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Review Article

New mechanisms of bacterial arsenic resistance

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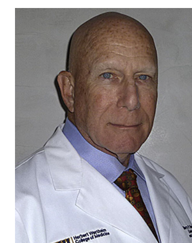

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ABSTRACT

Arsenic is the most pervasive environmental substance and is classified by the International Agency for Research on Cancer as a Group 1 human carcinogen. Nearly every organism has resistance pathways for inorganic arsenic, and in bacteria, their genes are found in arsenic resistance (*ars*) operons. Recently, a parallel pathway for organic arsenicals has been identified. The *ars* genes responsible for the organoarsenical detoxification includes *arsM*, which encodes an As(III) S-adenosylmethionine methyltransferase, *arsI*, which encodes a C–As bond lyase, and *arsH*, which encodes a methylarsenite oxidase. The identification and properties of *arsM*, *arsI* and *arsH* are described in this review.

Life arose before the atmosphere became oxidizing, when the concentrations of dissolved metal ions in primordial oceans were undoubtedly considerably higher than today [1]. One of the most important initial challenges of the earliest cells would have been the ability to detoxify the toxic arsenic. In response to this, the strong selective pressure, arsenic resistance mechanisms arose early and are present in nearly every extant organism. Without the arsenic detoxification systems, life would not exist.

Arsenic, the Group 1 human carcinogen, is the most prevalent environmental toxin. It ranks top on the Agency for Toxic Substances and Disease Registry priority list of Hazardous Substances. The Environmental Protection Agency asserts that arsenic poses a serious threat to our drinking water, and food supply. In Bangladesh, the arsenic contaminated groundwater has been considered the largest poisoning of a population in human history [2]. Exposure to arsenic not only leads to the various forms of cancer but also causes a range of illnesses, including cardiovascular and peripheral vascular diseases, neurological disorders, diabetes mellitus, and chronic kidney disease [3–6]. In addition, low birth rate, fetal death, and delayed infant development are

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closely linked to arsenic exposure during pregnancy [7]. Both inorganic and organic arsenicals such as monosodium methylarsenate (MSMA or MAs(V)), and roxarsone (4-hydroxy-3-nitrobenzene arsenate or Rox(V)) are still used for agriculture and animal husbandry. The ubiquitous presence of arsenic in our surroundings means that arsenic will contaminate our water and food supplies for the foreseeable future.

To cope with the arsenic toxicity, arsenic resistance (*ars*) genes can be found in the genome of nearly every bacterial species sequenced to date, showing that arsenic must still be ubiquitous in the environment and must provide a selective pressure to maintain them in present-day microbes. The minimal constituents are usually an As(III)-responsive repressor (ArsR) [8], and an As(III) efflux permease (ArsB [9] or ACR3 [10,11]) that functions to extrude trivalent As(III) from cells. The As(III)-stimulated ATPase (ArsA) [12], and the As(III) metallochaperone (ArsD) [13], which are always associated in *ars* operons, appears to be later adaptations that enhances the ability of ArsB to extrude As(III) and increase resistance. ArsC [14,15] and other arsenate reductases [16] are required for resistance to arsenate, which became the predominant arsenic species after oxygen appeared in the atmosphere [17].

