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MINI-REVIEW

Bacterial *mer* operon-mediated detoxification of mercurial compounds: a short review

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Abstract Mercury pollution has emerged as a major problem in industrialized zones and presents a serious threat to environment and health of local communities. Effectiveness and wide distribution of *mer* operon by horizontal and vertical gene transfer in its various forms among large community of microbe reflect importance and compatibility of this mechanism in nature. This review specifically describes *mer* operon and its generic molecular mechanism with reference to the central role played by *merA* gene and its related gene products. The combinatorial action of *merA* and *merB* together maintains broad spectrum mercury detoxification system for substantial detoxification of mercurial compounds. Feasibility of *mer* operon to coexist with antibiotic resistance gene (amp^r, kan^r, tet^r) clusters enables extensive adaptation of bacterial species to adverse environment. Flexibility of the *mer* genes to exist as intricate part of chromosome, plasmids, transposons, and integrons enables high distribution of these genes in wider microbial gene pool. Unique ability of this system to manipulate oligodynamic property of mercurial compounds for volatilization of mercuric ions (Hg^{2+}) makes it possible for a wide range of microbes to tolerate mercury-mediated toxicity.

Keywords *mer* operon · Mercury reductase · Oligodynamic effect · Mercury toxicity

Abbreviation

DGM	Dissolved gaseous mercury
HGT	Horizontal gene transfer
MeHg	Methylmercury
O/P	Operator/promoter
PCR	Polymerase chain reaction
PHB	Polyhydroxybutyrate

Introduction

Bacteria are known for exceptional level of adaptation to their environment. Even though they are ancient life-forms, their genetic and morphological flexibility along with immense variability in physiology enable them to survive in most extremist of the environmental conditions. From early origins of life, this very genetic flexibility and continuous course of evolution have enabled them to develop countless mechanisms relating to survival, proliferation, tolerance, and utilization of diverse resources. Environment itself is a global hub where intricate interactions among bacterial groups with themselves and with other organisms help regulate complex biogeochemical cycles and every group of organism has their own ecological niche (Fenchel et al. 1999; Vetriani et al. 2005). Mercury biogeochemical cycles are not an exception in support to this statement. Heavy metal-mediated toxicity has always

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remained one of the greatest barriers against survival of microbes (Sillanpää and Oikari 1996; Sorvari and Sillanpää 1996; Sillanpää et al. 2001). However, as single cellular organisms, bacteria have evolved multiple mechanisms to deal with this impediment (Baath 1989). Heavy metals and their compounds exert inhibitory effects on the functioning of bacterial enzymes and proteins thus rendering them useless. Phylogenetic and gene sequence analysis indicates that *mer*-related genes first originated among thermophilic microorganisms during the changes in geothermal environments (Wang et al. 2009).

In this review, we mainly focus on the mercurial compounds-mediated bacterial toxicity and describe the generic molecular models for its detoxification. The genetic system evolved as "*mer* operon" is in fact the only well-known bacterial metal resistance system with high yield transformation of its toxic target (Schaefer et al. 2002) into volatile non-toxic forms. Originally believed to be evolved in narrow groups of ancient species, efficacy and applicability of *mer* genes have enabled it to transfer and flourish in gene pools of wider microbial community. Basically, cysteine residues in proteins are the most vulnerable targets for Hg^{2+}-based toxicity as it has high affinity toward this site. However, protein products of *mer* genes efficiently utilize this very characteristic of mercurial compounds for their interactions, enzymatic degradation, and transportation (Barnes and Seward 1997; Moore 1960; Sadhukhan et al. 1997; Schelert et al. 2004). Bioavailability of the mercurial compounds has direct influence on the levels of bacterial-mediated volatilization of the mercury. This in turn is dependent on the nature and concentration of the binding phase controlled by redox status of surrounding environment (Kim et al. 2006). Thus, high efficacy of *mer* system has generated major interest in scientific community for its detailed studies and possible utilization as a biotechnological vehicle for employing such genetic resistance mechanisms for the remediation of mercury-related environmental pollution.

