Chapter 13
Heavy Metal Resistance in Prokaryotes: Mechanism and Application

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Abstract Metal-rich natural and artificial habitats are extreme environments for the development and evolution of unique microbial communities, which have adapted to the toxic levels of the metals. Diverse bacterial groups have developed abilities to deal with the toxic metals by bioaccumulation of the metal ions inside the cell actively or passively, extracellular precipitation, efflux of heavy metals outside to the microbial cell surface, biotransformation of toxic metals to less toxic forms, and metal adsorption on the cell wall. Metalophilic microbes are found in all bacterial and archaeal groups studied, but mostly appear among aerobic and facultative anaerobic chemoheterotrophic and chemolithoautotrophic microorganisms of the *Bacillus, Pseudomonas, Staphylococcus, Actinobacteria, Cuprividus, Acidobacterium, Acidithiobacillus, Thiobacillus*, *Ferroplasma,* and *Sulfolobus* genera. The phenomenon of microbial heavy metal resistance has fundamental importance and is particularly relevant in microbial ecology, especially in connection with the roles of microbes in biogeochemical cycling of heavy metals and in the bioremediation of metal-contaminated environments. The heavy metal resistance mechanisms and different applications of metal resistant/metalophilic bacteria and archaea have been expounded deeply in this chapter.

Keywords Heavy metals · Metalophilic microbes · Heavy metal resistance · Bioremediation · Bioleaching

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13.1 Heavy Metals and Its Toxicity on Microbes

There is no widely agreed criterion-based definition of a heavy metal. In metallurgy, a heavy metal may be defined on the basis of density, in physics the differentiating criterion might be atomic number, and in chemistry or biology the distinguishing criteria could be atomic mass (Hawkes 1997; Ali and Khan 2018; Meija et al. 2016). Based on density definition, the heavy metals are those elements that have a density above 5 g/cm^3 (Nies 1999). Based on atomic number definition, heavy metals are those elements which atomic number greater than 20 (Ca), sometimes this is capped at 92 (U). Definitions based on atomic number have been criticized for including metals with low densities. Atomic mass definitions can range: it reserved those elements with an atomic mass greater than Na (atomic mass 22.98), greater than 50 (Ni (58.69), Cu (63.54), Mo (95.95), etc.) or more than 200 (e.g., Hg (200), TI (204), Pb (207), Bi (209), and the Th series) (Baldwin and Marshall 1999; Ali and Khan 2018; Pourret and Hursthouse 2019).

Correspondingly, the list of heavy metals according to different definitions will include different elements. Of the 90 natural elements, 21 are non-metals, 16 are light metals, and the remaining 53 (including As) are heavy metals (Ali and Khan 2018).

Most heavy metals are transition elements with incompletely filled *d* orbitals. These *d* orbitals provide heavy metal cations with the ability to form complex compounds which may or may not be redox-active. Thus, the heavy metal cations which play an important role as micronutrients in the vital processes of microorganisms or other living organisms are essential metals. For example, Mo(II), Fe(II), Cu (II), Mn(II), Zn(II), Ni(II), and Co(II) are involved in the catalytic acceleration of biochemical processes. They can serve as cofactors or be part of enzymes such as nitrogenases, superoxide dismutases, dehydrogenases, cytochrome oxidases, ureases, etc. (Ehrlich 1997a; Nies 1999). Cu(II) and Ni(II) are involved in bacterial cell's redox processes (Nies 1999). Zn(II) ions stabilize the structure of DNA and proteins of the bacterial cell wall, since they have redox stability at certain pH and Eh values of biological media (Nies 1999). A significant number of bacteria and archaea are able to use ions of certain metals (Fe(III), Mn(II), Cr(VI), etc.) and metalloids as donors or acceptors of electrons in energy metabolism (Ehrlich 1997a). Thus, many archaeal and bacterial species have the ability to derive energy from the reduction of a variety of metals. Archaeal species *Archaeoglobus fulgidus*, *Pyrococcus furiosus,* and bacterial species *Desulforomonas, Desulfovibrio* are capable of reducing Fe(III), and two *Pyrobaculum* sp. can effectively grow respiring Fe(III) (Vargas et al. 1998; Feinberg et al. 2008; Kashefi et al. 2008). At least one archaeal species, *Pyrobaculum arsenaticum*, can use arsenate as a terminal electron acceptor for growth (Oremland and Stolz 2005).

Nickel is another important requirement for methanogens: it is required for methanogenesis in *Methanobacterium* strains (Hartzell et al. 1988) and in the methanogenic archaea *Methanobrevibacter smithii* and *M. barkeri* for incorporation

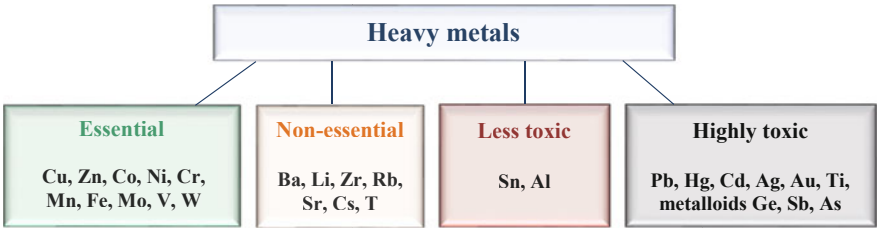

Fig. 13.1 Classification of heavy metals based on their biological role and effects

into cofactor, a yellow chromophore found in the methylreductase of *Methanobacterium* (Diekert et al. 1981; Ellefson et al. 1982).

Tungsten and molybdenum have similar chemical properties. Molybdenum is a trace metal required by virtually every species, and tungsten can replace molybdenum in some instances (Kletzin and Adams 1996). Tungsten is an essential trace metal for hyperthermophile archaea *P. furiosus*, as it involves in aldehyde oxidoreductases activity. *Thermococcus litoralis* uses another tungsten-containing enzyme, FOR (Dhawan et al. 2000). Several bacterial species, including strains of *Pseudomonas, Chloroflexus, Thiobacillus, Alcaligenes,* and *Thermus* genera and archaea *Pyrobaculum arsenaticum, P. aerophilum* can generate energy either by oxidation or reduction of specific arsenic oxyanions (Ben Fekih et al. 2018).

Some heavy metal ions, for example Cd(II), Pb(II), Sn(II), Hg(II), and Ag(I), do not have vital biological significance for microorganisms, besides form strong toxic complexes, which makes them too dangerous for any physiological function (Bruins et al. 2000). These heavy metals can also show more specific forms of chemical attack through mimicry. In this regard the toxic metals may act as mimics of essential metals, binding to physiological sites that normally are reserved for an essential element. Through mimicry, the toxic metals may gain access to, and potentially disrupt, a variety of important or even critical metal-mediated cellular functions (Cousins et al. 2006; Kasprzak 2002). In the Fig. 13.1 is presented the diagram showing the heavy metal's classification based on their toxicity.

At high concentrations, all heavy metals (both those that are essential and those that do not have biological significance) are toxic to microbes and other organisms (Nies 1999). Toxicity of heavy metals is manifested in detrimental effects on microorganisms, such as changes in the conformational structures of nucleic acids and proteins, in violation of redox processes and in maintaining the osmotic balance (Ehrlich 1997a; Nies 1999; Igiri et al. 2018). Cd, Hg, Ag ions tend to connect within the cell with sulfhydryl groups, inhibiting the activity of sensitive enzymes. The cations of some metals can replace physiologically significant ions in biomolecules, thereby violating their functions. Ni and Co ions can displace Fe, Zn—Mg ions, Cd and Zn ions—Ca ions (Ehrlich 1997a; Nies 1999). Heavy metal cations can combine with glutathione groups of gram-negative bacteria, forming a bisglutathione complex, which tends to interact with molecular oxygen to form oxidized glutathione (GS-SG) (Kachur et al. 1998). The latter can be reduced in NADPH-dependent reactions, and as a result, the formed metal cations bind other glutathione molecules,

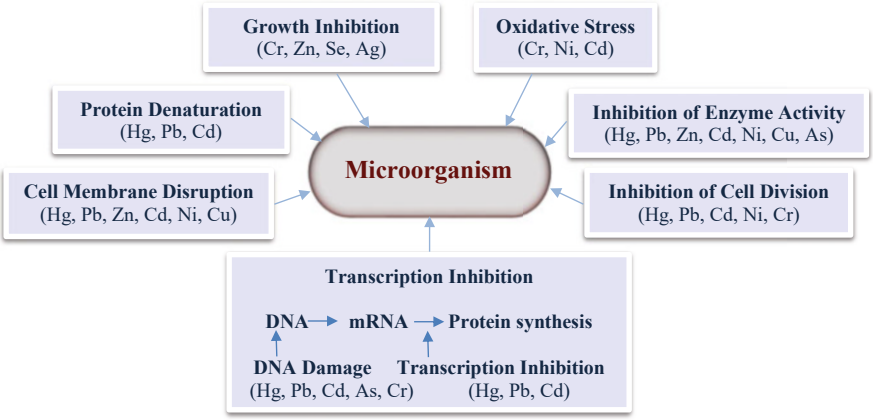

Fig. 13.2 Heavy metal toxicity mechanisms to microorganisms

thereby causing oxidative stress. Oxygen-containing anions of some heavy metals and metalloids can be involved in the metabolism of structurally similar anions of vital elements, such as S and P. For example, a chromate ion can affect the metabolism of a sulfate ion, arsenate—a metabolism of phosphate (Nies 1999; White and Gadd 2000). Cd and Pb pose deleterious effect on microbes, damage cell membranes, and destroy the structure of DNA. This harmfulness is generated by the displacement of metals from their native binding sites or ligand interactions.

Arsenic is a metalloid that occurs naturally in the environments mainly in tow forms: the trivalent species (As(III)), commonly as the oxyanion arsenite (AsO_2^-), and the pentavalent species (As(V)), or arsenate (AsO_4^{3-}). Arsenite is more toxic than arsenate as it is able to bind strongly to sulfhydryl groups in proteins and weakly to thiol groups, such as those in glutathione, lipoic acid, and cysteine. The primary toxic effects of arsenate arise from its transformation to arsenite, besides arsenate has ability to compete with phosphate oxyanions for both transport and energetics functions (Ben Fekih et al. 2018).

