Current Mechanism of Bacterial Resistance to Antimicrobials

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Abstract

Serious infectious diseases are caused by bacterial pathogens that represents a serious public health concern. Antimicrobial agents are indicated for the treatment bacterial infections.Various bacteria carries several resistance genes also called multidrug resistant (MDR). Multidrug resistant organisms have emerged not only in the hospital environment but are now often identified in community settings, suggesting the reservoirs of antibiotic resistant bacteria are present outside the hospital. Drug resistant bacteria that are selected with a single drug are also frequently multi-drug resistant against multiple structurally different drugs, thus confounding the chemotherapeutic efficacy of infectious disease caused by such pathogenic variants.

The molecular mechanisms by which bacteria have common resistance to antibiotics are diverse and complex. This review highlights the mechanism of bacterial resistance to antimicrobials.

1. INTRODUCTION

Antimicrobial resistance is a budding problem in the world today (CDS, Mission: Critical et al., 2014). It has been observed that 23,000 people die due to the infection caused by antibiotic resistance bacteria every year, and many people are hospitalized due to drug resistance stains of microorganisms (Antibiotic/Antimicrobial resistance et al., 2010; WHO et al., 2015; Center for disease control et al., 2013). The problem with drug resistant bacteria affected all the people working in healthcare to some extent, and this issue will likely only become more important in the future. Antibiotics and other antimicrobial medicines are important for treating infectious disease in humans, animals, and plants. Antimicrobial medicines help combat many common diseases including tuberculosis, malaria, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), sexually transmitted diseases and pneumonia. Antibiotic treat and prevent bacterial infections, making possible and improving the safety of chemotherapy, bone marrow or organ transplant, joint replacement and other surgery (Antibiotic/ Antimicrobial resistance et al.,2010; WHO et al., 2015; Center for disease control et al., 2013).

Drug resistance is an issue that has developed over decades, as an inevitable and natural process of over administering and over-utilizing antimicrobial drugs. It is important for healthcare workers to know and understand, how an antimicrobial agents works, the mechanisms of drug resistance, and how resistance develops, what are the problems caused by antimicrobial resistance and what is the possible solution to this problem (Antibiotic/Antimicrobial resistance et al.,2010; WHO et al., 2015; Center for disease control et al., 2013).

In the last 60 years, major improvements in the early recognition and the treatment of the infectious diseases have resulted in an extraordinary reduction in the morbidity and mortality associated with

these illnesses. This has been due, in part, to our better understanding of the fine molecular biological mechanisms of these diseases and to our improved understanding of their pathophysiology and their epidemiology but, most notably, to the rapid development of safe and effective new antimicrobial treatments that have been able to attack the specific agents causing the infection, thus helping the infected host to eliminate the infection being treated (Lerner PI. et al., 2004). Based on the work that he had done in his research laboratory, in an interview with the New York Times in 1945, Sir Alexander Fleming warned that the inappropriate use of penicillin could lead to the selection of resistant "mutant forms" of staphylococcus avers that could cause more serious infections in the host was in contact with and thus could pass he resistant microbes (Levy SB. et al., 2002). He was right and within 1 year of the widespread use of this drug a significant number of strains of this bacterium had become resistant to penicillin (Levy SB. et al., 2002).

The rise of antibiotic resistance is considered to be closely linked with the widespread use of antibiotic pharmaceuticals in humans and animals (Gaskins, H.R. et al., 2002; Levy, S.B. et al., 1998). The discovery, commercialization and routine administration of antimicrobial compounds to treat infections revolutionized modern medicine and changed the therapeutic paradigm.Indeed, antibiotics have become one of the most important medical remedies for the development of complex medicine. Such as cutting edge surgical procedures, solid organ transplantation and management of patients with cancer, among others (Antimicrobial resistance, et al., 2014). Infact, the world health organization (WHO) declared the name of antibiotic resistance as one of the three most important public health threats in the 21st century (Antimicrobial resistance, et al., 2014; Cosgrove S.E. et al., 2006; Diaz Granados et al., 2005; Sydnor E.R. et al., 2011; A.R. et al., 2013, 2015).

Antimicrobial resistance is very ancient and it is the expected result of the contact with many organisms with their environment. Most antimicrobial compounds are naturally-produced molecules. These organisms are often considered to be "intrinsically" resistant to one or more antimicrobial diseases (Clinical and L.B. et al., 2014). When treating antibiotic resistant bacteria, the interpretation of the patterns of sensitivity can vary according to the availability of clinical scenario and treatment options. In addition, *the in vivo* susceptibility of an organism to a particular antibiotic may vary according to the size of the bacterial inoculums, a situation that has been well documented in *staphylococcus aureus* infections with some cephalosporin. Indeed, their evidence to suggest that some cephalosporins may fail in the setting of high-inoculate deep-seated infections caused by cephalosporin's susceptible *S.aureus*. Thus, in the following sections, we will focus on the molecular and biochemical mechanisms of bacterial resistance, illustrating specific situations they are often encountered in clinical practice (Nannine E.C. et al., 2013).