Toxicity of mercury

Mercury is a toxic heavy metal and is ranked at sixth position among the top ten hazardous elements (Nascimento and Chartone-Souza 2003). Areas contaminated with mercury pose threat to both inhabitants and their environment (Virkutyte and Sillanpää 2006; Huang et al. 2008, 2009, 2011; Shrestha et al. 2010). Mercury exists in nature mainly as cinnabar ores (Barnes and Seward 1997), and several of its compounds enter aquatic environment through leaching, washing of soils sediments and rocks by rain (Shrestha and Sillanpää 2008; Sillanpää 2009). In addition, artificial mode of mercury pollution includes leakage from landfills, sludge applications, and byproducts from chemical industries (Vilhunen and Sillanpää 2009; Vilhunen et al. 2009, 2011; Rassaei et al. 2009; Sillanpää and Rämö 2009). These byproducts and chemical waste are responsible for massive amounts of organic as well as inorganic forms of mercurial compounds released into environment as indicated in the report of National Research Council (2000).

Mercury pollution in marine sediments and its effects through bioaccumulation in food chain are very serious emerging problems. Toxicity of mercury toward microbes is mainly through its oligodynamic effects (Hattemer 1954). Affinity of mercury toward organic molecules generally results in the formation of recalcitrant and highly toxic organomercurial complexes. Highly reactive mercuric ions are attributed to its binding to sulphydryl groups of the cysteine residue in essential enzymes and proteins, thus rendering them inactive and blocking vital cellular functions. The toxicity of Hg^{2+} ion is very swift and lethal as it is lipid soluble and readily binds to thiol group of proteins. Metallic and organomercurials can pass through biological membranes, and compounds like methylmercury (MeHg) can cause irreversible damage to nucleic acids, thereby altering normal configuration and biological activity of the cell. Mercury has been reported to react with the amino-, carboxyl-, phosphate-, and imidazole-group and diminish or inhibit (Grier 1977) the activities of vital enzymes like lactate dehydrogenase and glutathione peroxidase.

Possible mechanism of mercury detoxification

Constant exposure to mercurial compounds has enabled bacterial community to develop various types of resistance mechanism which allows them to resist the adverse effects of mercury-mediated toxicity (Osborn et al. 1997). Due course of time, evolution and enrichment of metal resistant organisms have added to diversity in tolerance mechanisms (Barkay 1987; Müller et al. 2001; Rasmussen and Sørensen 2001). Generally, detoxification of the mercury compound takes place by the volatilization or by putative entrapment (De et al. 2008). Development of *mer* operon and other related genetic system (Schaefer et al. 2004) is the outcome of such events. Significant levels of dissolved gaseous mercury (DGM) were detected in various types of coastal water bodies under dark condition (Fantozzi et al. 2009), which were assumed to be products of bacterial-mediated Hg^{2+} detoxification. Recently, genes in the conjugative transposon Tn6009 that contained Tn916 element (Soge et al. 2008) were found to resemble closely to the *mer* operon of Gram-positive bacteria like *S. aureus* which contain *merA*, *merB*, *merR,* and *merT* gene responsible for the detoxification of the mercury compound. Strangely,

purified cytochrome c oxidase from *Acidithiobacillus ferooxidans* was also reported to show detoxification activity against mercurial compounds after intracellular transport (Sugio et al. 2010). In addition, natural phenomenon of horizontal gene transfer (HGT) has contributed to wider spreading of such genes among diverse groups (Rasmussen and Sørensen 2001) of microbial communities. In general, mechanisms for heavy metal tolerance can be classified as: (1) Blocking, in which the toxic ion is prevented from entering the cell, (2) Active efflux of the metal ion from the cell by highly specific system encoded by resistant gene, (3) Intracellular physical sequestration of the metal by binding proteins, (4) Extracellular sequestration, often by extracellular polysaccharides on the cell wall, and (5) Enzymatic conversion of the metal to less toxic or volatile forms. In nature, role of mercury resistant microorganism is significant to mercury biogeochemistry as it plays a key role in degrading MeHg and reducing Hg^{2+} into volatile Hg^0 forms. This statement is supported by correlation among MerA activity (Siciliano et al. 2002), transcript abundance (Schaefer et al. 2004), and flux of intracellular Hg^0 to the atmosphere.

