Mechanisms of bacterial degradation of arsenic

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Abstract

Arsenic is a toxic metalloid that exists in two major forms (arsenate and arsenite). The anthropogenic activities of man are its major source in the environment. Bacteria have developed resistance against arsenic by using detoxification mechanisms such as oxidation of arsenite to arsenate with the aid of an enzyme arsenite oxidase and in the process gain energy, reduction of arsenate to arsenite through phosphate transporters by a reductase enzyme arsenate reductase and methylation of arsenite with the enzyme S-adenosylmethionine methyltransferases (SAM). The ars operon which mediates the extrusion of arsenic out of bacterial contains a three and five gene operon that assist bacterial with arsenic resistance respectively.

Keywords: Arsenic, Arsenate, Arsenite, Arsenate reductase, Arsenite oxidase, Phosphate transporters, Bioremediation.

Introduction

Arsenic is widespread and one of the most abundant toxic elements that are present in the environment with deleterious effects when in contact with and therefore regarded as a carcinogenic substance.¹ Reports put the human population exposed to arsenic to be around 200 million people globally.² When humans are exposed to arsenic through the activities of man such as mining, smelting, use of pesticides and herbicides, these activities lead to the contamination of soil, drinking water and food.³ Countries that have been reported with heavy Arsenic contamination of their groundwater are China, Bangladesh, Taiwan, India, Mexico, Argentina, Cambodia, and Nepal.^{4,5} Therefore, this toxic element has been designated by World Health Organization as one of the most toxic chemicals with a reference contaminant limit of 10 µg/L⁻¹ from the initial contaminant limit of 50 µg/L⁻¹, the reason being that many countries record different levels of arsenic concentrations in water.^{6,7} Arsenic exists typically in four oxidation states as arsenate (v), arsenite (III), arsenic (0) and arsine (-III), with arsenite and arsenate being the most common forms.^{8,9} Between the two common forms, arsenite is more toxic than arsenate due to its solubility and mobility.^{10,11} This solubility of arsenite has made it have a spontaneous liking for thiols of sulfur and pyruvate dehydrogenase leading to the formation of complexes with glutathione and other enzymes thereby inhibiting respiration in bacteria. Arsenate due to its close similarity with phosphate groups interferes with oxidative metabolism which is strongly needed by cells for energy purposes.¹² Hence there is an urgent need for the degradation of arsenic in the environment. Different methods of degradation have been suggested by different authors such as adsorption, reverse osmosis, coagulation, ion exchange, and filtration.^{13,14} These methods listed are expensive to carry out and most times not very effective for arsenic

degradation due to the concentration of arsenic. The best method employed for the degradation of arsenic is the use of microorganisms known as bioremediation which is environmentally friendly, cost-effective and can completely degrade arsenic irrespective of the concentration. Microorganisms have developed several mechanisms to withstand high concentrations of arsenic in the environment, which can be in the form of using arsenic as an energy source through arsenite oxidation by aox operons,^{15,16} arsenate reduction using ars operons¹⁷ and methylation of arsenic into organic compounds.¹⁸ The aim of this review is to give an extensive knowledge on the mechanisms by which microorganisms can degrade arsenic.

Arsenic Degradation and Bacterial Involved in Arsenic Degradation

Generally, arsenic is known to be a toxic metal and bacterial have devised several mechanisms such as arsenite oxidation, arsenate reduction and methylation to degrade this toxic substance and reduce its toxic effects. As they degrade arsenic in the process, they use it for their own growth through energy generating processes such as arsenite acting as an electron donor while arsenate acts as an electron acceptor.¹⁵ Wolfe-Simon and co-authors claimed that the bacterial strain GFAJ-1 in the process of trying to degrade arsenate in an environment with rich arsenate concentration can replace phosphate with arsenate in its DNA to support bacterial growth. The publication attracted a lot of controversies and the notion was debunked because many scientists carried out experiments on the bacterial incorporation of arsenate into the DNA of GFAJ-1 and could not arrive with the same conclusion of Wolfe-Simon and co-authors.¹⁹ Georgeta and co-authors did an experiment and were able to prove that arsenate can support the growth of bacterial using *Escherichia Coli* with a tagged radioactive RNA. The tagged RNA led to massive degradation of ribosomal RNA which allowed