The morphology, metabolism, and growth of microbes are affected by changing the nucleic acid structure, causing functional disturbance, disrupting cell membranes, inhibiting enzyme activity, and oxidative phosphorylation (Fig. 13.2) (Ahemad 2012; Igiri et al. 2018).

Cr(VI) is usually present as the oxyanion chromate and based on its high oxidizing potential, considered as the most toxic form of chromium. Toxic effects of chromate for bacteria are associated with its structural similarity to sulfate (SO_4^{2-}). The CrO_4^{2-} crosses the cell membrane in some species via the sulfate transport system and cases an oxidative damage to biomolecules. Cr(VI) does not interact directly with DNA, hence its genotoxicity is attributed to its intracellular reduction to Cr(III) via reactive intermediates. The resulting types of DNA damage that are produced can be grouped into two categories: (1) oxidative DNA damage

and (2) Cr(III)-DNA interactions (Cervantes and Campos-García 2007; Díaz-Magaña et al. 2009; Luo et al. 2019).

13.2 Microbial Heavy Metal Transporters

To have any physiological or toxic effect, most heavy metal ions should enter the microbial cell. Microorganisms have two main types of transport systems for heavy metal ions. The first type of transport system is fast, nonspecific, which is expressed constitutively and is controlled through the cytoplasmic membrane of bacteria by the proton gradient (pmf—proton motive force) (Silver 1996; Sar et al. 1998; Nies 1999). The second type is a substrate-specific slow transport, often requiring ATP as an energy source in addition to the proton gradient (Table 13.1). This "energetically expensive" type of transport system is inducible and is used by the cell in certain metabolic states, for example, in a state of hunger (Nies 2003, 2007; Nies and Silver 1995).

ATP-binding cassette (ABC) transporters are a major category of membrane-associated bacterial protein structures involved in the transport of a wide range of substrates including heavy metals. For example, Ni can be absorbed by the NikA-E transport system (ABC family transporter), which consists of five components (NikA periplasmic Ni-binding protein, NikB and NikC transmembrane pores for passage of Ni, NikD and NikE ions hydrolyze ATP and use energy to ion transport Ni(II)). The NikA protein can also bind Co, Cu, and Fe ions, but with a tenfold low affinity (Eitinger and Mandrand-Berthelot 2000; Mulrooney and Hausinger 2003). In different microbes, the Znu transport system of the ABC family absorbs Zn ions and has a similar structure to the Nik transporter.

Heavy metal ions like Ni, Co, Zn, and Mn can be accumulated also in gram-negative bacteria and archaea by the fast and nonspecific CorA system (metal inorganic transporter of the MIT family) (Smith and Maguire 1995; Hynninen 2010). In *B. subtilis*, Mg, Ni, Mn, Co, and Zn ions can be absorbed by the metal citrate transport protein CitM and CitH (Hantke 2001; Krom et al. 2000).

The fast ion transport along the concentration gradient is an important factor contributing to the toxicity of heavy metals. When cells are exposed to high concentrations of heavy metals, which can accumulate through nonspecific transport systems, the "passage" into the cytoplasm can remain open, even at "toxicologically dangerous" concentrations of metals in the cytoplasm, since this process is constitutive (Nies 1999). Despite heavy metal toxicity, microbes possessing different metal resistance strategies, such as detoxification, metal absorption, uptake and accumulation, extracellular precipitation, efflux of heavy metals from the cells.

Table 13.1 Heavy metal transporters in prokaryotic cells

Transporter type	Member	Organism	Function	Energy	Metal ions	Comments	Reference
ABC	NikA-E, ZnuABC, SitABCD, PsaABC, TroABC, MtsABC, FimA, Pzp 1, FepCDG, FecECD, FhuBBC, Sfu, Tfe, NiCoT, WtpA	*E. coli, Salmonella enterica, Streptococcus pneumonia, S. pyogenes, Treponema pallidum, Hemophilus influenzae, Methanosarcina acetivorans, M. barkeri, M. mazei, Sulfolobus solfataricus, Thermoplasma acidophilum, Methanomicrobium* sp., *M. acetivorans, Pyrococcus furiosus*	Uptake	ATP	Mn(II), Zn(II), Ni(II), Cu(II), Fe(III), Fe(II), W(VI), Mo(II)	2 membrane-integral partsa +2 ATPase parts = ABC core + periplasmic binding protein	Hohle and O'Brian (2009), Nies (2003), Porcheron et al. (2013), Zhang et al. (2009), Bini (2010) and Margaryan et al. (2013)
P-type	ZntA, CadA, PbrA, CopAB, MgtA, KdpB, Mt., Mba, Fa, Af	*Cupriavidus metallidurans, B. subtilis, Enterobacter hirae, Pseudomonas syringae, P. aeruginosa, X. campestris, E. coli, S. aureus, Stenotrophomonas maltophilia, Deinococcus*	Both	ATP	Mg(II), Mn(II), Ca(II), K(I), Cu(II), Zn(II), Cd(II), Pb(II), Ag(I)	1 membrane-bound protein as core	Rademacher and Masepohl (2012), Hantke (2001), Mills et al. (1994), Nies (2003), Aguilar-Barajas et al. (2010), Moraleda-Muñoz et al. (2010), Margaryan et al. (2013), De Hertogh et al.

		radiodurans, Methanocaldococcus jannaschii, Thermoplasma acidophilum, T. volcanium, Myxococcus xanthus, Methanobacterium thermoautotrophicum, Methanosarcina barkeri, Ferroplasma acidarmanus, Archaeoglobus fulgidus					(2004) and Adekanmbi et al. (2019)
MIT	CorA		Uptake	Chemiosmotic	Most cations	Membrane-integral protein (CorA)	Nies (2003)
MntH	–	*E. coli, Bradyrhizobium japonicum*	Uptake	–	Mn(II), Fe(II)	MntH family proteins are proton-driven metal ion transporters with homology to eukaryotic NRAMP proteins	Peng et al. (2018) and Hohle and O'Brian (2009)
HoxN			Uptake	Chemiosmotic	Co(II), Ni(II)	Membrane-integral protein	Nies (2003)
CBA family /RND	CzcABC, CusABC, CnrABC/NccABC	*R. metallidurans, Mesorhizobium loti, Alcaligenes eutrophus, Myxococcus xanthus, Pseudomonas aeruginosa*	Efflux	Proton gradient	Co(II), Zn(II), Cd(II), Ni(II), Cu(II), Ag(I)	1 CPM proton/cation antiporter + membrane fusion protein (dimer) + outer membrane factor:	Silver (1996), Collard et al. (1994), Diels et al. (1995), Hantke (2001), Moraleda-Muñoz et al.

(continued)

Table 13.1 (continued)

Transporter type	Member	Organism	Function	Energy	Metal ions	Comments	Reference
						CBA transport systems	(2010), Aguilar-Barajas et al. (2010) and Adekanmbi et al. (2019)
CDF	CzcD, ZitB, ZneA, CusA	*E. coli; B. subtilis; Staphylococcus aureus, Thermus thermophiles, B. subtilis, C. metallidurans*	Efflux	Chemiosmotic	Zn(II), Cd(II), Co(II)	Membrane-integral protein	Grass et al. (2001), Hantke (2001), Guffanti et al. (2002), Nies (2003), Spada et al. (2002), Anton et al. (1999) and Nikaido (2018)
CHR	ChrA, Orf1, Orf2, SrpC	*Pseudomonas aeruginosa, Cupriavidus metallidurans, Ralstonia metallidurans, Acinetobacter calcoaceticus, B. subtilis, Synechococcus* sp., *Synechocystis* sp., *Methanococcus jannaschii, Proteus mirabilis*	Antiport	Chemiosmotic	Chromate	ChrA is a membrane-integral protein that confers resistance to the toxic ion chromate through the energy-dependent chromate efflux from the cytoplasm. In P. aeruginosa and A. eutrophus, chromate is accumulated by sulfate uptake systems, and expression of ChrA leads to reduced	Nies (2003), Díaz-Pérez et al. (2007) and Díaz-Magaña et al. (2009)

						accumulation of chromium. ChrA protein of *A. eutrophus* may be a chromate uptake system when expressed alone. CHR family proteins can also catalyze chromate/sulfate antiport	
MerR	MerA, ZntA, PbrA	*E. coli, B. subtilis, R. metallidurans, Hydrogenobaculum* sp. *Hydrogenivirga* sp., *Thermus thermophilus*	Reduction/ efflux			MerA is the protein subunit of the homodimeric mercuric reductase (MR) enzyme, the central function of the mer system	Brown et al. (2003), Freedman et al. (2012) and Boyd and Barkay (2012)
Arsenical pump membrane protein	ArsB	*E. coli, Campylobacter jejuni*	Efflux	ATP	As(III), Sb(III)	ArsB is an antiporter that extrudes As(III) or Sb(III) from cells by $H^+/As(OH)_3$ exchange coupled to the electrochemical proton gradient. It has been proposed that ArsB transport a polymeric ring composed of three As $(OH)_3$ molecule	Garbinski et al. (2019) and Mourão et al. (2020)
BART (bile/ arsenite/	Acr3	*Alkaliphilus metalliredigens*	Efflux	ATP	As(III)	mAcr3–1 has 10 transmembrane-	

(continued)

Table 13.1 (continued)

Transporter type	Member	Organism	Function	Energy	Metal ions	Comments	Reference
riboflavin transporter superfamily)						spanning segments, with the N-and C-termini localized in the cytosol. Acr3 compared with ArsB, has two additional transmembrane-spanning segments. Two residues may be involved in metalloid translocation	
MFS	ArsK	*Agrobacterium tumefaciens, Bacillus* sp.	Efflux	–	As(III), Sb(III), MAs(III), Rox (III)	ArsK is a 411 amino acid residue transmembrane protein that can be predicted to have 12 transmembrane segment (TMs). ArsK has the broadest substrate specificity of any known trivalent arsenic efflux permease, including both inorganic and organic species	
	ArsJ	*Pseudomonas aeruginosa, E. coli*	Efflux	–	As(V)	ArsJ is a 410-residue membrane protein with	

						10 predicted TMs. It has a large putative extracellular loop between TMs 3 and 4, and a smaller intracellular loop between TMs 4 and 5	
MAs(III)-selective permeas	ArsP	*Campylobacter jejuni*	Efflux	–	As(V), methylarsenite (MAs(III)), roxarsone (Rox(III))	It is smaller than MFS transporters and is predicted to have only 8 TM. ArsP is an organic arsenic transporter for the pentavalent forms of roxarsone and nitarsone	
Feo	FeoB	*B. subtilis*, *E. coli*, *S. thermophiles*, *Pyrococcus furiosus*, *Klebsiella pneumoniae*, *L. pneumophila*, *Thermotoga maritima*, *Gallionella capsiferriformans*	Uptake	–	Fe(II)	Starting from the N-terminal end, the G-protein domain is the first protein domain of FeoB. The G-protein domain resides in the cytoplasm and is covalently tethered to the polytopic transmembrane region of FeoB through the so-called GDI-domain	Lau et al. (2016)

13.3 Heavy Metal Resistance in Prokaryotes

Heavy metal ions cannot undergo degradation or significant modification like toxic organic compounds in the environment. Microbes, leaving in the heavy metal-polluted environment, develop different mechanisms to tolerate toxic concentrations of the metals (Nies 2007). Microbes can have one or a combination of several different strategies of metal resistance (Bruins et al. 2000; Nies and Silver 1995).

