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Review Article

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Study of Genetic Determinants of Nickel and Cadmium Resistance in Bacteria-A Review

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A B S T R A C T

Microorganisms are ubiquitous in nature and are involved in almost all biological processes of life. With rapid urbanization and natural processes, heavy metals have been found in increasing proportions in microbial habitats. Metals have been known to play a major role either directly or indirectly in almost all metabolic processes, growth and development of microorganisms. Bacteria that are resistant to such heavy metals and have the ability to grow in high concentrations of these metals play an important role in their biological cycling which has great potential in bioremediation of poorly cultivable soil high in heavy metal content. This review describes the compilation of Nickel and Cadmium metal-resistance systems in bacteria.

Introduction

Heavy metals, having specific weight more than 5.0 g/cm^3, are generally categorized in three classes: toxic metals (e.g. Hg, Cr, Pb, Zn, Cu, Ni, Cd, As, Co, Sn, etc.), precious metals (e.g. Pd, Pt, Ag, Au, Ru, etc.) and radionuclides (e.g. U, Th, Ra, Am, etc.) (Nies, 1999; Bishop, 2002). Worldwide, smelting of metalliferous surface finishing industry, fertilizer and pesticide industry, sewage sludge, energy and fuel production, mining, agriculture, leatherworking, metallurgy, combustion of fossil fuels, electroplating, faulty waste disposal, electrolysis, electro-osmosis, photography, electric appliance manufacturing, metal surface treatments, aerospace and atomic energy installation and military operations have directly or indirectly released huge amounts of toxic heavy metals into the environment with a subsequent hazardous impacts on both ecological and human health principally in developing countries (Wang and Chen, 2006; Kotrba *et al.*, 2009; Ahemad and Malik, 2011). Heavy metal toxicity to various environmental niches is a great concern for environmentalists. Because these metals are difficult to be eliminated from the environment and unlike many other pollutants cannot be degraded chemically or biologically and are eventually indestructible and hence, their toxic effects last longer (Ahemad, 2012). Moreover, heavy metals display toxicity at low concentration (1.0–10 mg/L).

Surprisingly, Hg and Cd metal ions show toxicity even at concentration of 0.001–0.1 mg/L. Furthermore, some metals (e.g. Hg) may transform from less toxic species into more toxic forms under some environmental conditions (Wang and Chen, 2006; Alkorta *et al*., 2004). The metal concentration accumulated in soil is dependent upon the level of industrial discharge laden with metal species, the transportation of metals from the source to the disposing site and the retention of metals once these are reached (Ahemad, 2012; Alloway,1995). Although some of the heavy metals are required by organisms at low concentration and are essential for different metabolic activities (Adriano, 2001). For instance, zinc is the component of a variety of metalloenzymes or it may act as cofactor for several enzymes (dehydrogenases, proteinases, peptidases, oxidase) (Hewitt *et al*., 1983). Moreover, it is also required for the metabolism of carbohydrates, proteins, phosphates, auxins, RNA and ribosome formation in plants (Shier, 1994).

Likewise, copper at low concentration, contributes to several physiological processes, such as, photosynthesis, respiration, carbohydrate distribution, nitrogen synthesis, cell wall metabolism and seed production in plants (Kabata-Pendias *et al*., 2001). However, the elevated concentration of such metals above threshold levels in soils negatively affects the composition of microbial communities including Plant Growth Promoting Bacteria (PGPB) both quantitatively and qualitatively (Wani *et al*., 2008; Ahemad and Khan, 2012) which in turn, leads to substantial changes in ecological dynamics of rhizosphere niche (Gray, 2005). In addition, the higher concentration of metals not only affects the growth and metabolism but also decreases the biomass of naturally occurring soil microbial communities of beneficial microorganisms around the roots (Giller *et al*., 1998; Pajuelo *et al*., 2008). As well, they also exert a negative impact on plant growth (Rajkumar *et al*., 2006; Wani and Khan, 2010). For example, cadmium halts the enzymatic activities, DNA-mediated transformation, symbiosis between microorganisms and plants and makes the plant prone to fungal attack (Kabata-Pendias *et al*., 2001; Wani *et al*., 2008). The remediation of metal-contaminated soils consequently becomes imperative, because such soils generally cover large areas that are rendered inappropriate for sustainable agriculture. Soil is a complex ecosystem where different microorganisms play important roles in maintaining the soil fertility and plant productivity through the interactions with both biological and physico-chemical components (Ahemad *et al*., 2009; Ilieva *et al*., 2014; Kosev *et al*., 2014). Under metal stress, soil microorganisms including Plant Growth Promoting Bacteria (PGPB) have developed many strategies to evade the toxicity generated by the various heavy metals. These mechanisms include the expulsion of metal species outside the microbial cell surface, bioaccumulation the metal ions inside the cell actively or passively, biotransformation of toxic metals to less toxic forms and metal adsorption on the cell wall (Ahemad and Khan, 2012).