Exact mechanisms and complexity among the ecological niche of mercury resistant microbes are still not fully described. Some bacteria like *Cupriavidus metallidurans* whose MSR33 and CH34 strains contained polyhydroxybutyrate (PHB) granules after exposure to the mercury indicating that they contain gene for PHB synthesis which activates to tolerate the stress generated by mercury (Janssen et al. 2010). Recent advancement in biotechnological techniques is helping shift the focus toward implementation of various microbial process for bioremediation and bioaccumulation (Ruta et al. 2010). In accordance to this statement, expression of the bacterial polyphosphate kinase gene (ppk) in transgenic tobacco resulted in the increased accumulation of the Hg^{2+} from mercury-contaminated soil without releasing mercury vapor into the ambient, thereby protecting tobacco from its toxicity (Nagata et al. 2006). Some strains of *Enterobacter* sp. were found to bioaccumulate and simultaneously synthesize uniformly sized mercury nanoparticles (2–5 nm). These nanoparticles were recoverable and also prevented the vaporization of mercury back into environment (Sinha and Khare 2010). Since this article mainly focuses in genetic mechanism (*mer* operon) for detoxification of mercurial compounds, we will be considering genetic models for mercury tolerance in bacterial community.

Bacterial *mer* operon

Bacteria resistant to inorganic and organic mercury compound along with resistance to penicillin was first reported in clinical samples (Moore 1960). Prolonged exposure to Hg^{2+} increases likelihood of bacterial strain to tolerate high level of mercury contamination.

Gram-negative bacteria are found to be more extensively studied in terms of their *mer* operon as compared to Gram-positive bacteria even though both have similar sets of *mer* genes and are arranged in similar order. The *mer* locus is found to be widely distributed among eubacterial lineages, and *mer*-like sequence has been identified in several archea genomes such as *Sulfolobus solfataricus*, *Thermoplasma volcanicum,* and *Halobacterium species* (Barkay et al. 2003). Variation in structure and organization of *mer operon* are reported (Bogdanova et al. 1992) among different isolates, indicating mosaic nature of this operon. Few characteristic differences regarding *mer* genes exist between Gram-negative and Gram-positive bacteria. However, the *merB* gene is more common to Gram-negative *mer* operons than in Gram-positive (Barkay et al. 2003). Analysis of various sequence of *mer* operon revealed that most of *mer* operons consist of *merR* gene as a regulatory gene at one terminus that is subjected to be transcribed from the structural gene of *mer* Operator/Promoter (O/P) region.

A number of transport function encoding genes lie proximal to the *mer* O/P along with *merT* and *merP* genes. Likely, in some bacterial operon, *merC* and *orf*F have been attributed for encoding transport function proteins due to its homology to *merT* gene. MerC is typically a membrane bound protein showing high affinity to Hg^{2+} ions. This is supported by the findings (Inoue et al. 1996) which shows that increased uptake of $^{203}Hg^{2+}$ is dependent upon increasing levels of *merC* induction in *E. coli*. Studies conducted on *S. solfataricus* show that there is a presence of two additional *mer* genes namely *merH* and *merI* which are found to be present on either side of *merA* gene (Schelert et al. 2006). However, the exact mechanism of their activity is unknown. Bacterial community exposed to mercury contamination was found to have abundance *merA* gene and IncP-1 plasmid as compared to those in non-exposed environment. In addition, the plasmid IncP-1 and *merA* were the responsible factors for the acclimatization of microbial communities both in surface and sub-surface to mercury-contaminated areas (de Lipthay et al. 2008). Hence, HGT may have played a key role in the selection and dispersal of such plasmids and corresponding *mer* genes to the wider microbial community.

Mercury reductase has central role in mercury volatilization

The *mer* operon is one of the most widely distributed Hg^{2+} detoxification genetic system. Various genes are involved

in *mer* operon, which include *merR/merD* for detection, *merP/merT/merC* for transportation or mobilization, and finally *merB/merA* for enzymatic detoxification of inorganic and organic mercury compounds in bacteria (Schelert et al. 2004). Though these clusters of genes are present in bacteria, it remains vestigial until it gets exposed to mercurial compounds. These clusters of genes are generally under the regulation of the *merR* which gets activated during Hg^{2+} exposure. Upon transcription, the product of this gene activates other genes including mercury reductase enzyme (MerA). Mercury reductase, a flavin oxidoreductase (Summers and Sugarman 1974), is fundamentally responsible for the reduction in highly toxic ionic Hg^{2+} into less toxic and volatile Hg^0 in a NAD(P)H-dependent reaction. Finally, this volatile Hg^0 is fluxed out from cytosolic region into outer periplasm. Amino terminal domain of MerA is found to be homologous with small periplasmic mercury-binding protein MerP which transfers Hg^{2+} to MerT. Exact mechanism by which MerT transfers Hg^{2+} into cytosol is not clearly understood but it is predicted that a pair of cysteine residue is involved in the process.