In bacteria, all existing mechanisms that allow surviving in the presence of toxic concentrations of heavy metals in the medium can be attributed to several main types. This is an active release of metal from the cell, restriction of metal intake due to changes in cell permeability, intracellular metal binding and detoxification, extracellular binding, enzymatic metal detoxification into a less toxic form and a decrease in the metal sensitivity of cellular components (Fig. 13.3) (Nies and Silver 1995; Nies 2007; Bruins et al. 2000; Ahemad 2015).

Among the Archaea, thermophiles and hyperthermophiles of the Crenarchaeota and the methanogens and thermophiles of Euryarchaeota utilize P-type ATPases and

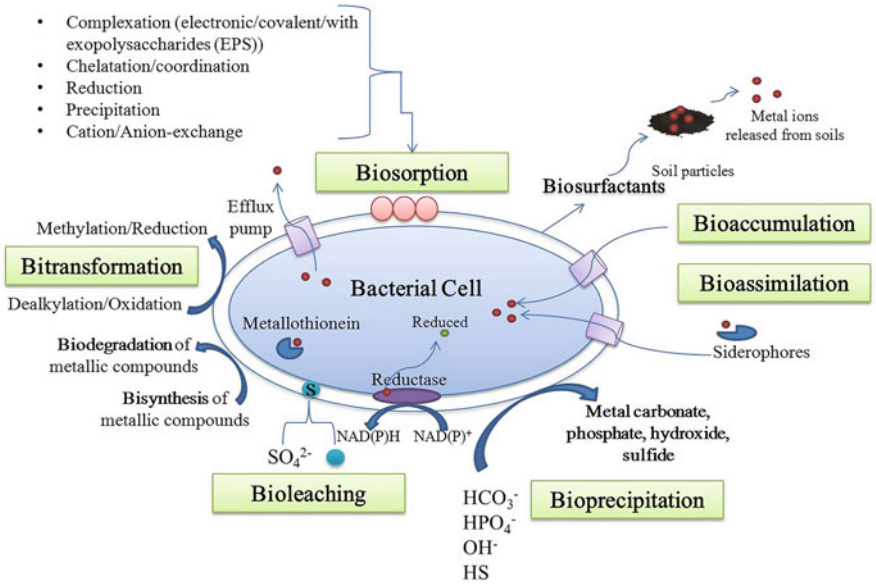

Fig. 13.3 Various bacterial interactions with heavy metals in metal-polluted soil. *Biosorption*: Precipitation/crystallization of metals occurs due to bacteria-mediated reactions or as a result of the production of specific metabolites. *Bioaccumulation:* Plasmid-DNA-encoded efflux transporters (e.g., ATPase pumps or chemiosmotic ion/proton pumps) expel the accumulated metals outside the cell. *Bioprecipitation:* Metals bind to the anionic functional groups (e.g., sulfhydryl, carboxyl, hydroxyl, sulfonate, amine, and amide groups) of extracellular materials present on cell surfaces. *Bioleaching:* Organic acids secreted by bacteria solubilize the insoluble metal minerals. *Biotransformation:* Some bacteria utilize methylation as an alternative for metal resistance/detoxification mechanism, which involves the transfer of methyl groups to metals and metalloids

ABC transporters for metal transport and homeostasis (Coombs and Barkay 2005; Bartolucci et al. 2013).

13.3.1 Active Transport of Heavy Metals

Microbes use active transport mechanisms to efflux toxic metals from the cytoplasm. Metals that do not have physiological significance usually enter into the cell through transport systems designed for the necessary cations, but then quickly get out of the cell by efflux pumps (Ehrlich 1997a). It was found that active ion efflux systems can be either ATP-independent or using ATP energy (see Table 13.1). All of them are highly specific for cations or anions that are exported from the cell (Nies and Silver 1995; Hynninen 2010). A large number of varieties of this mechanism of metal resistance in bacteria and archaea are described (Table 13.1). Three families of transport systems are mainly involved in the export of heavy metal ions from the cell: a three-component transmembrane transporter in Gram-negative bacteria is Capsule biogenesis/assembly (CBA) family transporter, which acts as a chemosmotic antiport; cation diffusion facilitator (CDF), which acts as a chemosmotic ion-proton exchanger and P-type ATPase located in the inner membrane and using ATP energy to export metal ions from the cytoplasm to periplasm (Fig. 13.4) (Hynninen 2010; Nies 2003, 2007; Grass et al. 2001).

13.3.2 CBA Family Transporters

CBA family transporters are a three-component protein complex that span the whole cell wall of Gram-negative bacteria and expel ions from cyto- and periplasm to

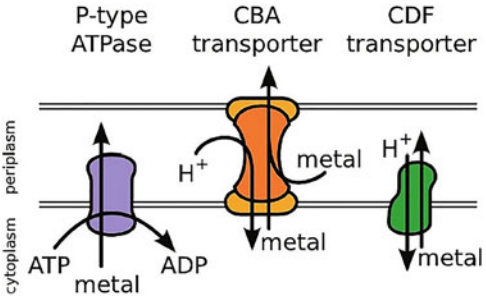

Fig. 13.4 The main transporter families that determine bacterial heavy metal resistance. *P-type ATPases* pump their substrates from cytoplasm to periplasm using energy provided by ATP hydrolysis. *CBA transporters* are three-component complexes in Gram-negative bacteria that efflux ions from cyto- and periplasm to outside using a chemiosmotic gradient. *CDF transporters* are driven by a proton motive force and they export ions from cytoplasm to periplasm (Hynninen 2010)

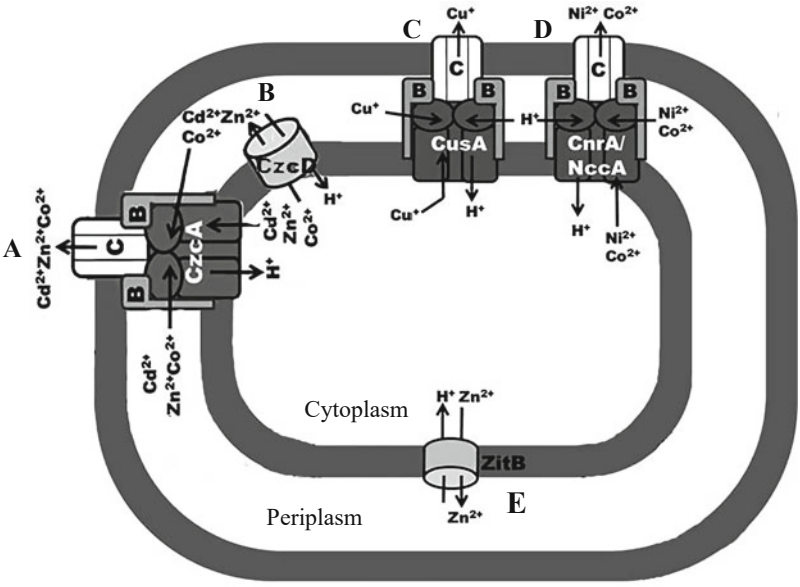

Fig. 13.5 Structural models of CBA and CDF families pumps. (**a**) Czc, functioning as a proton/cation antiport, consisting of intramembrane (CzcA), extramembrane (CzcC) and integral (CzcB) proteins, (**b**) CzcD, transporting Cd, Zn and Co ions in *B. subtilis*, (**c**) CusABC, and (**d**) CnrABC / NccABC are similar in structure and function to the CzcABC system, (**e**) ZitB is similar to the CzcD system (modified from Aguilar-Barajas et al. 2010)

outside using a chemiosmotic gradient. The most important component of the transporter is the intramembrane protein RND (resistance, nodulation, and division), which was first described as a bacterial transport protein involved in the resistance processes of heavy metals in *R. metallidurans*, nodulation of *Mesorhizobium loti*, and cell division of *E. coli* (Nies 2003).

An example of the RND family transporter is the Czc system for the active export of Cd(II), Zn(II), Co(II) cations from a bacterial cell. The Czc system is described and studied in detail in the facultative chemolithoautotrophic bacteria *Alcaligenes eutrophus* CH34. The Czc system is regulated by a proton concentration gradient across the inner membrane and is ATP-independent (Silver 1996; Collard et al. 1994; Diels et al. 1995). The Czc system consists of three main parts (Fig. 13.5) (Rosen 2002; Anton et al. 1999).

13.3.3 CDF Family Transporters

The cation diffusion facilitators (CDFs) are a family of membrane-bound proteins that maintain cellular homeostasis of essential metal ions. Proteins of the secondary cationic CDF transporter catalyzing the efflux of heavy metals and were found in

both prokaryotes and eukaryotes. All proteins of the CDF family are substrate-specific. The main substrate for CDF transporters is Zn(II) ions, but Co(II), Ni(II), Cd(II), and Fe(II) can also initiate transporter. The CDF system is regulated by a proton concentration gradient, $\Delta\Psi$, ΔpH, or K(I) concentration gradient (Nies 2007; Guffanti et al. 2002; Paulsen and Saier 1997).