Therefore, bacterial strains isolated from polluted environments were shown to be tolerant to higher concentrations of metals than those isolated from unpolluted areas (Rajkumar *et al*., 2010). Through these metal stress evading mechanisms, PGPB, when used as bioinoculant or biofertilizers, substantially improved the growth of plants implanted in heavy metal contaminated/ stressed soils by lowering the metal toxicity (Wani and Khan, 2010; Madhaiyan *et al*., 2007).

Mechanisms to overcome metal stress in bacteria

It is well known that heavy metal cations are essentially required as trace elements to carry out the various biochemical reactions in microbial cell metabolism (Ahemad and Khan, 2012). However, heavy metal ions form unspecific complexes in the microbial cells at concentrations above threshold levels thereby toxic effects of these metals are manifested. For example, heavy metals like, Hg^{+2}, Cd^{+2} and Ag^{+} form highly toxic complexes which adversely affect the physiological functions of bacteria cells (Nies, 1999). Metal concentration exceeding the biological requirement inhibits the bacterial growth or bacteria respond to the elevated levels of metals by various resistance mechanisms (Ahemad and Malik, 2011). For instance, an in vitro assessment of the sensitivity of plant growth promoting *Rhizobium*, *Bradyrhizobium* and *Pseudomonas* to Cu^{+2}, Co^{+2},Mn^{+2},Mo^{+2} and Fe^{+2} by Biro´ *et al.*(1995) revealed that *Rhizobium leguminosarum* stains were most sensitive to Cu^{+2}, Zn^{+2} and Co^{+2} while *Bradyrhizobium*, *Pseudomonas* isolates, however, tolerated the highest (10 µg/ml) dose of these metals. This study also showed that sulfate forms of Cu^{+2} and Zn^{+2} were more deleterious than the chloride counterparts. Generally, long term exposure of heavy metals to microorganisms enforces a selection pressure which facilitates the proliferation of microbes, tolerant/resistant to metal stress. This adaptive mechanism of metal resistance has been explored by assaying habitats exposed to anthropogenic or natural metal contamination over an extended period of time (Hutchinson *et al*., 1997), or by experimentally adding heavy metals to samples, and assaying changes over periods up to a few years (Diaz-Ravina *et al*., 1996). Hence, metal entry within the bacterial cell is first prerequisite to manifest the metal toxicity. Generally, bacterial cells uptake the heavy metal cations of the similar size, structure and valency with the same mechanism (Nies, 1999). Bacteria generally possess two types of uptake system for heavy-metal ions: one is fast and unspecific and driven by the chemiosmotic gradient across the cytoplasmic membrane and another type is slower, exhibits high substrate specificity, and is coupled with ATP hydrolysis (Nies *et al*., 1995). Bacteria including PGPB have devised several resistance mechanisms, by which they can immobilize, mobilize or transform metals, thus reducing their toxicity to tolerate heavy metal ion uptake (Ahemad, 2014). The major mechanisms are physical sequestration, exclusion, complexation and detoxification etc. In fact, binding of heavy metals to extracellular materials can immobilize the metal and further, prevent its intake into bacterial cell. For instance, many metals bind the anionic functional groups (e.g. sulfhydryl, carboxyl, hydroxyl, sulfonate, amine and amide groups) present on cell surfaces. Likewise, bacterial extracellular polymers, such as polysaccharides, proteins and humic substances, also competently bind heavy metals (biosorption) (Ahemad *et al*., 2013). These substances thus detoxify metals merely by complex formation or by forming an effective barrier surrounding the cell (Rajkumar *et al*., 2010). Moreover, siderophores secreted by a range of PGPB can also diminish metal bioavailability and in turn, its toxicity by binding metal ions that have chemistry akin to that of iron (Gilis *et al*.,1998; Dimkpa *et al.*, 2008; Rajkumar *et al*., 2010). Sometimes, crystallization and precipitation of heavy metals takes place because of bacteria-mediate reactions or due to the production of specific metabolites (Diels *et al*., 2003; Rajkumar *et al.*, 2010). Furthermore, numerous bacteria exhibit efflux transporters