a large amount of phosphate to support the growth of bacterial cells which are tolerant to arsenate.²⁰ Many bacterial species have been reported in the degradation of arsenic, and the first bacterium reported in the degradation of arsenic known as *herminiimonas arsenicoxydans*.²¹ Other bacterial involved in the metabolism of arsenic belongs to the species of *Bacillus*, *Delftia*, *Pseudomonas*, *Agrobacterium*, *Firmicutes*, *Acinetobacter*, *Crenarchaea*, *Stenotrophomonas*, *Achromobacter*, *Citrobacter*, *Rhodobium*, *Clostridium*, *Methanobacterium* and *Cyanobacteria*.²²⁻²⁴

Arsenite Oxidation

It is the oldest form of detoxification mechanism used by bacteria to get rid of excess arsenic from their environment. This detoxification mechanism is carried out by both heterotrophic and chemoautotrophic bacteria. In heterotrophic bacterial oxidation, the bacteria oxidize the toxic As(III) to less toxic As(V) before it is extruded out of the cell,²⁵ while chemoautotrophic bacterial utilizes As(III) as an electron donor during aerobic oxidation converting As(III) to As(V) and in the process gains energy. The only difference is that they both have different sources where they gain energy from.²⁶ Examples of chemoautotrophic bacteria that carry out this detoxification are *Alkalilimnicola ehrlichii* strain MLHE-1, *Rhizobium* strain NT-26, and *Acidovorax* sp. NO1.^{27,28} For bacteria to be able to detoxify arsenic present within its vicinity, it needs an enzyme called arsenite oxidase and this enzyme which was isolated from the gram-negative bacteria *Alcaligenes faecalis* and belongs to the dimethylsulfoxide (DMSO) reductase family.²⁹ The structure of the enzyme arsenite oxidase is such that it contains a small and large subunit.³⁰ Scientists have not fully agreed on the permanent nomenclature that should be assigned to the genes that are associated with arsenite oxidation. Therefore a series of names have been given to the genes with the current name been called *aioA* and *aioB* respectively.³¹ The oxidation of arsenite is carried out in the bacteria's periplasm. For oxidation of arsenite to occur, a sensor kinase called *aoxS*, detects arsenite and then quickly activates a regulator protein called *aoxR* which helps to initiate transcription of the arsenite oxidase in the bacteria.⁸ The sensor kinase and the regulatory protein are both involved in regulating the expression of *aioA* and *aioB* genes respectively.³² Diverse bacterial strains have been isolated and found to be associated with these genes. These strains of bacteria are grouped under the Alpha, Beta, and Gammaproteobacteria, Firmicutes, Chlorobi, and Chloroflexi.³³ A new arsenite oxidase that was discovered known as *ArxAB* has been identified in the purple sulfur bacterium called *Ectothiorhodospira* sp. strain PHS-1 and MLHE-1, wherein anoxic conditions it makes use of As(III) as an electron donor.³⁴ *ArxAB* oxidase has been reported to be distributed widely in

environment containing arsenic, thus was placed in between *AioAB* and *ArrA* (respiratory arsenate reductase) but closer to *ArrA* because of its gene relatedness to *ArrA*.^{35,34}