CDF coding genes were found in the chromosomes of a number of microorganisms, but protein functionality has been characterized only in few microbes. In *B. subtilis*, *czcD* genes are located in the operon along with *trikA* dehydrogenase gene (Nies 2003). The *czcD-trkA* operon is complementary to the K(I) transport system in *E. coli* (Guffanti et al. 2002). CzcD was first described in bacteria *Ralstonia metallidurans* CH34 as a regulator of *czcABC* gene expression, but CzcD (Fig. 13.5) can also participate in the transport of Cd(II), Zn(II), Co(II) in the absence of the CzcABC system (Anton et al. 1999; Nies 2003; Scherer and Nies 2009; von Rozycki and Nies 2009).

In *B. subtilis*, CzcD is regulated by a K(I) concentration gradient and leads to the emission of Cd(II), Zn(II) and Co(II) (Guffanti et al. 2002). In *E. coli* cells, the CzcD system is regulated by a proton concentration gradient and leads to the emission of Zn(II) and Cd(II) ions, but not Co(II) (Nies 2003; Paulsen and Saier 1997).

In *E. coli*, the ZitB protein (product of the *ybgR* gene) of the CDF family has also been described, which determines resistance to Zn ions, reducing ion accumulation (Fig. 13.5) (Grass et al. 2001).

In *Staphylococcus aureus*, CzcD determines resistance to Zn(II) and Co(II), in *Thermus thermophilus* determines resistance to Zn(II) and Cd(II). CDF proteins can also export Pb ions (Spada et al. 2002; Xiong and Jayaswal 1998).

13.3.4 P-Type ATPase Family Transporters

P-type ATPase is a family of transport protein that exports ions against a concentration gradient using ATP. It is highly substrate-specific. The substrates are Na, K, Mg, Ca, Cu, Ag, Zn, Cd, Co, and Pb cations. Heavy metal-transporting ATPases have a metal-binding domain (MBD) and are described in both gram-positive and gram-negative bacteria. Prototype of P-type ATPase is ZntA system for active efflux of Zn(II), Cd(II), and Pb(II) from *E. coli* cell (Fig. 13.6) and CadA for active efflux of Cd(II) from *S. aureus* cell (Fig. 13.6).

CadA consists with six domains located in the membrane, four of which are involved in translocation of cations, and a conservative Cys-Pro-Cys tripeptide. Two intracellular domains common to all P-type ATPases are aspartyl kinase and phosphatase domain. During metal transport, ATP phosphorylates the protein, probably at the location of the invariant aspartic acid (Asp 415). Phosphorylation occurs only in the presence of Cd ions (Tsai et al. 1992). The transport system CadA was also found in the bacteria *Bacillus subtilis, Pseudomonas metallidurans, Cupriavidus metallidurans*, *Synechocystis* sp. etc. (Lee et al. 2001; Scherer and Nies 2009).

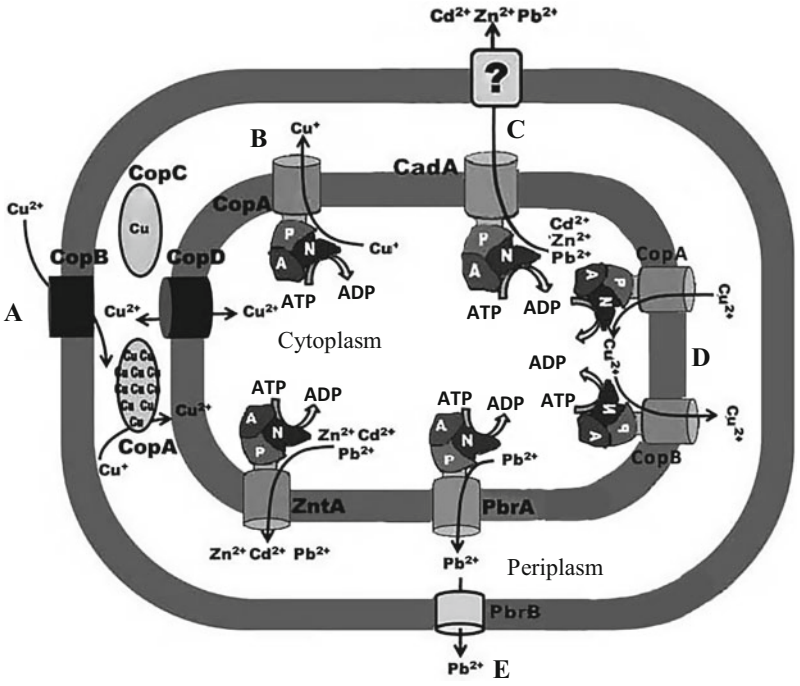

Fig. 13.6 Transport systems of metals—P-type ATPases: (**a**) CopABCD copper transport system; (**b**) CopA ATPase P-type transformation of Cu(I) into Cu(II); (**c**) CadA ATPase of the P-type, removal of Cd, Zn, and Pb ions from the cytoplasm; (**d**) CopA system of absorption of Cu(II) and CopB of Cu(II) export in *E. hirae* cells; (**e**) PbrA ATPase P-type removal of Pb ions from the cytoplasm; ZntA ATPase P-type removal of Zn, Cd and Pb ions from the cytoplasm (modified from Aguilar-Barajas et al. 2010)

PbrA system, the member of P-type ATPase, actively removes Pb ions from the cytoplasm of the bacterium *Cupriavidus metallidurans* (Fig. 13.6). The structure and function of the protein PbrA is similar to the CadA and ZntA. PbrB lipoprotein is located on the outer membrane, which probably transports Pb ions from periplasm to the environment (Aguilar-Barajas et al. 2010).

In *Enterobacter hirae* have been found the CopA and CopB system of the P-type ATPase family, which are for Cu(II) transport. CopA determines the absorption of Cu ions, and CopB efflux of Cu ions from the cytoplasm. The synthesis of the both proteins is regulated by operon genes (Fig. 13.6) (Argüello et al. 2013). The promoter region of the operon is controlled by the CopY repressor, regulated by Cu ions. CopZ protein, together with Cu ions, activates the promoter. The binding of copper to CopZ leads to the formation of the complex, which attached to CopY, as a result the operon, is activated (Rademacher and Masepohl 2012).

Homologous systems have been described in *Pseudomonas syringae, Xanthomonas campestris,* and *E. coli* (Cooksey 1994). In the copper metabolism of *P. syringae*, two regulatory *copRS* genes and four structural *copABCD* genes were

found, while in *X. campestris* and *E. coli,* the corresponding genes are called *pcoRS* and *pcoABCD*. The *copR* and *copS* genes are located immediately after the copper tolerance operon (*copABCD*) on the pPT23D plasmid and transcribed as an operon from two genes of the same constitutive promoter (Mills et al. 1994; Rademacher and Masepohl 2012) (Fig. 13.6).

The product of *copS* gene is the copper-sensitive CopS protein, which located in the inner membrane. The product of *copR* gene is the regulatory protein CopR, which located in the cytoplasm. With an increased periplasmic concentration of Cu (II), CopR transphosphorylates the CopS protein and activates transcription of the *cop* operon (Rademacher and Masepohl 2012; Mills et al. 1994).

The plasmid operon *copABCD* in the bacterium *Pseudomonas syringae* is one of the first described copper resistance systems in bacteria. The *copABCD* operon encodes a system that prevents the penetration of copper into the cell cytoplasm. CopA and CopC are periplasmic proteins that bind copper. The proteins CopA and CopC able to bind 11 and 1 copper atoms, respectively, on the same polypeptide (Aguilar-Barajas et al. 2010). The activation of transporters leads to the accumulation of copper in the periplasmic space, which protects the cell from the toxic effect of the ion. CopA also exhibits oxidase activity, transforming Cu(I) into Cu(II), thereby protecting the periplasmic enzymes from the toxic effect of copper (Argüello et al. 2013).

CopC is probably a chaperone protein that transports Cu ions to the integral CopD protein. CopD consists of eight transmembrane segments and transports copper both into the cytoplasm and from the cytoplasm to the periplasm. CopB is an outer membrane protein that absorbs copper (Aguilar-Barajas et al. 2010).

P-type ATPase has been found in 17 archaea species, by screening the databases from TIGR, NCBI, DOE, and TCDB. In all analyzed archaea species contained 1–3 metal ATPases, which belong to six different phylogenetic TC (Transport Classification) clusters. The proteins belonging to these clusters export (more rarely import), a variety of monovalent or divalent metals (copper, zinc, lead, cadmium, or silver) (De Hertogh et al. 2004). Only three transmembrane motifs for metal-transporting ATPases identified in archaea, which correspond to the group IB-1 (Cu(I)/Ag(I)), group IB-2 (Zn(II)/Cd(II)/Pb(II)), and group IB-3 (Cu(II)/Cu(I)/Ag(I)) motifs (Argüello et al. 2003).

Two metal-transporting ATPase genes *CopA* and *CopB* from the thermophilic archae *Archaeoglobus fulgidus* were cloned in *E. coli*, purified, and their ATPase activity were biochemically characterized (Mana-Capelli et al. 2003; Mandal and Argüello 2003). The thermophilic ATPase activity of *CopA* was best activated by the monovalent metals Ag(I) and Cu(I) while *CopB* was activated by the divalent Cu(II).

ATPases along with the ABC transporters, transcriptional regulators, and certain metallochaperones were found to be involved in metal resistance and homeostasis in the haloarchaeon *Halobacterium* sp. strain NRC-1 (Kaur et al. 2006). The list of archaea P-type ATPases are shown in the Table 13.2.