(e.g. ATPase pumps or chemiosmotic ion/proton pumps) with high substrate affinity by which they expel high concentration of toxic metals outside the cell (Ahemad, 2012; Haferburg *et al*., 2007). For instance, plasmid encoded and energy dependent metal efflux systems involving ATPases and chemiosmotic ion/proton pumps are also reported for arsenic, chromium and cadmium resistance in other bacteria. Moreover, several bacteria have developed a cytosolic sequestration mechanism for protection from heavy metal toxicity. In this process, metal ions might also become compartmentalized or converted into more innocuous forms after entering inside the bacterial cell. This process of detoxification mechanism in bacteria facilitates metal accumulation in high concentration (Ahemad, 2012; Haferburg *et al*., 2007). For this, a marvelous example is the synthesis of low-molecular mass cysteine-rich metal-binding proteins, metallothioneins which have high affinities for cadmium, copper, silver and mercury, etc. The production of these novel metal detoxifying proteins is induced by the presence of metals. In addition, certain bacteria utilize methylation as an alternative for metal resistance or detoxification mechanism. It involves the transfer of methyl groups to metals and metalloids. However, limitation of application of this methylation related metal detoxification is that only some metals can be methylated (Rajkumar *et al*., 2010; Ranjard *et al*., 2003). In addition, microorganisms can eliminate several heavy metals from the metal polluted soils by reducing them to a lower redox state. Bacterial species that catalyze such reducing reactions are referred to as dissimilatory metal-reducing bacteria, exploit metals as terminal electron acceptors in anaerobic respiration; even though, most of them use Fe^{+3} and S^{0} as terminal electron acceptors (Lovley, 1995; Jing *et al*., 2007). For example, the anaerobic or aerobic reduction of Cr(VI) to Cr(III) by an array of bacterial isolates is an effective means of chromium detoxification (Wang and Shen, 1995). Moreover, metal-chelating agents, siderophores secreted by different bacteria too have an important role in the acquisition of several heavy metals (Rajkumar *et al*., 2010).

Study of genetic determinants of metal resistance

Resistance to Nickel

Nickel enters the bacterial cell by the CorA system in bacteria and *Saccharomyces cerevisiae* (Hmiel *et al*., 1989; Snavely *et al*., 1989). An additional nickel transporter have been identified in *Alcaligenes eutrophus* (Lohmeyer and Friedrich, 1987) and later identified as part of the hydrogenase gene cluster (Eberz *et al*., 1989). Until recently, two major types of microbial high-affinity nickel and cobalt transporters were known: ATP-binding cassette (ABC) systems and secondary permeases of the NiCoT family (Nix A, UreH, HupN and HoxN) (Eitinger *et al*., 2005). The NikABCDE system of *Escherichia coli* belongs to the nickel/peptide/opine ABC transporter family and is composed of the periplasmic binding protein NikA, two integral membrane components (NikB and -C), and two ATPases (NikD and -E) (Navarro *et al*., 1993). Though distantly related ABC transporter systems from pathogenic *Yersinia pseudotuberculosis* and *Brucella suis* are also implicated in the high-affinity nickel uptake (Jubier-Maurin *et al*., 2001; Sebbane *et al*., 2002), many other representatives of this ABC transporter family are involved in uptake of other compounds, i.e., dipeptides and oligopeptides (Abouhamad *et al*., 1995;

