.¹⁷⁶ As a consequence, microbial metaproteomics and
450 metabolomics had to be used to identify the repertoire of proteins and small molecular
451 metabolites that microbes use to adapt to complex and dynamic environments. In this
452 way, the metabolic activities of a microbial community in specific environments at the
453 moment of sampling could be elucidated.¹⁷⁰

454 **4.3 Metaproteomics and metabolomics**

455 Metaproteomics and metabolomics are the comprehensive methods by which proteins
456 produced by microbes and metabolites released by microorganisms into the
457 environment are characterized and quantified using a combination of liquid or gas
458 chromatography-based separations and mass spectrometry-based identification
459 techniques.^{177, 178} The study of microbial proteome and metabolome can provide
460 valuable information about the function of microbial communities and the interactions
461 of the microbial communities with the environment.^{179, 180} When the diversity of
462 arsenic-adapted prokaryotic communities in mildly arsenic-contaminated sediments
463 was analyzed using meta-proteomic and 16S rRNA amplification, the results indicated
464 that the data sizes provided by metaproteomics are less than those provided by
465 metagenomics and metatranscriptomics.¹⁸¹ So far, metabolomics has been used

466 mainly to analyze low molecular mass metabolites within a tissue, biofluid, a cell or
467 cell compartment of an organism including plants, animals, bacteria, and humans
468 exposed to an environmental stressor.¹⁸⁰ High-throughput metabolomics has been
469 applied to the analysis of metabolites in the liver of mice when co-exposed to high fat
470 and cholesterol diets and arsenic-contaminated drinking water.¹⁸² However,
471 application of metaproteomic and metabolomic techniques to real environment is
472 limited due to difficulties with amplification and the low quantities of extractable
473 proteins and metabolites because of the interferences with many components present
474 in complex environmental systems, such as soil.^{180,183}

475 **4.4 Integrating meta-omic techniques**

476 From the above, meta-omics are key techniques in elucidating the dynamic and
477 complex interactions between microbial communities and the environment.
478 Integrating multiple meta-omic datasets will provide a complete exhibition from
479 genes to biogeochemical cycles. Metatranscriptomic and metagenomic techniques
480 were combined to detect large numbers of novel genes from complex marine
481 microbial communities.¹⁷³ Datasets of meta-genomics were integrated with
482 metabolomics to reveal how a microbial community interacts with the environment
483 and responds to environmental parameters.¹⁸⁴ Taken together, meta-omic
484 technologies offer an unprecedented opportunity to elucidate the functions of
485 microbes that are not readily cultured under normal laboratory conditions in
486 biogeochemical cycles.

487 Recently, "Arsenomics" was termed as an approach to focusing on the analysis
488 of alterations in transcriptome, proteome and metabolome occurring in microbes
489 exposed to arsenic.^{185, 186} With the application of meta-omics to environmental

490 science, we believe that Arsenomics will evolve to include the analysis of
491 metagenomic, metatranscriptomic, metaproteomic, and metabolomic changes in
492 microbial communities from the real environment where they are exposed to arsenic.

493 **4.5 Integrating environmental meta-omics into biogeochemical models for** 494 **arsenic**

495 Microbes are ubiquitous in diverse environmental niches including soil, oceans,
496 sediments, freshwater environments, and inside the body of animals or plants, and
497 exert great influence on biogeochemical cycles in these habitats.¹⁸⁷ For example,
498 microbes involved in arsenic transformation are ubiquitously distributed in paddy
499 soils, resulting in various concentrations and percentage of inorganic and methylated
500 arsenic species among different rice plants.^{188, 189, 190, 191} Since higher plants appear
501 not to methylate arsenic,¹⁹² microbial methylation is probably the primary source of
502 methylated arsenic in plants, which occurs in soil prior to plant uptake.