Table 13.2 The list of archaeal P-Type ATPases (De Hertogh et al. 2004)

Microorganism	Substrate	Function	TC typical organism
Aeropyrum pernix	Zn(II), Cd(II), Pb(II)	Efflux	Bacteria; plants; fungi; protozoa
Archaeoglobus fulgidus	Cu(I)/Ag(I)	Efflux	Archaea (CopA), Bacteria
Ferroplasma acidarmanus	Cu(II)	Uptake	Bacteria
Halobacterium sp.	Cu(II)	Uptake	Bacteria
	Zn(II), Cd(II), Pb(II), Cu(I)/Ag(I)	Efflux	Bacteria; plants; fungi; protozoa, archaea (CopA)
Methanosarcina acetivorans	Cu(I), Ag(I), Zn (II) Cd2C-, Pb2C	Efflux	Bacteria; plants; fungi; protozoa
Methanosarcina barkeri	Mg(II)/Ni(II), Cu(I), Ag(I), Zn(II), Cd(II), Pb(II)	Efflux	Archaea, eukaryotes (Wilson's disease), Bacteria; plants; fungi; protozoa
Methanosarcina mazei	Cu(I), Ag(I)	Efflux	Eukaryotes (Wilson's disease), Bacteria
Methanobact. thermoautotrophicum	Cu(I), Ag(I), Zn(II), Cd(II), Pb(II)	Efflux	Archaea (CopA), Bacteria; plants; fungi; protozoa
Pyrobaculum aerophilum, Pyrococcus furiosus, Sulfolobus solfataricus, Sulfolobus tokodaii, Thermoplasma acidophilum, Thermotoga maritima, Thermoplasma volcanium	Cu(I)/Ag(I)	Efflux	Archaea (CopA)

13.3.5 *Limitation of Metal Intake Due to Changes in Cell Permeability*

When a cell is exposed to concentrations of heavy metals in the environment, the microbe may undergo structural changes in the cell wall, membrane, and cytoplasmic membrane. These processes are not always the result of the toxic effects of the metals. They can be a manifestation of induced defense mechanisms that limit the flow of toxic ions into the cell cytoplasm (Bruins et al. 2000; Ehrlich 1997a).

The first sites of cell and heavy metal interaction are at the cell surface. The bacterial cytoplasmic membrane, and to a lesser extent the outer membrane in Gram-negative bacteria, are a major barrier to the entry of hydrophilic substances, including metal ions, into the interior of the cell. In Gram-negative bacteria, like *E. coli*, the outer membrane contains protein channels called porins, that allow low-molecular-weight substances such as metal ions to diffuse across the membrane into the periplasmic space. In *E. coli* synthesis of the major porin can be prevented by

mutations in a single gene resulting in increased metal resistance. The outer membrane can also act as a limited (i.e., saturable) trap for heavy metals by nonspecifically binding them, therefore contributing to the natural metal tolerance of cells (Rouch et al. 1995).

An unusual mechanism of metal resistance is found in *Pseudomonas syringae,* which accumulate blue Cu(II) ions in the periplasmic space and outer membrane. At least part of this copper sequestering activity is determined by copper-binding periplasmic CopA protein products of the copper resistance operon (*cop*). Copper resistance operons related to *cop* have been described in the related plant pathogen *Xanthomonas campestris* and in *E. coli*, but these resistance systems may differ functionally from the *P. syringae* system (Cooksey 1994).

A significant advantage for survival in environments contaminated with heavy metals is reducing bioavailability or mobility of heavy metal ions by the released exopolysaccharide (EPS). Anionic property of EPS allows the biopolymer to effectively sequester positively charged heavy metal ions and restricts the entry of metal ions into the cell. The anionic property of EPS imparts by abundant active and ionisable functional groups and non-carbohydrate substituents like phosphodiester (techoic acid), phosphate, hydroxyl groups, or acetamido group of chitin, structural polysaccharides of fungi. On contrary to homopolysaccharides, extracellular heteropolysaccharides are often polyanionic due to association of some of such functional groups with polysaccharide backbone. The sorption and immobilization again occurs via different mechanisms like ion exchange, complexation, precipitation, etc. (Gupta and Diwan 2017). As an example can be serve *Ochrobactrum anthropi*, isolated from activated sludge. This bacteria producing the most EPS for the removal of Cr(VI), Cd(II) and Cu(II) (Ozdemir et al. 2003).

Staphylococcus xylosus and *Staphylococcus carnosus* strains were characterized by production of surface-exposed chimeric two different polyhistidyl peptides, His_3-Glu-His_3 and His_6 due to the expression of recombinant plasmid genes designed for binding to divalent metal ions. As a result, the entry of Cd ions and other toxic metals into the cell is limited, which suggests that such bacteria could find use in bioremediation of heavy metals (Samuelson et al. 2000).

It has been shown, that EPS synthesized by *Arthrobacter viscosus* accumulate 2.3 times more Cd(II) than an equivalent weight of intact cells and have 13.7 times the sorptive capacity of *Arthrobacter globiformis* cells, which do not produce EPS (Hrynkiewicz et al. 2015).

Numerous halophilic bacteria and archaea can also tolerate high concentrations of heavy metals by secrete EPS. *Halomonas* strains can tolerate high concentrations of Pb(II) and Cd(II) (5 mM) by the EPS-mediated adsorption of the metallic ions (Voica et al. 2016). Dry biomass of the haloarchaeon *Halobacterium* sp. GUSF was an effective adsorbent for Mn(II) from saline solutions, the process of adsorption involving cell surface carboxyl, amino, phosphate and hydroxyl groups (Naik and Furtado 2014). The high EPS-producing halotolerant cyanobacterium *Aphanothece halophytica* grown at 6% NaCl (w/v) was capable of accelerated Zn (II) adsorption up to a critical cell density that may result in aggregation, reducing the matrix surface available for metal binding (Incharoensakdi and Kitjaharn 2002).

13.3.6 Intracellular Binding of Toxic Metals and Their Detoxification

The accumulation of metal in the cytoplasm and its detoxification can occur due to the binding of toxic ions to specific proteins, like low-weight cysteine-rich proteins and peptides. A variety of metal-binding peptides like glutathione (GSH) and proteins like metallothioneins and phytochelatins produced by certain microbes like *Cyanobacterium synococcus, Synechococcus* sp., *E. coli, P. putida* (Gupta and Diwan 2017; Bruins et al. 2000; Silver 1996).

Citrobacter sp., isolated from metal-polluted soil can resist Cd(II) toxicity by forming insoluble complexes of Cd-phosphate ($CdHPO_4$); this transformation is mediated by a cell-bound phosphatase that precipitates inorganic phosphate with heavy metals. A strain of *Pseudomonas putida* isolated from sewage can sequester intracellular Cd(II) by producing three low-molecular-weight cysteine-rich proteins related to eukaryotic metallothioneins, while *K. aerogenes* excretes sulfur into the surrounding environment to immobilize Cd(II) ions as insoluble Cd-sulfide (Hrynkiewicz et al. 2015). The ability to intracellularly accumulate lead phosphate in the form of granules was exhibited by the *P. aeruginosa* (Naik et al. 2012). For Mycobacterium scrofulaceum, the ability to intracellular accumulation of Cu(II) in the form of sulfide was found (Bruins et al. 2000).

Cyanobacteria at toxic concentrations of free Cu ions in the medium produce extracellular chelating ligands that bind to Cu(II) ions, reducing their bioavailability. In *Synechococcus* spp., a ubiquitous and important group of phytoplankton, synthesis of chelating ligands is regulated by the concentration of free Cu(II) ions in the medium according to the feedback mechanism (Moffett and Brand 1996).

In some cases, the formation of metal precipitating anions may result from normal cellular metabolism, such as the formation of sulfides under anaerobic conditions by sulfate-reducing bacteria of the genus *Desulphovibrio*. In other cases, the process is inducible under certain environmental conditions, for example, the formation of sulfides by bacteria of the genus *Clostridium* (Karnachuk et al. 2003).

Metallothioneins and phytochelatins are not represented in archaeal genomes, however members of the CutA family of metal-binding proteins are found in archaea, bacteria, and eukaryotes. The crystal structure of the *Pyrococcus horikoshii* CutA has been determined with and without copper, contributing to the clarification of the protein's function. In fact, binding of heavy metals induced the reversible multimerization of CutA. Thus, a role has been proposed for CutA in the capture and precipitation of metal ions. Interestingly, while the metal-binding site of the *E. coli* homolog contains Cys and His residues, these amino acids are absent in the *Pyrococcus* protein (Bini 2010).

13.3.7 Reduction of Heavy Metal Ions and Enzymatic Detoxification

Bacteria and Archaea are reducing a broad spectrum of heavy metal ions: chromate, molybdate, vanadate, iron, etc. (Table 13.3). Some bacteria and archaea can use metals and metalloids as electron donors or acceptors for energy generation. Metals in the oxidized form could serve as terminal acceptors of electrons during anaerobic respiration.

The most studied example of the manifestation of the metal resistance mechanism in bacteria associated with the process of intracellular enzymatic metal detoxification is the Hg ion resistance system (Nies 1999). Stability is due to the functioning of the operon and was revealed both in gram-positive (*S. aureus, Bacillus* sp.) and gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa, Serratia marcescens, Thiobacillus ferrooxidans*) (Bruins et al. 2000). As a result of the expression of the genes that make up the *mer* operon, Hg(II) in two stages is reduced to metallic mercury, which then diffuses through the cell membrane and is released into the environment (Fig. 13.7). Due to the volatility of metallic mercury, its content in the medium can rapidly decrease (Silver 1996).

In *Alcaligenes faecalis* bacteria, the mechanisms of enzymatic oxidation of As (III) compounds present in the form of AsO_2 to As(V) compounds in the form of AsO_4, which are less toxic, have been studied and described (Anderson et al. 2003).