Levdikov e*t al*., 2005). Nickel/cobalt permeases of the NiCoT family are widely distributed in bacteria and are also present in some archaea and fungi. The substrate preferences of many representatives have been analyzed in detail (Degen *et al*., 2002; Degen *et al*., 1999; Hebbeln *et al*., 2004). The NiCoT family includes at least one nickel-specific permease and many proteins with mixed metal ion specificities that have a preference for either nickel or cobalt ions. Two other families of putative secondary metal transporters, HupE/UreJ and UreH, are distantly related to NiCoTs, and certain members of these families have recently been shown to mediate nickel transport (Eitinger *et al*., 2005). HupE/UreJ proteins are widespread among bacteria and often encoded within (NiFe) hydrogenase(HupE) and urease (UreJ) gene clusters. Subgroups of UreH proteins are found in marine cyanobacteria and in plants. The cyanobacterial variants are encoded adjacent to (Ni) superoxide dismutase genes predicting a role in nickel uptake. Smith (1967) first reported that nickel resistance in bacteria is plasmid mediated. The best known mechanism of nickel resistance has been extensively studied in the bacteria *A. eutrophus* CH34. The organism harbors two plasmids pMOL28 which is responsible for Ni, Hg and Cr resistance and another plasmid pMOL30 which constitute the genetic determinants for Cd, Co, Zn, Hg and Cu resistance (Mergeay *et al*., 1985; Nies *et al*., 1989; Mergeay, 1995) Nickel efflux driven by a RND transporter is the basis of resistance in this strain. Two operon systems have been studied, a nickel-cobalt resistance Cnr (cnrCBA structural resistance genes with cnr YXH regulatory genes) (Liesegang *et al*., 1993) and a nickel-cobalt-cadmium resistance, Ncc (Ncc CBA operon) (Schmidt and Schlegel, 1994). Ni resistance has been studied among other bacterial strains like *A. eutrophus* KT02 was isolated from the wastewater treatment plant of Göttingen (Timotius and Schlegel, 1987); it is a lithoautotrophic bacterium and harbors the following three plasmids: plasmid pGOE1 (250 kbp), which determines cadmium and zinc resistance, plasmid pGOE2 (210 kbp), which encodes nickel and cobalt resistance, and plasmid pGOE3 (170 kbp), for which no function is known (Schmidt *et al.*, 1991). *A. xylosoxidans* 31A was isolated from the metalworking industry in Holzminden, Germany. It is an organotrophic bacterium and harbors two large plasmids, pTOM8 (340 kbp) and pTOM9 (200 kbp), both of which determine resistance to nickel, cobalt, zinc, cadmium, and copper ions (Schmidt and Schlegel, 1989).Recently, there are two distinct nickel resistance loci on plasmid pTOM9 from *Achromobacter xylosoxidans* 31A, *ncc* and *nre*. Expression of the *nreB* gene was specifically induced by nickel and conferred nickel resistance on both *A. xylosoxidans* 31A and *Escherichia coli. E. coli* cells expressing *nreB* showed reduced accumulation of Ni, suggesting that NreB mediated nickel efflux. The histidine-rich C-terminal region of NreB was not essential but contributed to maximal Ni resistance (Grass *et al*., 2001). *A. denitrificans* 4a-2, isolated from the wastewater treatment plant in Dransfeld, Germany, and *Klebsiella oxytoca* CCUG 15788, isolated from the metalworking industry in Göttenberg, Sweden, are so far the only strains which have been shown to carry nickel resistance genes on the chromosome (Stoppel *et al.*, 1995; Kaur *et al.*, 1990). In *E. coli*, nickel overload is avoided via the repressor NikR, which binds to the promoter region of the *nikABCDE* operon when nickel is present (Chivers *et al*., 2000; De Pina *et al*.,1999). NikR has both strong (in the pM range) and weak (nM) Ni-binding sites, allowing sensing of nickel at concentrations corresponding to the range from 1 to 100 molecules per cell (Bloom *et al*., 2004).

