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Metallo -β-Lactamases: A Review

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Abstract

Metallo-beta- lactamases (MBLs) are a diverse set of enzymes which have the ability to inactivate all beta lactam drugs**.** These enzymes have a common sandwich fold (αβ/βα) in the active site. Based on amino acid sequence identity and utilization of zinc ion, three subclasses of MBLs have been characterized B1,B2 and B3 when subclass B1 has emerged as the most important one .Genes encoding MBLs can be carried on mobile genetic elements such as plasmid, transposons and inetgrons. The dissemination of MBLs- encoding genes among bacteria has made them an important issue for antibiotic resistance. This review aimed to summarize the characters of metallo beta lactamase and focus on the most prominent transferable types.

Keywords: β-lactamases**,** Antibiotics resistance, Metallo β- lactamases.

Introduction

Resistance to antimicrobials is a worrisome challenge threating public health worldwide (Salahuddin *et al*.,2018). Bacteria have several mechanisms to minimize the effects of antibiotics including effulx pump, reduced outer membrane permeability, target modification, and inactivation by β-lactamases (Kapoor *et al*.,2017). Production of beta-lactamase enzyme is the main and important defense mechanism against beta- lactam antibiotics especially among Gram-negative bacteria (Queenan and Bush,2007).Bacterial β-lactamases are a group of enzymes capable of hydrolysis the amide bond in the β-lactam ring of β-lactam antibiotics

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like penicillins, cephalosporines, monobactams and carbapenem (Bodey, 1990; Queenan and Bush,2007;Hamed *et al*.,2013). Genes encoding these enzymes can be carried on bacterial plasmid or chromosome (Palzkill,2013). β- lactamases harboring pathogens have emerged not only in clinical settings but they are distributed in the environment as well (Abbas,2017;Dehbashi *et al*.,2020). β-lactamases have been classified into molecular classes: A, B, C, and D, on the basis of amino acid sequence of enzyme (Ambler *et al*.,1991). Classes A,C and D include serine beta lactamases which rely on serine residues in their active sites while molecular class B are metalloenzymes which rely on zinc ion (Zn) (at least one active –site) for full catalytic activity (Bush and Jacoby,2010;Zmarlicka *et al*.,2015). All serine β- lactamase enzymes have the same two domain (α and α/β) fold but there is a difference in amino acid sequence identity (Salahuddin *et al*.,2018).These enzymes were initially identified for being highly specified for penicillins or cephalosporins antibiotics (Fisher *et al*.,2005). *Klebsiella pneumoniae* carbapenemase (KPC) and OXA enzymes of serine-beta-lactamases , and the metallo-beta-lactamases are the most remarkable types of carbapenemases (Nordmann *et al*.,2011). This review aimed to describe the characters of metallo beta lactamase and highlights the most prominent transferable types.

Metallo β- lactamases

Metallo β- lactamases are diverse group of metalloenzymes have the ability to hydrolysis almost all beta- lactam antibiotics (except monobactams) and they are not susceptible to inhibition by commercially available β- lactamase inhibitors like sulbactam, tazobactam, or clavulanic acid (Perez-Llarena and Bou,2009; Drawz and Bonomo,2010). Additionally they are not inhibited by NXL-104 that are active against β- lactamase enzymes of class A and C (Stachyra *et al*.,2010).

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Because of zinc utilization, metal chelators like ethylenediaminetetraacetic acid (EDTA) can inhibit their activity (Drawz and Bonomo,2010). Class B β-lactamases (MBLs) have a common αβ/βα sandwich fold and a metal- binding motif located at the interface of two αβ domains (Garau *et al*., 2004). Based on sequence homology and dependency on zinc ion, three subclasses of MBLs have been identified, namely B1, B2 and B3 when subclass B1 enzyme has raised as the main important one (Galleni *et al*.,2001; Mojica *et al*;2016). Subclasses B1 and B3 have a wide substrate hydrolysis profile including penicillins, cephalosporins and carbapenems, whereas subclass B2 has the ability to hydrolysis carbapenem only (Bebrone *et al*.,2009;Salahuddin *et al*.,2018).