Microorganisms have developed, or acquired, various genetic systems to cope with arsenic toxicity. These systems include the *ars* operons, groups of genes widely

Table 13.3 Reduction of metals and metalloids by different microorganisms (modified from Ianeva 2009)

Reduction process	Microorganism
Hg(II)/Hg(0)	*Bacillus cereus, Klebsiella pneumonia, P. stutzeri*
Fe(III)/Fe(II)	*Geobacter* sp., *G. metallireducens, Bacillus thermoamylovorans, Ferroplasma* spp., *Thermoplasma* spp.
Cr(VI)/Cr(III)	*Desulfomicrobium norvegicum, Microbacterium* sp., *Ochrobacterium intermedium, Brevibacterium* sp., *Pseudomonas* spp.
As(V)/As(III)	*S. aureus*
U(VI)/U(IV)	*Desulfovibrio desulfuricans, Shewanella putrefaciens, Thermoterrabacterium ferrireducens, Metallosphaera prunae, M. sedula*
Mn(IV)/Mn(II)	*Shewanella putrefaciens*
Se(VI)/Se(IV)/ Se(0) Se(IV)/Se(0)	*R. metallidurans, B. thermoamylovorans, Shewanella oneidensis*
V(V)/V(IV)	*S. oneidensis, G. metallireducens*
Tc(VII)/Tc(IV)	*Geobacter sulfurreducens, S. putrefaciens*
Mo(VI)/Mo(V)	*Thiobacillus ferrooxidans*
Au(III)/Au(0)	*Stenotrophomonas* sp.
Te(IV)/Te(0)	*B. thermoamylovorans, S. oneidensis*

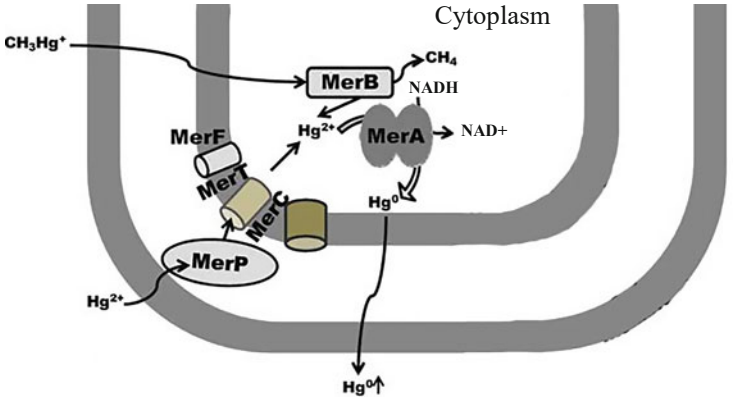

Fig. 13.7 Mechanism of detoxification by the Hg(II) Mer system (Aguilar-Barajas et al. 2010)

distributed in bacterial and archaeal species. *ars* operons frequently occur in most prokaryotic genomes, and it has been stressed that they are more common than genes for tryptophan biosynthesis. This operon first has been found in the plasmid pI258 in the clinical bacteria *Staphylococcus aureus*. The plasmid pI258 was found to encode multiple resistances to antibiotics, arsenate, arsenite and other heavy metal derivatives (Ben Fekih et al. 2018; Novick and Roth 1968). Arsenic resistance genes have identified in R773 plasmid in *Escherichia coli* strain isolated from a patient with a urinary tract infection (Hedges and Baumberg 1973). The nucleotide sequence of the determinants from the *E. coli* R773 plasmid identified the *arsRDABC* operon involved in the arsenic resistance phenotype, and staphylococcal plasmids pI258 and pSX267 both contained similar, but simpler *arsRBC* operons encoding proteins with homology to those encoded by R773 (Ben Fekih et al. 2018). The distribution of *ars* operon genes in bacteria and archaea are presented in the Table 13.4.

Nearly every organism has resistance pathways for inorganic arsenic. The minimal constituents are usually an As(III)-responsive repressor (ArsR), and an As(III) efflux permease (ArsB or ACR3) that functions to extrude trivalent As(III) from cells. The As(III)-stimulated ATPase (ArsA), and the As(III) metallochaperone (ArsD), 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 and other arsenate reductases are required for resistance to arsenate (Yang and Rosen 2016; Ben Fekih et al. 2018). Recently, a parallel pathway for organic arsenicals has been identified. The ars genes responsible for the organo-arsenical detoxification include *arsM*, which encodes an As(III) S-adenosylmethionine methyltransferase, *arsI*, which encodes a CeAs bond lyase, and *arsH*, which encodes a methylarsenite oxidase (Fig. 13.8).

Pentavalent inorganic arsenate (As(V)) is reduced by the ArsC arsenate reductase to trivalent arsenite (As(III)). Some microbes encode As(III) S-adenosylmethionine methyltransferases ArsM protein, that transform As(III) into the considerably more toxic (for humans, carcinogenic) organo-arsenical MAs(III). Other microbes can

Table 13.4 Distribution of *ars* genes in arsenic-resistant bacteria and archaea

Microbe	Plasmid/ Chr	Operon/gene	Comments	Reference
E. coli	R773	*arsRDABC*	The ArsB is an integral membrane protein which acts as an anion channel. The ArsA protein is the energy-transducing ATPase subunit, with specific-binding sites for ATP and arsenite. Binding of ArsC to the complex either changes the specificity to arsenate or increases the range of substrates to allow recognition of both arsenate and arsenite. The ArsR and ArsD are regulatory proteins	Chen et al. (1986) and Carlin et al. (1995)
Acidiphilum multivorum	pKW301			Suzuki et al. (1998)
Staphylococcus aureus	pI258	*arsRBC*	*ars* operon induced by arsenate [As(V)], arsenite [As(III)], and antimonite Sb(III)	Ji and Silver (1992)
S. xylosus	pSX267			Rosenstein et al. (1992)
E. coli	Chr			Carlin et al. (1995)
Pseudomonas aeruginosa	pKW301			Cai et al. (1998)
P. fluorescens				Prithivirajsingh et al. (2001)
Rhodopseudomonas palustris	Chr	*arsRCBH arsRM arsRC*	ArsM catalyzes the formation of a number of methylated intermediates from [As(III)], with trimethylarsine as the end product	Qin et al. (2006)
Bacillus subtilis	Tn	*arsRBC*	ArsR, ArsB, and ArsC function as a negative regulator, a membrane-associated protein need for extrusion of arsenite, and arsenate reductase, respectively	Sato and Kobayashi (1998)
Serratia marcescens	IncHI2	*arsR, arsB, arsC, and arsH*	272-kb plasmid encoding a variety of antibiotic and heavy metal resistances including resistance to arsenate, arsenite, antimony, mercury, tellurite, tetracycline, chloramphenicol, and kanamycin	Ryan and Colleran (2002) and Whelan and Colleran (1992)
P. putida	Chr	*arsRBCH*	The operon encodes self-repressed transcriptional regulator (ArsR), a membrane-bound transporter that extrudes AsIII out of the cell (ArsB), an arsenate reductase (ArsC) for transformation of AsV to AsIII and an ArsH of unknown function but also important for arsenic resistance	Páez-Espino et al. (2015)

(continued)

Table 13.4 (continued)

Microbe	Plasmid/ Chr	Operon/gene	Comments	Reference
Streptomyces sp.	pHZ227	*arsRBOCT*	*arsO* encodes putative flavin-binding monooxygenase) and *arsT* encodes a putative thioredoxin reductase)	Wang et al. (2006)
Corynebacterium glutamicum	Chr	*arsRBC, ars1, ars2*	ArsB a regulatory protein, ArsB an arsenite permease, and ArsC an arsenate reductase, the operon *ars1* contains an additional arsenate reductase gene (*arsC1*). Additional arsenite permease and arsenate reductase genes (*arsB3* and *arsC4*) scattered on the chromosome were also identified	Ordóñez et al. (2005)
Shewanella oneidensis	Chr	*arsDABC*	ArsB and ArsC may be useful for As(V)-respiring bacteria in environments where As concentrations are high	Saltikov et al. (2003)
Leptospirillum ferriphilum	Chr TnLfArs	*arsRCB arsRCDA arsB*	ArsR in a negative regulator, ArsC is a arsenate reductase, ArsD is a second repressor and ArsA is an ATPase that associates with ArsB and links arsenite export to ATP hydrolysis. These genes are followed by genes encoding ORF7 (an NADH-like oxidoreductase), ORF8 (a cystathione-β-synthase (Tuffin et al.) domain-containing protein), and ArsB, the arsenite-efflux pump	Tuffin et al. (2006)
Acidithiobacillus caldus	TnAtcArs	*arsRCDADA arsB*	A series of genes consisting of *arsR*, two tandem copies of *arsA* and *arsD*, two *ORFs* and *arsB* is situated between the resolvase and transposase genes	Tuffin et al. (2005)
A. ferrooxidans	Chr	*arsCR, arsBH*	ArsR is promoter in response to arsenic and antimonite	Butcher and Rawlings (2002)
Thiobacillus ferrooxidans	Chr	*arsB, arsC, arsH, and* a putative *arsR*	Genes encoding for ArsB (arsenite export) and ArsC (arsenate reductase)	Butcher et al. (2000)
Ferroplasma acidarmanus	Chr	*arsR, arsB*	Genes encoding for ArsR (arsenite-sensitive regulator) and ArsB (arsenite-efflux pump)	Gihring et al. (2003)
Halobacterium sp.	Chr pNRC100	*arsB arsADRC, arsR2M*	It is suggesting *arsM* gene produced a second novel mechanism of arsenic resistance involving a putative arsenite(III)-methyltransferase	Wang et al. (2004)

Herminiimonas arsenicoxydans	Chr	*aoxABCD, aoxRS, arsRCBCH, arsM*	Expression of the *aoxAB* operon promotes [As(III)] oxidation. *arsRCBCH* operone code an ArsR regulator, an [As (III)] extrusion pump, one or two arsenate reductases (ArsC), an ArsH putative flavoprotein, *arsM* gene expose arsenic methylation activity	Muller et al. (2007)
Desulfovibrio desulfuricans	Chr	*arsRBCC, arsC1*	*arsR* operon gene is encoded the repressor protein, which control operon. *arsC1* gene constitutively expressed and allows a rapid response to an influx of arsenate into the cell, as the arsenate is reduced by ArsC1	Li and Krumholz (2007)
Sinorhizobium sp.	pSinA	*arsRC, arsRCB, arsHR*	Removal of this plasmid from cells of the host strain caused the loss of resistance to arsenic and heavy metals (Cd, Co, Zn, and Hg)	Drewniak et al. (2013)
Sinorhizobium meliloti	Chr	*aqpS, arsC, arsH*	The *ars* operon includes an aquaglyceroporin (*aqpS*) in place of *arsB*, that facilitates transport of arsenite. ArsH is involved in [As(III)] detoxification	Ye et al. (2007) and Yang et al. (2005)
Ochrobactrum tritici	Chr	*ars1, ars2*	*ars1* operon contains five genes encoding the following proteins: ArsR, ArsD, ArsA, CBS-domain-containing protein and ArsB. The *ars2* operon is composed of six genes that encode two other ArsR, two ArsC (belonging to different families of arsenate reductases), one ACR3 and one ArsH-like protein	Branco et al. (2008)
Geobacillus kaustophilus	Chr	*arsRBC, arsC*	Operon consists with *arsC1, arsC2, arsC3* genes. *arsC3* is a monocistronic locus, sequencing of the regions flanking *arsC1* and *arsC2* revealed the presence of additional genes encoding a putative arsenite transporter and an ArsR-like regulator upstream of each arsenate reductase, indicating the presence	Cuebas et al. (2011)
Thermomonospora curvata	Chr	*arsI, arsM*	ArsI is a microbial non-heme, ferrous-dependent dioxygenase that transforms toxic methylarsenite (Nadar et al.) to less toxic inorganic arsenite [As(III)] by C–As bond cleavage	Nadar et al. (2016)