Other resistant genes in *E.coli* includethe rcnA (yohM) gene responsible for nickel and cobalt efflux (Rodrigue *et al*., 2005). In the unicellular cyanobacterium *Synechocystis* sp. PCC 6803, a nickel resistance operon (*nrsBACD*) formed by four open reading frames (ORFs) has been described previously (García-Domínguez *et al*., 2000). NrsB and NrsA proteins are homologues to CzcB and CzcA, respectively and they very probably form a membrane-bound protein complex catalysing Ni efflux by a proton/cation antiport. NrsC is not homologous to proteins encoded by the *czc* or related operons, and its role in Ni export is unknown. Finally, NrsD is a membrane protein belonging to the major facilitator superfamily of transport proteins. NrsD is highly homologous to NreB from *Achromobacter xylosoxidans* (Grass *et al*., 2001). In *Cupriavidus metallidurans* CH34 genome contains an ortholog of Atm1p named AtmA alongwith its cnr CBA operon(in *C.metallidurans* CH34) or ncc CBA operon (in *C.metallidurans* 31A). The atmA gene is located on chromosome 1 of strain CH34 and probably not part of an operon. Atm A increased Nickel and Cobalt resistance in both *C. metallidurans* and *E. coli* and probably worked in concert with other resistance operons (Mikolay *et al*., 2009). In other systems such as *Helicobacter pylori* Czn operons (Cd,Zn and Ni resistance)(a type of HME-RND transporter) (Stahler *et al*., 2006) or pNi15 plasmid coded nrp operon (containing Nrp A and B genes till date identified) found in *Enterobacter* sp. Ni15 (Lee *et al*., 2006) were also studied.

Resistance to Cadmium

Cadmium enters bacterial cells by the transport systems for essential divalent cations such as Mn^{2+} (Tynecka *et al*., 1981) or Zn^{2+} (Laddaga and Silver, 1985). Microbial resistance to cadmium is usually based on energy-dependent efflux mechanisms (Silver, 1996). Microorganisms resist Cd by at least six different ways. These include enhanced transcription of metalothionein genes (McEntee *et al*., 1986), gene amplification (Beach and Palmiter, 1981), active Cd efflux (Tynecka *et al*., 1981), deposition of the toxic metal in the cell wall and altered accumulation of the toxic compound, alternation of the cell wall-plasmamembrane complex (Mitra and Berstein, 1977). One of the best-characterized bacterial cadmium resistance mechanisms is determined by the cadmium-transporting ATPase found initially in Gram-positive bacteria (Silver and Phung, 1996). The cadmium-transporting ATPase is a P-type ATPase, a member of the cation-transporting ATPases found in both Bacteria and Eucarya (Silver, 1996). It is widespread in *S. aureus* (Nucifora *et al*., 1989) and *Listeria monocytogenes* (Lebrun *et al*., 1994). The ATPase is encoded by *cadA*, which is usually plasmid-borne and associated with transposons in *L. monocytogenes* (Lebrun *et al*., 1992; Lebrun *et al*., 1994). The cadmium efflux genes in *S. aureus* are both plasmid-borne and chromosomal. The chromosomal locus of *S. aureus* is similar to *cadAC* of the plasmid-borne genes but confers resistance to low concentrations (MIC of 128 µg/ml) of cadmium nitrate (Witte *et al*., 1986). CadC, encoded immediately downstream of *cadA*, is a regulatory protein, which is also required for cadmium resistance in Gram-positive bacteria. CadC binds to the promoter-operator area of the *cadA* gene and works as a transcriptional repressor *in vitro* (Endo and Silver, 1995). Another class of cadmium resistance genes in *S. aureus* includes *cadB* or the *cadB*-like *cadD*, which confers a different mechanism of resistance (Crupper *et al*., 1999). The function of *CadB* is not well defined, but it may protect