Arsenate is universally taken into cells by phosphate transport systems, but, again cells took up As(III) before As(V) was even present environmentally, so As(III) uptake must be much more ancient. In 1997 As(III) was shown to be taken into *Escherichia coli* by GlpF, a member of the aquaglyceroporin (AQP) superfamily [18]. Since then AQPs have been shown to be a major route of bidirectional movement of As(III) into and out of eukaryotic cells, with human AQP9 the likely pathway for arsenic uptake into and methylarsenite (MAs(III)) efflux out of liver [19,20]. AQPs have since been shown to be the universal route of arsenic uptake [21]. Arsenic uptake by AQPs is of considerable relevance to human health and disease, and an understanding of both metalloid chemistry and the molecular details of metalloid transport systems is essential for the rational design of new drugs and for treating drug-resistant cells, and microorganisms. One example is that AQP9 is the pathway for uptake of the arsenic chemotherapeutic drug trisenox into leukemia cells [22]. A second example is a demonstration that LmAQP1, a leishmanial AQP, takes up the activated form of the drug pentostam from the macrophage into the amastigote form of the parasite [23]. Moreover, in plants the AQPs were recently shown to take up the essential metalloids boron [24], and silicon [25]. In present-day, the seawater contains approximately 0.4 mM borate and 0.1 mM silicate, but only submicromolar arsenic. This suggests that boron and silicon oxyacid might be physiological substrates of AQPs whereas arsenic might be taken up adventitiously only when present as high-level contaminants. Additionally, there is a single instance of an atypical AQPs called *aqpS* replacing *arsB* in the *ars* operon of *Sinorhizobium meliloti*. [26] AqpS mediates to the efflux of internally generated As(III). Also As (III) has been shown to be taken up by glucose permeases, including the yeast transporters [27], and human GLUT1, and GLUT4 [27–29]. Arsenite in solution is an inorganic mimetic of polyols, which allows it to be taken up by glycerol and sugar transporters.

The arsenic methylation cycle

This review will focus on new genes and their functions in *ars* operons. The revolution in genomics has provided a wealth of sequence information about *ars* genes in thousands of organisms. New genes have been found in *ars* operons with functions that are not obvious. Recently, a global cycle of arsenic methylation has been identified that includes ArsM methyltransferases, ArsI C–As bond lyases, and ArsH NADPH-flavin mononucleotide (FMN) - dependent oxidoreductases.

ArsM, an As(III) S-adenosylmethionine methyltransferase

Members of every kingdom, from bacteria to humans, methylate arsenite, producing the trivalent species MAs(III), dimethylarsenite (DMAs(III)), and volatile trimethylarsine (TMAs(III)) [30,31] catalyzed by As(III), S-adenosylmethionine (SAM) methyltransferases (AsMTs) (EC 2.1.1.137).

To understand on one hand how microorganisms remodel the environment in arsenic-rich regions and how arsenic methylation is involved in carcinogenesis, on the other hand, it is essential to understand the AsMT catalytic cycle. The enzyme, that catalyzes this reaction in humans and other mammals has been termed AS3MT [32]. It is found predominately in the liver, where the intermediates, in particular, MAs(III) and DMAs(III), are potent toxins and carcinogens responsible for a majority of arsenic-related human diseases [30]. Whether the AsMTs detoxify the arsenic or transform it into more toxic products depends in part on their enzymatic mechanism. Challenger proposed that the mechanism is an alternate series of oxidative methylations and reductions, with the pentavalent species as products [33]. This hypothesis is supported by the fact that humans excrete MAs(V) and dimethylarsenate (DMAs(V)) in urine. An alternate proposal by Hirano is that there is no change in oxidation state during the catalytic cycle and that products are all trivalent methylarsenicals [34]. If the primary intracellular products of methylation are the pentavalent species, then arsenic would have limited carcinogenic potential. On the other hand, if the trivalent species are the major methylated intracellular products, then the methylation would increase the carcinogenicity of arsenic. Whether the oxidized species found in the urine of mammals or the growth medium of microbes are the products of the AsMTs, or are the result of non-enzymatic oxidation of the unstable trivalent species is controversial [35], but, with careful handling, the trivalent forms have been detected in urine [36,37]. Thus, a detailed knowledge of the enzymatic pathway is important. However, AS3MT has proven difficult to characterize biochemically [38], so microbial AsMTs have been used as models. The first identified microbial AS3MT ortholog was from an *ars* operon in *Rhodopseudomonas palustris* and was named *arsM* [39]. More useful has been the CmArsM from the Yellowstone thermoacidophilic eukaryotic alga *Cyanidioschyzon merolae*. [40] This heat-stable and highly active enzyme has been invaluable as a model for biochemical [41], and crystallographic analysis of AsMTs [42,43]. The apo structure was solved at 1.6 Å, as well as

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