Chr chromosomal genes

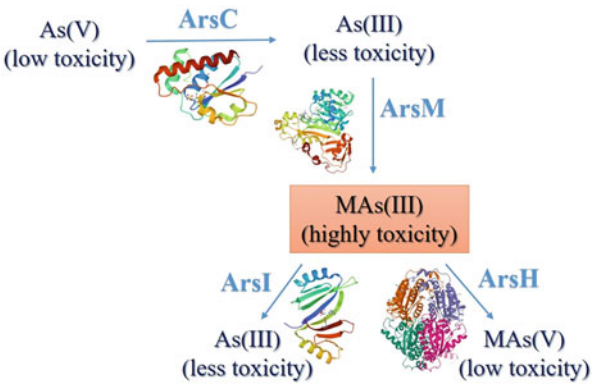

Fig. 13.8 Enzymes of organo-arsenical production and detoxification

produce the ArsI C-As lyase, a dioxygenase that cleaves off the methyl group, forming inorganic As(III). Since As(III) is less toxic than MAs(III), this reaction detoxifies the organo-arsenical product. Other bacteria have the ArsH NADPHFMN oxidoreductase that oxidizes MAs(III) to relatively nontoxic pentavalent MAs(V), also a detoxification process (Yang and Rosen 2016). The protein structure of the ArsC (from *S. aureus*), ArsM (from *Cyanidioschyzon* sp.), ArsI (from *T. curvata*) and ArsH (from *S. meliloti*), presented in the illustration, were used from Protein Data Bank (https://www.rcsb.org/).

Outer example of the heavy metal detoxification is hexavalent chromate reduction. Bacterial developed the mechanisms for reduction of Cr(VI) to the Cr(III) species and efflux of chromate from cell cytoplasm. Several chromate reductases have been identified in diverse bacterial species (Table 13.5). Most characterized enzymes belong to the NAD(P)H-dependent flavoprotein family of reductases.

Candidatus "Methanoperedens" independently utilizes chromate as electron acceptor to form Cr(III) compounds, or it can oxidizes methane to generate intermediates or electrons, which will be utilized to reduce chromate to Cr(III) compounds by unknown chromate reducers synergistically (Luo et al. 2019).

Efflux of chromate by the ChrA membrane transporter, a plasmid-encoded protein, has been demonstrated in *Pseudomonas* and *Cupriavidus* species (Fig. 13.9). Chromate efflux by ChrA consists of an energy-dependent process driven by the membrane potential. The CHR protein family, which includes putative ChrA homologs, currently contains about 135 sequences from all three domains of life. Other mechanisms of bacterial resistance to chromate involve the expression of components of the machinery for repair of DNA damage as well as free-radical scavenging enzymes (Cervantes and Campos-García 2007; Díaz-Magaña et al. 2009).

Table 13.5 The sours and properties several chromate-reducing enzymes (Pradhan et al. 2016; Singh et al. 2015)

Organism	Enzyme (function)	Substrates
P. ambigua G-l	Chr (chromate and nitroreductase)	Chromate, nitro-compounds
P. putida	Chr (chromate and quinoneductase)	Quinones, chromate, 2,6-Dichloroindo phenol, potassium Ferricyanide
E. coli	YieF, ChrA (chromate and quinone)	Quinones, chromate, 2,6-Dichloroindo phenol, potassium Ferricyanide, V(V), Mo(VI)
	NfsA (chromate and nitroreductase)	Chromate, nitro-compounds
	NemA (chromate reductase)	Chromate
E. coli K12	ChrR (quinoneductase)	Quinones
T. scotoductus SA-01	Chr (chromate reductase)	Chromate
Rhodobacter sphaeroides	Chr (chromate reductase)	Chromate
	ApcA (chromate and azoreductase)	Chromate, chromate bitrate, TNT
Vibrio harveyi	NfsB (nitroreductase)	Nitrofurazone, Trinitroluene, chromate
Gluconobacter hansenii	Gh-ChrR (chromate reductase)	Chromate uranyl
B. subtilis	YcnD (FMN reductase)	Chromate, Nitroaromatic compounds, Quinones
Desulfovibrio vulgaris	Cytochrome c_3 (periplasmic c type cytochrome)	Chromate
D. desulfuricans	Thioredoxin oxidoreductase	Chromate, Mo, U, Se, Te
D. alaskensis		
Desulfuromonas acetoxidans	Cytochrome c_7 (periplasmic c type cytochrome)	Chromate
Acidiphilium cryptum	ApcA (chromate and azoreductase)	Chromate, chromate bitrate, TNT
Methanobacterium sp.	FMN reductase	Chromate

13.4 Application and Prospects of Heavy Metal Resistant Microbes

Accumulation of high concentrations of heavy metals in environments can cause many human health risks and serious ecological problems. The ability of microorganisms to adsorb heavy metals or change the forms of their presence in the environment attracts wide attention of researchers in connection with the possibility of biotechnological use of heavy metal resistant bacteria or archaea for wastewater treatment, bioremediation of contaminated environments, as well as in biogeotechnology of metals (Volesky 1994; Gadd 2005; White and Gadd 2000).

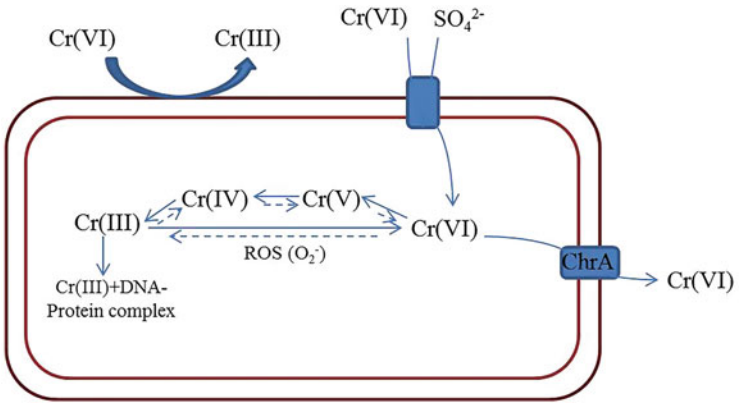

Fig. 13.9 Schematic diagram of Cr(VI) transport into bacterial cell, its reduction pathways, and efflux (modified from Pradhan et al. 2016)

Bioremediation using microorganisms is receiving much attention due to their good performance and employed in order to transform toxic heavy metals into a less harmful state (Ndeddy Aka and Babalola 2016; Akcil et al. 2015) or using microbial enzymes to clean-up polluted environment (Okoduwa et al. 2017). The technique is environmentally friendly and cost effective in the revitalization of the environment (Turpeinen et al. 2004; Ma et al. 2016). In the Table 13.6 showed a number of microbes which can be used for removing metal ions from solutions. However, bioremediation of heavy metals has limitations. Among these are production of toxic metabolites by microbes and non-biodegradability of heavy metals.

Bioremediation of the environment from toxic metal can be achieved by biosorption ability of the microbes. Biosorption is the group of all processes, during which alive or dead microbial biomass removes heavy metals or other pollutants from solutions (Gavrilescu 2004). Biosorption occurring with the participation of microorganisms may be conducted by surface adsorption concerning the gathering of metals on the cell surface and linking them with extracellular polymers, such as exopolysaccharide (EPS). EPS released out of self-defense against harsh conditions of starvation, pH and temperature, hence it displays exemplary physiological, rheological and physiochemical properties. The ionic nature of metals, its size and charge density in turn regulates its interaction with negatively charged EPS (Gupta and Diwan 2017). In the Table 13.7 is given some microbial EPS involved in heavy metal remediation.

It is often when biosorption occurs as the first phase of the following intracellular accumulation and the process of surface adsorption occurring very fast—during several minutes may have a dominant role in metal linking or may lead to high metal accumulation in the middle of the cell in a longer time (Gavrilescu 2004).

The practical application of biosorption to the removal or the recovery of heavy metals is mainly the result of the reversibility of this process. Desorption allows the recovery of metals (which is profitable in the case of more valuable heavy metals like

Table 13.6 Remediation of heavy metal by microorganisms (modified from Igiri et al. 2018)

Bioremediator	Metals	Metal ion concentration (mg/L)	Sorption efficiency (%)
Acinetobacter sp.	Cr	16	87
Sporosarcina saromensis (M52)		50	82.5
Bacillus cereus		1500	81
B. cereus (immobilized)		1500	96
B. circulans MN1		1100	71.4
B. cereus plus 0.5 glucose		1	78
B. cereus		1	72
Bacillus sp. SFC		25	80
		50	43
B. subtilis		057	99.6
Desulfovibrio desulfuricans (KCTC 5768) (immobilize on zeolite)		200 100 50	56.1 99.8 99.6
Staphylococcus sp.		4.108	45
Bacillus sp. (B2)		50–37.06 200–81.5	74.1 40.75
Bacillus sp. (B4)		50–36.57	73.14
Bacillus sp. (B9)		50–30.75 100–60 200–78.7	61.5 60 39.39
Bacillus sp. (B2)		100–42.15	42.15
Bacillus sp. (B4)		100–73.41 200–97.76	73.41 48.88
Micrococcus sp.		100	90
Acinetobacter sp. B9 (MTCC10506)		7 15 16 30	93.7 81 78 67
Streptomyces sp.		6.42	72
Immobilized *B. subtilis*		570–2	99.6
Bacillus subtilis		570–2	99.6
Immobilized *P. aeruginosa*		570–4	99.3
Pseudomonas aeruginosa		570–2	99.6
Stenotrophomonas sp.		16.59	81.27
Spirulina sp.		5	98.3
Acinetobacter sp. + *Arthrobacter* sp.		16	78
P. aeruginosa + *B. subtilis*		570–2	99/5
Pseudomonas aeruginosa	Hg	150	29.83
Vibrio parahaemolyticus (PG02)		5 10	90 80
Bacillus licheniformis		0.1	73
Vibrio fluvialis		0.25	60
Klebsiella pneumonia		100	28.65

(continued)

Table 13.6 (continued)