According to the WHO report, bacterial infection is more prevalent in the world, which causes fatal bacterial infections worldwide. Such as respiratory tract Infections, Diarrhea, Tuberculosis, Syphilis meningitis, and Gonorrhea (WHO et al., 2002). Staphylococcus aurous separated from clinical samples, now showing resistance with more than three drugs, that's why they are called many drug-resistances bacteria. In the case of streptococcus pyogenes, world-scale resistance rate of penicillin is 50% and the resistance rate of erythromycin is 80% (Styers, D. et al., 2006; Gandhi, N.R. et al., 2006).

Bacteria that are causative agents of infectious disease represent a serious public health concern globally. Antimicrobial agents are indicated for the treatment of bacterial infections. Bacteria may be

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intrinsically resistant to anti-bacterial agents or acquire resistance by mutation or acquisition of resistance determinants. Multidrug resistance may be recalcitrant to clinically relevant chemotherapeutic agents, resulting in treatment failures of infectious diseases. Study of these antimicrobial resistance mechanisms in infectious disease causing microorganisms is therefore, necessary in order to find ways to circumvent conditions that foster such recalcitrant pathogens. Molecular, biochemical, physiological and structural analyses of bacterial multiple drug resistance mechanisms will foster their putative modulation and may possibly the restoration of the efficacy of infectious diseases chemotherapy (Iwu, M.W. et al., 1999; Bush, K. et al., 2004).

The problem of antibiotic resistance is not only spread in the Indian subcontinent but it is a global problem. In 1900s, one option was given to medical science, but this antibiotic become very ineffective soon. Antibiotic resistance in most likely bacteria is usually a natural phenomenon for the optimization of an antimicrobial agent. Once bacteria become resistant to some antibiotic, they pass on this characteristic to their progeny through horizontal or vertical transfer. These days' irrational uses have prompted the bacteria to develop new resistant strains, which have become a major problem at this time (Iwu, M.W. et al., 1999; Bush, K. et al., 2004).

The problem of drug resistance is a dangerous situation for scientists and medical professionals, for whom they should be search for alternative treatments or new drug should be developed to fight drug resistant bacteria (Venkateswaran et al., 1987; Lery S.B. Et al., 1998).

2. ANTIBIOTIC RESISTANCE: A LONG-TERM, SERIOUS PROBLEM

Antibiotic resistance and the resulting risk for ineffective treatment of infections are serious and growing problems. WHO defines antimicrobial resistance as a microorganism resistance to an antimicrobial drug that was once able to treat an infection by that microorganism. A person cannot become resistant to antibiotics. Resistance is a property of the microbes, not a person or other organism infected by a microbe. All living organisms keep trying to be environmentally friendly to survive in the environment. In some parts of this adaptive cycle includes adjustment in the presence of weather, food and water and in many cases the presence of oxygen and the presence of deadly or dangerous external agent (Kollef M.H. et al., 2001; Sipsas N.V. et al., 2005).

With the discovery of antimicrobials in the 1940s, scientists prophesied the defeat of infectious diseases that have plagued humankind throughout history, However, the remarkable healing power of antibiotics invites widespread and often in appropriate use. This misuse and over use of antibiotics leads to antibiotic resistance among bacteria and consequent treatment complications and increased health care costs.

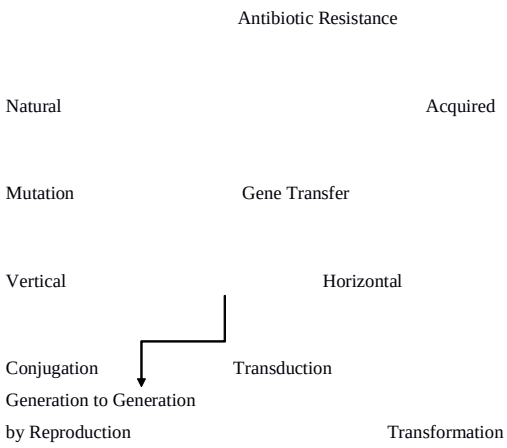

Fig.1: Classification of Antibiotic Resistance

According to the David hopper, Antimicrobial resistance in bacteria is a serious problem in healthcare today. Although most patients with infection will not necessarily have a resistant one, bacterial resistance can occur in a substantial minority of infected patients and particularly those

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who underlying health conditions, frequent hospitalizations, or recurrent exposures to antimicrobial agents.