Activities of *merA* in anaerobic environment significantly affect MeHg production by competing for Hg^{2+} with methylating microbes, including sulfate-reducing bacteria (Barkay et al. 2003). MerA and its activities were well documented among strict anaerobes, and formation of Hg^0 in anoxic sediments has also been investigated with significant results (Rudrick et al. 1985; Weber et al. 1998). Comparative studies of *mer* operon and its related gene products in denitrifying soil bacteria suggest that the activity of *mer* genes is induced at higher concentration of Hg^{2+} during anaerobic as compared to aerobic conditions. However, analysis from *mer-lacZ* gene fusion experiment suggests that the level of Hg^{2+} intake into bacterial cytosol decreases with the lowering of redox activity in mercuric ions (Schaefer et al. 2002).

Deinococcus/Thermus phylum is the deepest-branching bacterial lineage that was found to have homolog of *merA* gene responsible for the production of mercury reductase (Wang et al. 2009). Recently, bacterial mercury reductase has been used in various industrial processes for the removal of Hg^{2+} which also included strategies involving the construction of bioreactor that contained immobilized MerA enzyme (or resistant bacteria) or by the overexpression of *merA* gene in bacteria, algae, or plants (Lyyra et al. 2007). Similarly, *merA* gene from *Bacillus megaterium* strain MB1 was used for the transformation of eukaryotic microalga, *Chlorella* sp. DT, which was then able to encode MerA in the algae (Huang et al. 2006). Hence, such scientific achievements show feasibility of bacterial genetic mechanism to detoxify mercurial compounds for biotechnological use.

Role of MerB gene in organomercurial mercury volatilization

MerB gene generally code for the organomercury lyase which is one of the key enzyme for the detoxification and bioremediation of the organomercurial compound. The processed products by organomercury lyase are finally volatilized by MerA gene. The *merB* gene is considered as an ancillary component of the *mer* operon (Mei-Fang Chien et al. 2010). In most cases, *merB* gene was found to be mapped immediately downstream of *mer*A gene. Phylogenetic analysis of various bacteria shows that MerB is one of the unique enzymes whose homolog forms are not known (Barkay et al. 2003). MerB catalyzes the protonolysis of carbon–mercury bound, thereby releasing less toxic and less mobile Hg^{2+} species which is further acted upon by MerA enzyme for complete volatilization of organomercurial compounds (Murtaza et al. 2005).

Crystallography studies of MerB enzyme revealed two conserved cysteines residue namely Cys-96 and Cys-159 that are considered as substrate binding region. This region plays a crucial role in cleavage of the carbon–mercury bond, thereby releasing ionic Hg^{2+} form of mercury. Similarly, Asp-99 residue of MerB enzymes was found to play active role in proton transfer during protonolysis cleavage (Vanasse et al. 2008) of carbon–mercury bond.

MerA and MerB together act as broad spectrum mercury detoxification system

Mainly two types of mercury resistant mechanism are prevalent in nature: (1) narrow spectrum and (2) broad spectrum. In narrow spectrum, only *merA* gene is present and resistance mechanism is limited to enzymatic detoxification of only inorganic mercury compound. In case of broad spectrum, tolerance is exhibited to organic as well as inorganic mercurial compounds by converting both forms of compounds to their volatile forms (Sadhukhan et al. 1997).

Broad spectrum mercury-tolerant bacteria (Fig. 1) contain extra gene *merB* which codes organomercurial lyase (Griffin et al. 1987; Silver and Phung 1996) for the cleavage of carbon–mercury bond in organomercurial compounds. In general, narrow spectrum mercury-resistant operon (e.g., *mer*RTPADE) confers resistance to only inorganic mercurial compounds, while the board spectrum mercury-resistant operon (e.g., *mer*RTPAGBDE) confers resistant to both inorganic and organic mercurial compounds (Rojas et al. 2011).