Arsenate Reduction

Arsenate reducing bacteria makes use of different reduction systems to get rid of arsenate from their environment as a detoxification mechanism. They do this by converting arsenate to arsenite leading to its extrusion. One of the reduction mechanisms is through the use of cytoplasmic arsenate reduction system (*ArsC*).¹⁷ When As(V) enters the bacterial cell through *Pit* or *Pst* (known as phosphate transporters), an arsenate reductase enzyme called *ArsC* (13-15 kDa) mediates the reduction of As(V) to As(III) utilizing ferredoxin or glutathione as an electron donor leading to As(III) being forced out or extruded out of the cell through an *ArsB* efflux pump.³⁶ Some bacteria may have an edge over other bacteria when they possess an ATPase called *ArsA* that is bound to *ArsB* for extrusion of arsenite.³⁷ Another mechanism in which arsenate can be reduced is when some bacteria make use of As(V) during anaerobic respiration as a terminal electron acceptor. These bacterial that makes use of As(V) as a terminal electron acceptor and in the process gain energy are called dissimilatory arsenate respiring prokaryotes (DARPS).³⁸ The dissimilatory arsenate respiring prokaryotes are diverse in nature phylogenetically and they include members such as *Chrysiogenes arsenatis*, Firmicutes γ -, δ -, and ϵ -Proteobacteria.⁸ The respiratory arsenate reductases contain genes that are coded in the *arr* operon. The genes are *arrA* and *arrB*.³⁹ Purification and characterization of the *Arr* proteins from *Chrysiogenes arsenatis*,⁴⁰ *Bacillus selenitireducens*,⁴¹ and *Shewanella* strain ANA-3⁴² revealed that the heterodimer *ArrAB* is a member of the dimethylsulfoxide (DMSO) reductase family. In *C. arsenatis* and *Shewanella* strain ANA-3, the enzyme is located in the soluble fraction of the periplasm and uses the only arsenate as an electron acceptor,^{40,41} while the enzyme of *B. selenitireducens* is membrane-bound and may act on other electron acceptors.⁴⁰ In *C. arsenatis*, the large subunit *ArrA* (87kDa) was proposed to contain a Mo atom with a molybdopterin co-factor and a [4Fe-4S] center, while the small subunit *ArrB* (29 kDa) supposedly contains several other Fe-S units.³⁹

Arsenic Methylation

Methylation is a kind of detoxification mechanism used by bacteria to degrade arsenic. A kind in the sense that the by-products that result from it are toxic than the inorganic forms; Arsenate and arsenite.⁴³ The scientist Frederick challenger explained methylation of arsenic using a fungus called *Scopulariopsis brevicaulis*.⁴⁴ In the process of detoxification, arsenite is methylated to methylarsonic acid and methyl arsonic acid undergoes a

series of reduction and methylation reaction steps which results in dimethylarsinic acid, dimethyl arsine and finally extruded as trimethylarsine oxide. Bacteria get rid of arsenic through the volatilization of trimethylarsine oxide.⁴⁵ The methylated forms of arsenic are mediated by the enzyme S-adenosylmethionine methyltransferases which is the source of the methyl group and the reduction reaction steps are mediated by glutathione and thiol containing compounds.^{46,18} like I mentioned earlier, the products of arsenic methylation such as dimethylarsinic acid, dimethyl arsine, and trimethylarsine have been shown to be more toxic than the inorganic forms of arsenic which indicate that the products of arsenic methylation still contains some level of toxicity.⁴³ Therefore, many authors do not regard methylation as a complete detoxification mechanism for bacteria.⁴⁷ Bacteria such as *Methanobacterium formicum*, *Desulfovibrio gigas*, *Clostridium collagenovorans* and other aerobic and anaerobic bacteria have been found to be involved in arsenic methylation.^{48,49} The mechanism of demethylation of arsenic is a process that is not fully well understood. Many scientists argue that demethylation does not necessarily follow the reverse processes of methylation, more research still needs to be carried out to know how bacteria make use of it as a form of detoxification.

Genes Associated with Arsenic Resistance

In bacteria, the *ars* operons contain genes that confer resistance when they are exposed to the toxic effects of arsenic. *E. coli* and *Staphylococcus aureus* contains a three-gene operon (*arsRBC*) and five gene operon (*ars RDABC*) respectively.⁵⁰ The cytoplasmic arsenate reductase (*ArsC*) is a small molecular mass protein (13 to 15 kDa) that mediates the reduction of arsenate to arsenite it does this by binding arsenate to

arginine residues; it then forms a covalent bond with a residue of cysteine at the N terminus, between cysteine in *ArsC* and a cysteine in glutathione a disulfide bond is quickly formed and reduction of the disulfide bond allows electrons to pass through glutaredoxin thereby reducing arsenate to arsenite.⁵¹ Then arsenite is expelled or extruded through a trans-membrane carrier protein *ArsAB* arsenite efflux pump that is coupled to an ATPase, which helps to increase the resistance to high levels of arsenite.^{37,11} The function of *ArsA* is to provide the energy needed by *ArsB* to expel arsenite. Some bacteria make use of other genes or proteins to substitute for *ArsB* in expelling arsenite, an example is the alpha-proteobacteria. This bacterium contains a protein *Acr3p* which replaces *ArsB* to expel arsenite.⁵² Another example is the bacterium *Sinorhizobium meliloti*, which carries an aquaglyceroporin gene which replaces *arsB* that is involved in arsenite expulsion.^{53,54} The gene operon *arsR* is a transcriptional regulator and *arsD* is a chaperone which transfers arsenite to *ArsA* which is a subunit of the *ArsAB* arsenite efflux pump, are both regulatory components that act as transcriptional repressors.^{55,56}