Metallo β- lactamases have rasied as a major resistance mechanism towards carbapenem which is the last resort of therapy for infections caused by multi-drug resistance phenotype strains (Walsh *et al*.,2005). Currently, these enzymes are distributed in various bacterial species of Gram-negative, and their existence is often correlated with resistance to different types of antibiotics, hence therapeutic options became limited (Queenan and Bush,2007). Higher rates of morbidity and mortality were observed in clinical infections associated with MBL-producer strains (Deshmukh *et al*., 2011). A set of metallo-β-lactamase determinants are chromosomal enzymes in bacterial strains originating from environment or opportunistic pathogens, e.g. L1 from *Stenotrophomonas maltophilia*, GOB1 from *Elizabethkingia meningoseptica* and BcII from *Bacillus cereus* (Lim *et al*., 1988;Walsh *et al*., 1994; Bellais *et al*., 2000).Also, they are frequently carried on mobile genetic elements like plasmid, transposons and inetgrons which can disseminate into different bacteria such as *Enterobacteriaceae* and *Acintobacter* spp.(Kateete *et al*.,2016). However, the most relevant types are carried on mobile

genetic elements like IMP (Imipenemase), VIM (Verona Integron-encoded Metallo-β-lactamase) and NDM (New Delhi Metallo-β-lactamase).

Imipenemase (IMP)

IMP was detected as the first mobile MBLs, originating from *Pseudomonas aeruginosa* clinical isolate recovered in 1988 in Japan (Watanabe *et al*.,1991). Currently, more than 37 types of IMP-MBLs have been reported, IMP-1 was firstly discovered in Japan in 1991 and IMP-4- types were reported in Hong Kong in 2000s for the first time (Ito *et al*.,1995; Haruta *et al*.,2000; Hawkey *et al*.,2001). Approximately 20 various IMP subtypes have been characterized in association with *Acinetobacter* spp. *Pseudomonas* spp. and *Enterobacteriaceae* infections around the world (Munita, and Arias,2016).

Verona integron-encoded metallo-β-lactamase (VIM)

VIM-1 MBL- enzyme conferred resistance was first detected in Verona, Italy in *Pesudomonas aeruginosa* isolate in 1997 (Lauretti *et al*.,1999). Soon after VIM-2 type was identified in France (Poirel *et al*.,2000). *Pesudomonas aeruginosa* isolate remains the most prevalent reservoir for VIM-1 and VIM-2 enzymes although they have been characterized in enterobacterial species (Walsh *et al*.,2005). Since then, there are more 40 different VIM variants have been reported worldwide (Mojica *et al*.,2016).Like IMP, VIM enzyme was also harbored on a gene cassette inserted into a class 1 integron, if cloned into *Escherichia coli*, resulted in a significant reduction in susceptibility to a wide range of beta-lactam antibiotics (Lauretti *et al*.,1999).

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New Delhi metallo-β-lactamase (NDM)

bla$_{NDM-1}$ gene was reported from *Klebsiella pneumoniae* and *Escherichia coli* strains in 2008 for the first time from a patient suffering urinary tract infection in New Delhi, it has been detected with higher frequency among *Enterobacteriaceae* family in India, then subsequently reported in bacterial strains around the world (Yong *et al*.,2009). *bla*$_{NDM-1}$ gene has little identity with other types of MBLs. VIM-1/VIM-2 were the most similar MBLs which it has only 32.4% similarity, and able to hydrolyze all β-lactams with the exception of aztreonam (Halat and Moubareck,2020). Moreover, six variants of NDM namely (NDM-2 to -7) have been characterized. NDM-1 gene has a broad substrate profile, can hydrolysis carbapenems, penicillins and cephalosporins (with low activity against ceftazidime and cefoxitin) (Yong *et al*.,2009). Several types of plasmids can harbord *bla*$_{NDM-1}$ such as IncL/M, IncA/C and IncF which can be disseminated into different Gram-negative bacteria, NDM-1 gene also be detected in integron structures, additionally, insertion element (ISAba125) play a role in transference of this genes (Palzkill,2013).

Conclusions

MBLs constitute a critical risk due to their broad spectrum profile and their resistance to serine beta-lactamase inhibitors. The easy mobilizations of MBLs-encoding genes by transferable genetic elements raising the possibility for further dissemination among different bacterial species which create a greater antibiotic selective pressure. Recent molecular techniques for MBLs detection are required in order to develop programs that minimize the spread and dissemination of resistant isolates.

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