bacterial cells by binding cadmium in the membrane. A positive response regulator gene, *cadX*, was found in the *cadB*-like operon on plasmid pLUG10 in *S. lugdunensis*. *CadX* is similar to CadC of the *cadA* operon but acts as a positive regulator. *CadD* of *S. aureus* is similar to *CadB* of *S. lugdunensis*. Hydropathy analysis of the *CadD* from plasmid pRW001 revealed transmembrane domains with potential cadmium cation-binding motifs in the cytosolic domain (Crupper *et al*., 1999). In *B. subtilis* Cd resistance is mediated through a mutation in the chromosome, which caused a change in the membrane Mn transport system and thereby prevented intracellular accumulation of Cd (Laddaga and Silver, 1985). In Gram-negative bacteria, *Alcaligenes eutrophus*, well-characterized cadmium resistance system is the cadmium, zinc, and cobalt (*czc*) resistance determinant (Diels *et al*., 1995). The CzcC, CzcB, and CzcA proteins comprise an active efflux mechanism driven by a cation-proton antiporter, rather than a cation-transporting ATPase (Nies *et al*., 1989). Homologs of the *czc* genes, called *czr*, which conferred cadmium and zinc resistance, were recently identified in the chromosome of *Ps. aeruginosa* and appear to be highly conserved in environmental isolates of that species (Hassan *et al*., 1999). In addition, a homolog of the *cadABC* operon, found previously only in Gram-positive bacteria, was identified in the Gram-negative bacterium *Stenotrophomonas maltophilia* (Alonso *et al*., 2000). The flanking insertion sequences and unusual G+C content of the locus was suggestive of its transfer from Gram-positive bacteria. Recently, the genome sequences of several Gram-negative bacteria have revealed homologs of *cadA*. Functional analysis of their role in metal resistance has been conducted in *Helicobacter pylori* (Herrmann *et al*., 1999) and with the *E. coli cadA* homolog, *zntA* (Rensing *et al*., 1997). ZntA was originally described as a zinc-transporting ATPase, but it also confers resistance to cadmium and lead. Recent studies proposed that CadA of *S. aureus* and ZntA of *E. coli* are Pb(II)-transporting ATPases (Rensing *et al*., 1999; Sharma *et al*., 2000) In contrast to cadA of Gram-positive bacteria, *zntA* expression is regulated by *zntR*, encoding a MerR homolog, but located in another region of the *E. coli* chromosome from *zntA* (Outten *et al*., 1999). Metallothioneins are small, cysteine-rich proteins (Hamer, 1986), synthesized under heavy metal stress conditions that have been found in both prokaryotes (Olafson *et al*., 1988) and eukaryotes (Palmiter, 1998). The only known bacterial metallothionein locus, designated *smt*, that has been cloned and structurally characterized is that in *Synechococcus* sp. strain PCC 6301 (Robinson *et al*., 1990) and in strain PCC 7942 (Huckle *et al*., 1993). The *smt* locus consists of two divergently transcribed genes, *smtA* and *smtB* (Huckle *et al.*, 1993), and mediates resistance to zinc and cadmium (Turner *et al*., 1995).

In conclusion, although some heavy metals are important and essential trace elements, at high concentrations, such as those found in many environments today, most can be toxic to microbes. Microbes have adapted to tolerate the presence of metals or can even use them to grow. Thus, a number of interactions between microbes and metals have important environmental and health implications. Some implications are useful, such as the use of bacteria to clean up metal-contaminated sites. Bacteria exhibiting multiple plant health and development enhancing traits coupled with the excellent potential to resist the heavy metal stress in soils, may eventually find wide-ranging applications in the development of

bioremediation strategies for heavy metal decontamination. In heavily contaminated soils where the metal content exceeds the limit of plant tolerance, it may be possible to treat plants with PGPB thereby stabilizing, re-vegetating, and remediating metal-polluted soils. In addition, the application of the heavy metal resistant and plant beneficial bacteria can be considered as bioremediating tools with great economical and ecological relevance. Other implications are not as beneficial, as the presence of metal tolerance mechanisms may contribute to the increase in antibiotic resistance. Overall, it is most important to remember that what we put into the environment can have many effects, not just on humans, but also on the environment and on the microbial community on which all other life depends.

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