Bioremediator	Metals	Metal ion concentration (mg/L)	Sorption efficiency (%)
Cellulosimicrobium sp. (KX710177)	Pb	50 100 200 300	99.33 96.98 84.62 62.28
Gemella sp.		0.3	55.16 ± 0.06
Micrococcus sp.		0.3	36.55 ± 0.01
Pseudomonas sp.		1	87.9
Staphylococcus sp.		0.183	82.6
Streptomyces sp.		0.286	32.5
B. iodinium		100–1.8	87
Desulfovibrio desulfuricans (KCTC 5768) (immobilize on zeolite)	Cu	50 100 200	97.4 98.2 78.7
Staphylococcus sp.		1.536	42
Streptomyces sp.		1.129	18
Enterobacter cloacae		100	20
Desulfovibrio desulfuricans (immobilize on zeolite)		100	98.2
Flavobacterium sp.		1.194	20.3
Arthrobacter strain D9		0.05	22
Enterobacter cloaceae		100	65
Micrococcus sp.		0.3	38.64 ± 0.06
Gemella sp.		0.3	50.99 ± 0.01
Pseudomonas sp.		1	41
Flavobacterium sp.		0.161	25
A. faecalis (GP06)		100–19.2	70
Pseudomonas aeruginosa (CH07)		100–17.4	75
Desulfovibrio desulfuricans (immobilize on zeolite)	Ni	50 100 200	90.3 90.1 90.1
Micrococcus sp.		50	55
Pseudomonas sp.		1	53
Acinetobacter sp. B9		51	68.94
Enterobacter cloacae	Co	100	8
Bacillus firmus	Zn	–	61.8
Pseudomonas sp.		1	49.8
Aeratedmicrobial sediment fuel cells (A-SMFCs)	Cr Cu Ni	–	80.7 72.72 80.37
Non-aerated microbial sediment fuel cells (NA-SMFCs)	Cr Cu Ni	–	67.36 59.36 52.74

Table 13.7 Heavy metal remediation by microbial EPS

EPS-producing microbes	Metal ion removed	Remarks	Reference
Hyphomonas MHS-3, *Hyphomonas* sp.	Cu(II), Hg(II), Pb(II), Cd(II), Zn(II)	Adsorbent system was effective over wide range of pH (1–11) and temperature range (0–200 °C). The marine strains were able to remove the metal ions from an initial concentration of 50–100 ppb to US EPAa drinking water standards	Chmurny et al. (1998)
Arthrobacter viscosus	Cr(VI)	Devised for industrial applications for hexavalent chromium removal, through the retention of metal ions in the biofilms, in solutions with concentrations between 50 and 250 mg/L	Tavares and Neves (2008)
Ochrobactrum anthropi	Cr(VI), Cd (II), Cu(II)	57.8 mg Cr(VI)/g EPS at initial metal load of 280 ppm, 26 mg Cu(II)/g EPS at initial metal load of 91.6 ppm	Ozdemir et al. (2003)
Acetobacter	Fe(III), Cu (II), Mn(II), Zn(II), Co(II)	90% reduction from initial metal load of 0.1 mmol/dm^3 (Fe(III) > Cu (II) > Mn(II) > Zn(II); Co(II))	Oshima et al. (2008)
Bacillus firmus	Pb(II), Zn(II), Co(II)	1103 mg Pb(II)/g EPS (98.3%,), 860 mg Cu(II)/g EPS (74.9%)	Salehizadeh and Shojaosadati (2003)
Methylobacterium organophilum	Pb(II), Cu(II)	21% Cu(II),18% Pb(II) removal from 0.04 ppm initial metal load	Kim et al. (1996)
Herminiimonas arsenicoxydans	Arsenic	Up to 5 mmol/L metal ion uptake	Marchal et al. (2010)
Halomonas sp.	Trace metals	Metal analysis of the purified EPS revealed that it contained high levels of K, Ca, Mg and several essential trace metals, including Zn, Cu, Fe and the metalloid Si Capacity to sequester trace metals and mediate their bioavailability to eukaryotic phytoplankton	Gutierrez et al. (2012)
Shewanella oneidensis	Cd(II)	80% Cd(II) removal	Ha et al. (2010)
Azotobacter chroococcum	Pb(II), Hg(II)	40.48% Pb(II)(33.5 mg Pb(II)/g of EPS); 47.87% Hg(II) (38.9 mg of Hg (II)/g EPS)	Rasulov et al. (2013)
Cupriavidus pauculus	Cd(II), Ni(II), Cu(II), Co(II)	The tolerance levels of *C. pauculus* 1490 to Cd(II), Ni(II), Cu(II) and Co (II) were 300 mg/L, 400 mg/L, 400 mg/L and 400 mg/L, respectively. EPS yield reaching 956.12 ± 10.59 mg/g(DW) at 100 mg/L	Zeng et al. (2020)
Anabaena spiroides	Mn(II)	8.52 mg Mn(II)/g EPS	Freire-Nordi et al. (2005)

(continued)

Table 13.7 (continued)

EPS-producing microbes	Metal ion removed	Remarks	Reference
Gloeocapsa gelatinosa	Pb(II)	82.22 _ 4.82 mg Pb(II)/g CPS	Raungsomboon et al. (2006)
Calothrix marchica		65 mg Pb(II)/g CPS	Ruangsomboon et al. (2007)
Cyanospira capsulata	Cu(II)	115 mg Cu(II)/g EPS at 12.3 ppm initial metal load	De Philippis et al. (2007)
Nostoc PCC7936		85.0 ± 3.2 mg Cu(II)/g EPS at 12.3 ppm initial metal load	Sharma et al. (2008)

gold, copper, and zinc) or their removal (Wang and Chen 2009). As the biosorbents can be:

- Biomass of microorganisms is the secondary product in the sewage or pharmaceutical industry and in sewage treatment processes;
- Microorganisms from cultured and proliferated on a special base indicating the ability to efficiently metals;
- Sorbents of vegetable or animal origin (as nutshells, crust-rich tannins, sea plants, humus, moss peat, etc.).

The direct use of microorganisms with distinctive features of catabolic potential and/or their products such as enzymes and bio surfactant is a novel approach to enhance and boost their remediation efficacy (Le et al. 2017; Schenk et al. 2012). Different alternatives have also been anticipated to widen the applications of microbiological techniques toward the remediation of heavy metals. For instance, the use of microbial fuel cell to degrade recalcitrant heavy metals has been explored. Biofilm mediated bioremediation can be applied for cleaning up of heavy metal-contaminated environment.

High bioremediation potential and feasibility of the microbial detoxification of arsenic by reduction, oxidation, and methylation process, make bacteria an impending foundation for green chemistry to exterminate arsenic in the environment (Sher and Rehman 2019).

Many microorganisms are capable of precipitating metal ions. The method of precipitation of metals in the form of sulfides is based on the ability of sulfate-reducing bacteria (*Desulfovibrio, Desulfotomaculum, Desulfomonas, Desulfobacter, Desulfobulbus, Desulfococcus, Desulfosarcina, Desulfonema*) to form H_2S, which precipitates metals from solutions almost completely. Thus, from solutions containing 8.6 g/L Cu, the extraction of Cu was 98.5%. Toxic metals can also precipitate during their recovery. For example, chromium-reducing bacteria under anaerobic conditions reduce Cr(VI) to Cr(III), which is precipitated (Cervantes and Campos-García 2007).

Soil microorganisms, including plant growth promoting bacteria, through toxic metal stress evading mechanisms, can be used as bioinoculant or biofertilizers, which substantially improve the growth of plants implanted in heavy

Table 13.8 Microorganisms important for biohydrometallurgy

Microbes	Energy source	Optimum growth condition	Reference
Bacteria			
Acidithiobacillus ferrooxidans	Sulfide minerals, S, S (II), Fe(II), FeS_2	pH 1.7–2.0 (1.0–5.5); 30–35 °C (2–40 °C); O_2	Quatrini and Johnson (2019)
Leptospirillum ferrooxidans	Fe(II), FeS_2	pH 2.0–2.5 (1.0–4.0); 30–45 °C (2–50 °C); O_2	Sand et al. (1992)
A. thiooxidans	S, S(II)	pH 2.0–2.5 (0.5–6.0); 30 °C (2–40 °C); O_2	Yang et al. (2019)
A. caldus	S, S(II) Fe(II), S, S(II), sulfide minerals	pH 2.0–2.5 (0.5–6.0); 45 °C (30–52 °C); O_2	Chen et al. (2012)
Sulfobacillus thermosulfidooxidans, S. acidophilus		pH 1.7–2.4 (1.1–5.0); 48–50 °C (20–60 °C); O_2	Norris et al. (1996)
Archaea			
Acidianus brierleyi	S, S(II), Fe(II)	pH 1.5–2.0; 70 °C (45–75 °C); O_2	Segerer et al. (1986)
Metallosphaera sedula		pH 1.0–4.5; 75 °C (50–80 °C); O_2	Huber et al. (1989)
Sulfolobus metallicus	S, sulfide minerals, Fe (II) FeS_2	pH 1.0–4.5; (50–75 °C); O_2	Huber and Stetter (1991)
Ferroplasma acidiphilum		pH 1.7–1.8 (1.3–2.2); 35 °C (15–45 °C); O_2	Golyshina et al. (2000)

metal-contaminated soils by lowering the metal toxicity (Madhaiyan et al. 2007; Wani and Khan 2010; Khan et al. 2012). In addition, there are other mechanisms of plant growth promotion by bacteria e.g., they protect colonizing plants from the pathogens attack directly by inhibiting/killing pathogens through the production of antibiotics, hydrogen cyanide, and phenazines, etc. (Saravanakumar et al. 2007; Cazorla et al. 2007).

Metalophilic bacteria and archaea play an important role in the process of leaching of metals from ores, concentrates, rocks and solutions, thus they are widely used in biogeometallurgy. In the Table 13.8 showed chemolithotrophic bacteria that oxidize Fe(II), S(II), S, and sulfide minerals important for biohydrometallurgy (Sand et al. 1992; Ehrlich 1997b; Vardanyan and Vardanyan 2018).

Many prokaryotes, including archaea, are capable of transforming the oxidation state of metals in processes leading to either their solubilization or biomineralization. Although these phenomena have been observed in the environment and studied in cultures, there is still much to be learned about the genetic determinants of these metal transformations.

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