A typical periplasmic protein MerG in Gram-negative bacteria is found to provide resistance against organomercurial in *merB* deficient strains (Barkay et al. 2003). Hence, presence of *merA* along with *merG* may still show the effect

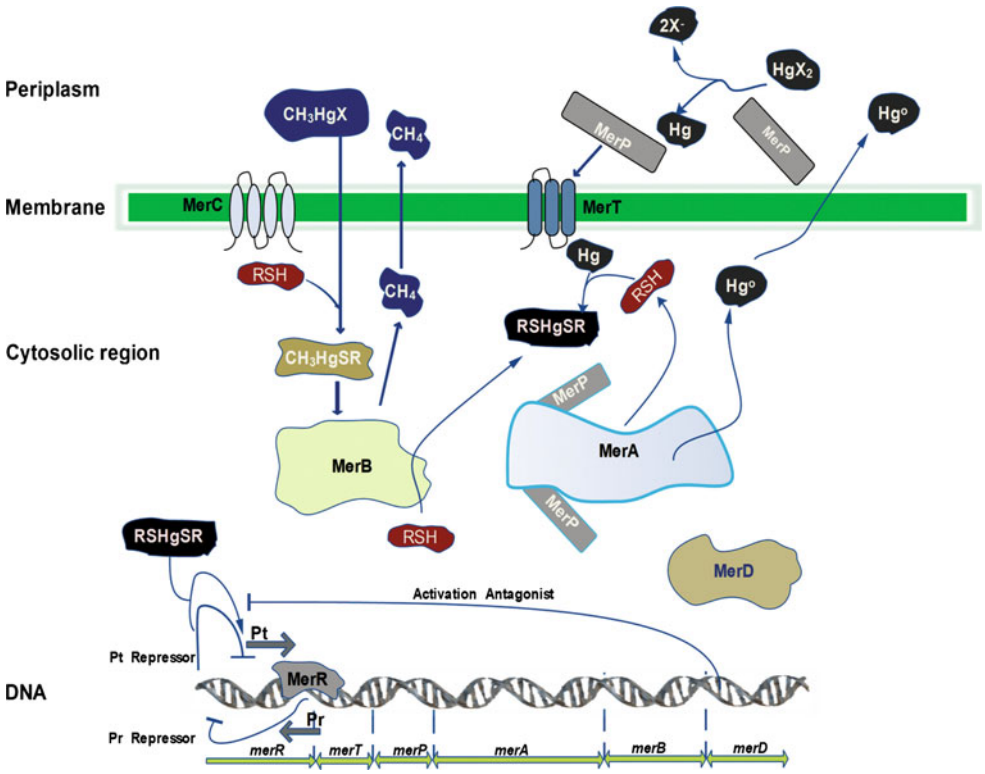

Fig. 1 Generic *mer* operon in typical Gram-negative mercury-resistant bacteria. RSH represents low molecular mass compounds and X is a nucleophilic solvent. RSHgSR and CH_3HgSR are reaction intermediates. Both organic (CH_3HgX) and inorganic (HgX) forms of mercurial compounds passes via MerC and MerT inner-membrane proteins into cytosol where the action of enzyme MerA or both MerA and MerB results in volatilization and cellular release of only Hg^0 or both Hg^0 and CH_4, respectively

of broad spectrum mercury detoxification in such bacterial strains. Interestingly, nucleotide sequencing of Incp-1b plasmid isolated from mercury-contaminated river revealed *mer* genes existing as a part of transposon Tn50580 (Smalla et al. 2006). Likely, various species of floras including *Arabidopsis*, tobacco, and *chlorella* have been biotechnologically modified to incorporated *merA* and *merB* genes that carried out detoxification of mercury-contaminated soil (Ruiz and Daniell 2009) as a part of bioremediation. This further supports the flexibility and adaptability of bacterial *mer* operon as an inter-species compatible genetic mechanism for tolerance against mercurial toxicity.

Primers help identify mercury resistant determinants among bacterial population

Mercury resistance mechanisms have widely been distributed among bacterial populations and are even more common in Gram staining bacteria. Two separate set of primers are needed for Gram-negative and Gram-positive bacteria as the sequence of *merA* gene differs among species (Chatziefthimiou et al. 2007). The *mer* genes can be located in plasmids, chromosomes and have also been identified as components of transposons and integrons (Zeyaullah et al. 2010).

Multiple genes for detection, mobilization, and enzymatic detoxification of mercurial compounds are distributed among closely linked gene clusters. Within these clusters, the *merA* gene has remained in focus for primer design (Barkay et al. 2010) and detection of mercury resistant species via polymerase chain reaction (PCR). Use of primer enables exact identification and even helps to pinpoint the precise location of particular gene. Most widely used primers have been designed based on conserved regions of *merA* and *merB* genes. However, as suggested by multiple research data (Table 1), primers have been designed for different target genes within *mer* operon including *merA*, *merB*, *merD*, *merP* as well as transposons and integrons. The *mer* operon-related sequence homology studies conducted using PCR in thermophilic bacteria and other Hg^{2+} resistance microbes also support the statement that HGT may have played major role in wide distribution of *mer* operon (Zeyaullah et al. 2010; Lal and Lal 2010).