Recently identified *ars* operons such as *arsP*, *arsN*, *arsO*, *arsTX* and *arsH* have their different functions in arsenic resistance. The function of *arsP* is that it codes for a putative membrane organoarsenical permease,⁵⁷ *arsN* codes for an acetyltransferase-like protein,⁵⁸ *arsO* codes for Putative Flavin- monooxygenase,⁵⁹ *arsTX* codes for Thioredoxin system in the bacterium *Microbacterium* sp. A33,⁶⁰ and the oxidase of organoarsenicals, which confers resistance also to the organoarsenicals is the function of *arsH*.⁵⁷ The table below summarizes the functions of *ars* operons in a bacterial system.

Table 1: Genes associated with arsenic resistance and their functions

Mechanism	Gene	Function	References
Resistance	<i>arsB/acr3p</i>	Transmembrane carrier pump/efflux pump	11
	<i>arsC</i>	Arsenate reductase	51
	<i>arsD/arsR</i>	Transcriptional repressors	56
	<i>arsA</i>	ATPase for arsenite extrusion	61
	<i>arsP</i>	Putative membrane organoarsenical permease	57
	<i>arsN</i>	Acetyltransferase	58
	<i>arsO</i>	Putative Flavin-monooxygenase	59
	<i>arsH</i>	Oxidase of organoarsenical	57
	<i>arsB</i>	Membrane associated protein involved in arsenate reduction	41
	<i>arsM</i>	Oxidative methylation	62

Bacteria Uptake of Arsenic

According to,⁶³ bacteria most times have developed survival mechanisms to survive extreme environmental

conditions. With no designated system for the uptake of arsenic, bacterial makes use of existing transporters because of their structural

similarities to other molecules such as phosphate and glycerol. In bacteria, phosphate transporters (Pit and Pst) are involved in the uptake of arsenate while aquaglyceroporin facilitates the transport of arsenite.¹⁷ A typical study of the phosphate transporters of *Escherichia coli*, on one hand, shows how arsenate is conducted in the cell of the bacteria.⁵¹ The phosphate transporter, Pit which is a phosphate inorganic transporter is majorly involved in the transport of arsenate which catalyzes the intracellular arsenate or phosphate in a bacterial cell for extracellular arsenate and has a bi-directional flow of ions thereby transporting arsenate more efficiently. The Pst phosphate transporter is a specific transport system that transports arsenate less efficiently in the bacterial cell by reducing the uptake of arsenate in an environment of high arsenate concentration.^{63,17 64} On the other hand aquaglyceroporin in *E.coli* facilitates the transport of arsenite across the cell membrane through a glycerol transporter called GlpF.⁶⁵ Apart from *E.coli*, homologs of GlpF for the transportation of arsenite have been reported for other bacteria. An example of such bacteria is *Leishmania major*.⁶⁶ Although GlpF homologs have been reported for a few bacteria involved in arsenite transportation, there are other bacteria that can transport arsenite inside the bacterial cell without GlpF homolog. Thus this indicates that there are other genes that have not yet been discovered that are involved in the transport of arsenite in some bacteria that do not possess GlpF homolog in their genome.⁶⁷

Conclusion

This work highlighted the various mechanisms by which bacteria can degrade arsenic in their environment. Bacterial oxidation and reduction of arsenic seem to be a very efficient way of detoxifying arsenic from its toxic form to harmless substances. This is not the same with methylation as a form of detoxification due to the fact that the by-products of methylation are even more toxic than the inorganic forms of arsenic. Thus methylation is not generally regarded as a complete method of bacterial degradation of arsenic. Also, due to the limited information on demethylation, further studies need to be carried out on demethylation to understand the mechanism of degradation of arsenic by bacteria. Genome data available will help researchers to learn more about genes that are yet to be discovered that play crucial roles in the degradation of arsenic. More research still needs to be carried out to determine other mechanisms which bacteria make use of to degrade arsenic in their environment.

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