3. MECHANISM OF BACTERIAL RESISTANCE TO ANTIMICROBIALS:

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

3.1 Drug Inactivation or Modification

Bacteria have developed many mechanisms for providing antimicrobial inactivation, such as enzymatic hydrolysis of antibiotics and redox reaction (Aminov R.I. et al., 2009; Datta N. et al., 1965). For example enzymatic deactivation of penicillin G in some penicillin-resistance bacteria through the production of beta-lactamass (Datta N. et al., 1965). Some pathogenic microorganisms are resistant to beta-lactum antibiotic by modifying antibiotics or leaving some enzymes. Such as transferases which break down or obstruct the chemical composition of antibiotics (Wright G.D. et al., 2005). Plasmid is additional (extra) chromosomal content present in the bacteria and is gene, which converts the resistance against certain type of antibiotics. Most of the beta-lactum ring inclusive antibiotics such as, ampicillin, penicillin, amoxicillin, piperacillin, imipenem, ceftazidime etc. Due to the production of beta-lactum enzyme, it becomes ineffective, which act as a hydrolysis of amide bond in beta-lactum ring (Wilkes M.S. et al., 2005).

3.2 Alteration of target or binding site

Antimicrobial agents work on an exclusive (particular) site, they bind there and warn the normal function; this is called as target site. Due to the amendment of this particular site, bacterial cells become resistant to some antibiotics. The change or amendment of the target site can be the result of formed and unreliable enzyme produced by bacteria (Campbell E.A. et al., 2001). For example; alteration of PBP,the binding target site of penicillin's in MRsA and other penicillin-resistant bacteria. Another protective mechanism found among bacterial species is ribosomal protection proteins. These proteins protect the bacterial cell from antibiotics that target the cell's ribosomes to inhibit protein synthesis. The mechanism involves the binding of the ribosomal protection proteins to the ribosomes of the bacterial cell, which in turn changes its conformational shape. This allows the ribosomes to continue synthesizing proteins essential to the cell while preventing antibiotics from binding to the ribosome to inhibit protein synthesis (Kataja, J. et al., 1998; Campbell E.A. et al., 2001).

The target site is the most common mechanism of antibiotic resistance in bacterial pathogens, which affects almost all families of antimicrobial compounds. These target changes may consist of: (a) Enzymatic transformation of the binding site. (b) Substitution or bypass of the original target. (c) Point mutations in thegenes encoding the targetsite. As if not paying attention to the type of change the last effect is always the same. A reduction in the affinity of the antibiotic for the target site (Kataja, J. et al., 1998; Campbell E.A. et al., 2001) .

3.3 Reduced Permeability

Due to the inability of the antimicrobial agent to enter the cell, a bacterium can contain a drug resistant phenotype, where the drug targets are located (Kumar A. et al., 2005). One mechanism that reduces the permeability of low drug in bacteria is the cell wall lipopolysaccharide (LPS), which consists of lipid A, an origin consisting of polysaccharide and O-antigen (Delcour A.H. et al., 2009; Wiese A. et al., 1999). Bacteria that ground / anchorage. LPS half/moiety shows resistance to erythromycin, roxithromycin, clarithromycin and azithromycin in gram-negative bacteria. Such as strains of pseudomonas aeruginosa, V.cholera and

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S.enteria, all of which are serious pathogens, particularly in patients who compromise with immunity. Reduced drug accumulation by decreasing drug permeability or increasing active efflux of the drug acrose the cell surface. These pumps within the cellular membrane of certain bacterial species are used to pump antibiotics out of the cell before they are often activated by a specific substrate associated with an antibiotic as in fluoroquinotone resistance (Monack D.M. et al., 2012; Kitaoka M. et al., 2011).

Intera cellular bacteria is targeted in many antibiotics used in clinical practice or in the case of gram-negative bacteria, it is located in the inner membrane (Pages J.M. et al., 2008). Therefore, the compound should penetrate the outer and cytoplasmic membrane (cell-free membrane) to apply his antimicrobial effects. Bacteria have developed the mechanism to prevent antibiotic from reaching its periplasmic target /intracellular/ endocrine goal by reducing the uptake of the antibiotic molecules (Pages J.M. et al., 2008).

3.4 Active drug efflux

One of the most universal drug resistance mechanisms is active efflux of drugs from the inside of bacterial cells. Such drug resistant bacteria harbor energy-driven drug efflux pumps which extrude antimicrobial agents thus reducing their intracellular concentrations to sub or non-inhibitory levels. Antibiotic active efflux is applicable for antibiotics that work inside the bacteria and takes place when the microorganisms is capable of increasing an active transport mechanism that pumps the antibiotic molecules that penetrated into the cell to the outside milieu until it reaches a concentrations below that needed for the antibiotic to have antimicrobial activity (Jacob F. et al., 1959; Piddock L.J. et al., 2006). This means that the efflux transport mechanism must be stronger than the influx transport mechanism, in order to be effective. Efflux was first described for tetracycline and macrolide antibiotics but it is now general for many other antibiotics such as fluroquinolones.