503 *In situ* measurements or prediction of arsenic transformations contribute to
504 analysis of the dynamics of arsenic and prediction of arsenic bioavailability. *In situ*
505 measurements of As(V) reduction in Mono Lake, California (dissolved inorganic
506 arsenic ~ 200 μM), made with radiotracers (⁷³As and ³⁵S) of mass balance
507 considerations, revealed that As(V) reduction occurred in the monimolimnion waters
508 with the highest rates between 18 and 19 meters (rate, ~ 5.9 $\mu\text{M}/\text{day}$) and sulfate
509 reduction rates increased with depth at depths of 21 meters and below with the highest
510 rates at 28 meters (rate, ~ 2.3 $\mu\text{M}/\text{day}$).¹⁹³ The radioisotope method was further
511 employed to examine the As(V) and sulfate reduction processes in sediments of two
512 arsenic-rich soda lakes, Mono Lake (moderately salt, ~ 90 g/L) and Searles Lake
513 (saturated salt, ~ 340 g/L).¹⁹⁴ The rate constant [k] of As(V) reduction was 0.103 to
514 0.04 h⁻¹ in Mono Lake and 0.012 to 0.002 h⁻¹ in Searles Lake, and sulfate reduction

515 was only detected in Mono Lake ($k=7.6\times 10^4$ to 3.2×10^{-6} h⁻¹). Denatured gradient gel
516 electrophoresis (DGGE) of 16S rRNA genes amplified from Mono Lake and Searles
517 Lake sediment DNA indicated that microbial communities from two sediments were
518 distinct from each other. More *arrA* gene signal was found in Mono Lake than in
519 Searles Lake, where higher As(V) reduction activity was observed, due to PCR biases,
520 the presence of novel *arrA* genes, or higher expression of low-abundance *arrA* genes.

521 ¹⁹⁴

522 Characterization of genes involved in arsenic biotransformation and application
523 of multiple meta-omics in environment analysis will lead to insights into the microbial
524 world, as limited information on functional genes cannot predict the status of arsenic
525 in the environment. The information of field/*in situ* characterization of functional
526 genes/functional microbial communities and biogeochemical fluxes should be
527 integrated into biogeochemical models to complete the transition from lab to the field,
528 from biochemistry to biogeochemistry, and from genes-genomics to microbial
529 communities. This integration will help to predict the dynamics of arsenic in the
530 environment, and to improve the effectiveness of mitigation technologies. Many
531 strategies have been developed to model low complexity environments. For example,
532 recent work integrating environmental genomics and qPCR in biogeochemical models
533 explored the nexus between microbial community and geochemistry in the Arabian
534 Sea oxygen minimum zone. ¹⁹⁵ Metabolic processes coupling C, N, and S
535 transformations in the Saanich Inlet oxygen-starved zone were integrated using a
536 biogeochemical model that integrates multi-omic information and geochemistry. ¹⁹⁶
537 These studies indicated that such integrated modeling approaches can provide a novel
538 insight into microbial metabolic networks in water bodies, and pave a road for
539 prediction of elemental cycling.

540

541 **5 Perspectives**

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

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

561

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1183

1184 Legends

1185

1186 Figure 1. Proposed pathways for arsenic redox reactions and synthesis of novel

1187 organoarsenicals.

1188

1189 Figure 2. The model of effect of Fe, N, S and natural organic matter (NOM) on

1190 microbes involved in arsenic biogeochemical cycling highlights proteins associated

1191 with elemental metabolisms. Green ovals denote arsenic transporters, yellow ovals

1192 denote transmembrane enzymes. Red words are enzymes, blue words are related

1193 arsenic compounds. The full name of enzymes that were not mentioned in the text was

1194 provided in the follow, NarG, transmembrane nitrate reductase that drives the nitrate

1195 reduction to nitrite; Nas, cytoplasmic-assimilatory nitrate reductase that drives the
1196 nitrate reduction to nitrite; NapA, periplasmic-dissimilatory nitrate reductase; Nir /Nrf
1197 (associated with NapA), nitrite reductase that drives the nitrite reduction to nitric
1198 oxide; NorB/C, nitric oxide reductase that drives the nitric oxide reduction to nitrous
1199 oxide; NosZ, nitrous oxide reductase that drives the nitrous oxide reduction to
1200 nitrogen; Nif, nitrogenase that catalyzes the nitrogen fixation to ammonia; Hs,
1201 hydrazine synthase that catalyzes the production of nitrogen from nitrous oxide and
1202 ammonia; cyt, cytochrome.