Antibiotic resistance is generally linked to Hg^{2+} resistance

Antibiotic resistance is presumably one of the most common features of bacterial adaptation (Boni and Feldman 2005). However, co-transfer of mercury and antibiotic resistance genes have immensely been found in nature as well as experimental conditions. Both antibiotic and metal resistances can occur on same conjugative plasmids, chromosomes as well as transposons elements (Roberts

Table 1 PCR primers used for the study of mercury-resistant determinants

Target gene	Primer sequence	Reference
merA	F 5′CGGGATCCATGAGCACTCTCAAAATCACC3′	Zeyaullah et al. (2010)
merA	R 5′TCCCCCGGGATCGCACACCTCCTTGTCCTC3′	Zeyaullah et al. (2010)
merA	F 5′TCGTGATGTTCGACCGCT3′	Martins et al. (2008)
merA	R 5′TACTCCCGCCGTTTCCAAT3′	Martins et al. (2008)
merB	F 5′TCGCCCCATATATTTTAGAAC3′	Liebert et al. (1997)
merB	R 5′GTCGGGACAGATGCAAAGAAA3′	Liebert et al. (1997)
merD	F 5′CCAGGCGGCTACGGCTTGTT3′	Liebert et al. (1997)
merD	R 5′GGTGGCCAACTGCACTTCCAG3′	Liebert et al. (1997)
merA	F 5′AGAGTTTGATCCTGGCTCAG3′	Ramond et al. (2009)
merA	R 5′TACCTTGTTACGACTTCA3′	Ramond et al. (2009)
merB	F 5′TCGCCCCATATATTTTAGAAC3′	Rojas et al. (2011)
merB	R 5′GTCGGGACAGATGCAAAGAAA3′	Rojas et al. (2011)
chrB	F 5′GTCGTTAGCTTGCCAACATC3′	Abou-Shanab et al. (2007)
chrB	R 5′CGGAAAGCAAGATGTCGAATCG3′	Abou-Shanab et al. (2007)

Primers for the indicated *mer* genes include both forward and backward primer as a set arranged in pairwise manner

et al. 2008). In addition, multiple antibiotic resistance carrying plasmids have been found to carry Hg^{2+} resistance genes (Foster 1983). Studies on mercury-tolerant *Pseudomonas*, *Kleblessa*, *Enterobacteriaceae,* and other Gram-negative bacteria (Summers et al. 1993) suggest a kind of genetic linkage that results in co-transfer of both traits. Multiple researches conducted on Hg^{2+}-resistant microbes (Zeyaullah et al. 2010; Lal and Lal 2010) also suggest that HGT played a key role in high distribution of *mer*-related genes along with antibiotic resistance genes in microbial gene pool. Even though current findings does not present a generic conclusion regarding this linkage, existence of *mer* and antibiotic loci at similar or close proximity may have a key role in their co-transfer (Summers et al. 1993). Transformations of experimental bacterial strains with derivatives of antibiotic and Hg^{2+} sensitive natural isolates or competent cells as recipients have shown (Wireman et al. 1997) that most Hg^{2+} resistant strains co-transferred Hg^{2+} linked arrays of antibiotic resistance markers (amp^r, kan^r, tet^r) along with the target Hg^{2+}-resistant genes. IncP-1 plasmid is perhaps the only known genetic system which only consists of mercury resistance transposon element but no antibiotic resistance genes (Smalla et al. 2006).

Conclusions

Detoxification of mercurial compound mediated by *mer* operon is one of the oldest studied bacterial mechanisms against heavy metal toxicity. Even though multiple genes plays integral role in constituting the resistance, activity of *merA* has remained central to enzymatic transformation of mercurial compounds during detoxification process. Despite availability of huge information regarding the genes involved in this operon, new insights into gene regulation and enzymology are constantly emerging. Presence of *merA* and *merB* in its various forms among wide range of microbes as a primary mechanism for mercury detoxification reflects the adaptability and importance of this mechanism in natural world. Relations between Hg^{2+} and antibiotics resistance are not clearly defined and are a subject of further studies. As multiple ongoing researches relating to microbe-mediated hazardous metal detoxification mechanisms and their possible applications in bioremediation are being considered, better understanding of the *mer* operon and their gene products becomes essential.

Conflict of interest Authors declare no conflict of interest.

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