Most of the efflux mechanism systems in bacteria are non-drug specific proteins that identify and expel chemicals, antimicrobial agents and structurally dissimilar compounds without any charges and degradation of drugs.

There are 5 major families of efflux pumps, including- (1) The major facilitator super family (MFS) (2) The small multidrug resistance family (SMR) (3) The resistance- nodulation-cell-division family (RND) (4) The ATP-binding cassette family (ABC) (5) The multidrug and toxic compound extrusion family (MATE). These families differ in terms of structural conformation, energy source, and variety of substrates they are capable to extrude (Mitchell P. et al., 1977; Henderson P.J. et al., 1990; 1993; Jacob F. et al., 1959; Piddock L.J. et al., 2006).

3.4.1 The major facilitator super family (MFS)

The MFS was exposed by Prof. Peter Henderson and colleagues. They noticed that members of the MFS had structurally various substrates, similar deduced amino acid sequences, similar predicted secondary membrane structures, and shared a common evolutionary origin. Taken together these similarities suggest that the seemingly diverse transporters share a common transport mechanism. A model MFS transporter is the lactose permease of *E.coli*, a component of the well known*lac operon*, in which mutation with altered sugar binding specificities energy-coupling, expression, salt-bridging between charge amino acids and loss of the proton translocation have been discovered (Varela M.F, et al., 1996; Jacob F, et al., 1959). The proton motive force is produced by cellular respiration resulting in the outside proton concentration being greater than that inside, producing a proton gradient across a membrane that can be used for biological work such as solute transport.

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The proposed drug efflux transport mechanism is as follows: (a) the hydrogen binds the outside of empty pumps. (b) the drug binding affinity inside increases (c) the drug binds the inside of pump (d) a conformational change occurs where drug and proton binding sites switch orientation so that the bound drug faces outside, and the bound hydrogen faces inside (e) the drug is released outwardly (f) the hydrogen is released inwardly (g) the efflux pump then reorients drug binding site back to the inside and the hydrogen binding site back to the outside. The empty efflux pump is thus ready to start another drug transport cycle (Kramer R. et al., 1994; Yamato I. et al., 1992).

3.4.2 Secondary active multidrug efflux pumps from bacteria

Several major groups of secondary active multidrug efflux pumps have been discovered in prokaryotes and eukaryotes. One group is multidrug and toxic compound Extrusion (MATE) efflux pump family. Another efflux pump system is comprised within the resistance- nodulation-division (RND) superfamily (Kumar S. et al., 2012; Saidijam M. et al., 2006; Paulsen I.T. et al., 1996; N. Kaido H. et al., 2009; Kuroda T. et al., 2009)

3.4.3 The tetracycline efflux pumps

The first antimicrobial efflux pump was discovered by Stuart Levy and co-workers in which the bacterium *E.coli* harbored an integral membrane protein specific for the efflux of the tetracycline. The tetracycline efflux pump is a secondary active transporter as it is energized by a membrane proton gradient. The tetracycline efflux pumps are referred to as TetA and fall into several classes, such as TetA (A), TetA (B), TetA(C), TetA (D), etc. (Alekshun M.N. etal., 2007; Nelson M.L. etal., 2011; Levy S.B. etal., 2002).

4. CONCLUSION

Antimicrobial drug resistance occurs everywhere in the world and is not limited to industrialized nations. Hospitals and other healthcare settings are battling drug-resistant organisms that spread inside these institutions. Drug-resistant infections also spread in the community at large. Antibiotic resistance has rapidly evolved in the last few decades to become now one of the greatest public health threats of the 21st century. Indeed, infections that are untreatable due to multidrug resistance of the infected organism have become more common in clinical settings. This dire scenario has been worsened by a shortage of research and development on antibiotics. Policies such as antibiotic stewardship programs have developed in many hospitals in order to analyze and attempt to control the spread of antibiotic resistant infections. It is important for anyone working in health-care to have at least a basic understanding of the issue of antibiotic resistance. With the knowledge of action of antibiotics and drug resistance mechanisms function, the reasons behind drug resistance and the problems associated with antibiotic resistant infections, health-care workers will be better equipped to work with the problem of antibiotic resistance. The irrational use of antimicrobials is certainly a complex and multi factorial problem in developing countries and a proper understanding of the problem is necessary for effective control policies.

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