1203

1204 Table 1. The genes involved in arsenic metabolisms

Gene	Protein	Protein abbreviation	function	Reference
<i>As(III) oxidation</i>				
<i>aioA</i> and <i>aioB</i>	As(III) oxidase	AioAB	Oxidate As(III)	9
<i>arxA</i>	As(III) oxidase	ArxAB	Oxidate As(III)	10
<i>arxB/arxB2</i>	[4Fe-4S] containing protein	ArxB/ ArxB2	Unknown function	11
<i>aioX/arxX</i>	As(III)-binding protein	AioX/ArxX	Involved in As(III)-based signaling and regulation of As(III) oxidation	12, 11
<i>aioS/arxS</i>	sensor histidine kinase	AioS /ArxS	One part of two-component signal transduction system	9, 11
<i>aioR/arxR</i>	transcriptional regulator	AioR/ArxR	Regulate the expression of <i>aio/arx</i> operon	9, 11
<i>moeA</i>	molybdenum cofactor biosynthesis protein	MoeA	Synthesize the molybdenum cofactor of AioAB oxidase	9
<i>arxC</i>	membrane anchoring and quinol oxidoreductase subunit	ArxC	Involved in As(III) oxidation	11
<i>arxD</i>	TorD-like molybdoenzyme chaperone	ArxD	Involved in As(III) oxidation	11
<i>arsH</i>	organoarsenical oxidase	ArsH	Oxidate trivalent methylated and aromatic arsenicals, reduce chromium and iron	13, 14
<i>As(V) reduction</i>				
<i>arrA</i> and <i>arrB</i>	As(V) respiratory reductases	ArrAB	Reduce As(V)	15, 16
<i>arrC</i>	As(V) reductase membranous subunit	ArrC	Involved in As(V) reduction	17
<i>arrD</i>	As(V) reductase chaperon	ArrD	Involved in As(V) reduction	17
<i>arrS</i>	sensor histidine kinase	ArrS	Regulate the expression of <i>arr</i> operon	17
<i>arsC</i>	As(V) reductase	ArsC	Reduce As(V)	18
<i>ACR2</i>	As(V) reductase	ACR2	Reduce As(V)	19

<i>ACR1</i>	transcriptional regulatory protein	ACR1	Regulate the expression of <i>ACR</i> genes	19
<i>arrR/arsR</i>	arsenic-responsive repressor	ArrR /ArsR	Regulate the expression of <i>arr/ars</i> operon	17, 20
<i>GstB</i>	glutathione S-transferase B	GstB	Reduce As(V) to As(III) with reduced GSH	21
<i>arsN</i>	acetyltransferase	ArsN	Putative As(V) reductase	22
<i>Arsenic methylation and demethylation</i>				
<i>arsM</i>	As(III) S-adenosylmethionine (SAM) methyltransferases	ArsM	Methylate arsenic	23
<i>arsI</i>	A C · As lyase	ArsI	Catalyze demethylation of trivalent organoarsenicals	24
<i>Arsenic transport</i>				
<i>arsB</i>	As(III)-pump protein	ArsB	Extrude As(III) from the cell	25
<i>arsA</i>	As(III)-pump ATPase	ArsA	The catalytic subunit of an oxyanion-translocating ATPase	26
<i>arsD</i>	arsenical metallochaperone	ArsD	Transfer trivalent metalloids to ArsA	26
<i>apqS</i>	aquaglyceroporin	AqpS	Extrude As(III) from the cell	27
<i>ACR3</i>	As(III) permease	ACR3	Extrude As(III) from the cell	19
<i>Ycf1p</i>	yeast cadmium factor protein cytosolic	Ycf1p	Sequester cytosolic As(III)/glutathione complex into vacuoles	28
<i>arsJ</i>	organoarsenical efflux permease	ArsJ	Extrude organoarsenicals from the cell	29
<i>arsP</i>	efflux system specific for trivalent organoarsenicals	ArsP	Extrude trivalent organoarsenicals from the cell	30
<i>pgpA</i>	P-glycoprotein-related protein	PgpA	Recognize and transport thiol-metal conjugates	31
<i>Unknown functions</i>				
<i>arsO</i>	putative flavin-binding monooxygenase	ArsO	Unknown function	32
<i>arsT</i>	putative thioredoxin reductase	ArsT	Unknown function	32