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A review on new approaches to control multi drug resistance staphylococcus aureus

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Abstract

The researches of new antibacterial compounds represent a hot topic which implies both academics and economical factors. The programs of fundamental research in the field of antibiotics have been almost exclusively left in charge of pharmaceutical companies. For the past decades, a regress in the development of new antibiotics efficient in the fight against drug resistance has been registered, partly because of a decreased interest of most large pharmaceutical companies in the antibiotics research and development. The spread of resistant bacteria mutants is an inevitable phenomenon, a real public threat which has reached alarming and unprecedented levels. Community and hospital acquired infections caused by several resistant pathogens, e.g. methicillin-resistant Staphylococcus aureus (MRSA), penicillin-resistant Streptococcus pneumoniae (PRSP), vancomycin-resistant Enterococcus (VRE) and multi-drug resistant in Mycobacterium tuberculosis (MDR) are of particular interest. Multidrug resistance is an important threat in hospitalized patients and also long term hospitalization of the patients will develop resistance. To overcome these problems a target based Insilico drug design is an alternative therapy for treatment of Staphylococcus aureus infections and this review focuses on these aspects.

Introduction

The time to the emergence of drug resistance varies largely among organisms. In several cases, resistance to a new antibiotic may arise after four years of its approval by the Food and Drug Administration (FDA). Antibiotic research efforts have in the last decades provided only analogues of the well-known antibiotics and attempts to develop novel classes of antibiotics with novel mode of action were unsuccessful. Partly for these reasons, pharmaceutical companies are drastically decreasing the investments in antibiotic research. Despite these problems, there is a serious need for applying innovative solutions and strategies to develop new antibiotics with new mechanisms of action to treat drug-resistant infections.

Multi drug Resistance Staphylococcus aureus

Stapylococcus aureus the organism first described by the Alexander Ogston (1881) over a hundred year ago, Originally proposed name by Rosenbach *et al.,* (1884) was the first to adopt the name *Staphylococcus* as the genetic name. Migula *et al.,* (1894) grouped Rosenbach's *Staphylococci* in the genus *Micrococcus* which is gram positive bacteria usually arranged in clusters. There is no universally accepted classification scheme for *Staphylococcus*, but many researchers have classified it on the basis of different properties.

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Baird-Parker *et al.,* (1965) made the use of phosphates, voges-proskauer test and the fermentation of the sugars aerobically and anaerobically, and he classified it among 6 biotypes of which *S. aureus* is of biotype-I. The coagulase test can be used to distinguish the pathogenic and the non pathogenic form of *Staphylococcus* that was first introduced by Loeb, (1903).

Schlefer and Kloos (1975) demonstrated that most *Staphylococci* are associated with skin and mucous membrane. The major habitats of *Staphylococci* in man include the anterior nares, axillae, perineum, toewebs, general skin surface, hands, etc.

Staphylococcus aureus has persisted and is now resurging as an important hospital and community acquired pathogen. The pathogen could result the wide spectra of pathogenic diseases that could include bacteremia, endocarditis, osteomyelitis, and the nosocomial infection. Although a remarkable progress has been made in the arena of development of antibiotics, still the community acquired and nosocomial infections remain significant and formidable consequence of hospitalization (Lowy, 1998). The cause attributed towards it is the unique epidemiological pattern of *S.aureus* in human that can be carried asymptomatically in a large number of body size, the others demonstrated the ability to intrigue changes in patterns of susceptibility to a range of antibiotics and hence putting forth the challenge to the human civilization for the containment of *S.aureus.*

Development of multi drug resistance by *Staphylococcus Aureus*

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The development of resistance to a wide range of antibiotics in *S. aureus* is diversified, such as resistance to methicillin that takes the account of *S. aureus* to most β-lactams, macrolides and aminoglycosides. MRSA is the most profound in community craves for the bacteriological surveillance that includes the study encompassing origin and spread of MRSA.

Recently, strains of multiple drug resistant *S. aureus* have appeared and proven very difficult to treat (Prescott, 2005). During the late 1950s and early 1960s, *Staphylococcus aureus* caused considerable morbidity and mortality as a nosocomial or hospital acquired pathogen and has become the leading cause of nosocomial infection during the last 2 decades (Nimmo and Phyford, 2003). Since then penicillinase resistant semi synthetic penicillin has proved to be successful antimicrobial agents in the treatment of *Staphylococcus* infections. Unfortunately, MRSA strains isolated are on increasing resistance to antimicrobial drugs. Recent report of vancomycin-resistant *S. aureus* has shows an area of chemotherapy in which effective bactericidal drugs to treat infections with this organism may not be readily available (Cookson, 2002).

MRSA is a problematic pathogen in human medicine and appears to be emerging in the world. Historically, hospital associated MRSA infections have predominated in human and contributed to significant illness and death. Recently a shift in the epidemiology of MRSA infections have been documented, where by community associated methicillin-resistant *S. aureus* (CA-MRSA) infections have become more common. CA-MRSA may arise from the hospital origin clone that are carried into the community and then transmitted between the communities and then transmitted between or from *de novo* development of resistance through acquisition of resistance gene (*mecA*) by methicillin sensitive strains of *S. aureus.*

MRSA strains carrying the *mecA* gene that codes for an altered form of penicillin-binding protein (PBP), called PBP2a, have a reduced affinity for beta-lactam antibiotics, including methicillin. Consequently, MRSA strains that produce PBP2a continue to thrive in the presence of β-lactam antibiotics (Chambers and Sachdeva, 1990). More than 90% of clinical MRSA isolates carry *mecA* on their chromosomes (Hiramatsu, 1995). Any mutation in the *mec* complex that may affect the function of these genes is expected to affect methicillin resistance as well.

Target based approach

If modern medicine will continue in its actual form (antibiotic over use), new classes of antibiotics must enter regularly into the marketplace. New strategies for developing novel antibiotics are needed to manage the increasing resistance of bacteria to antibiotics. In this connection, the target-based approach of antibiotic discovery is based on targeting either whole cells of viable multiplying bacteria (intact bacteria), or molecules of bacterial cells, e.g. enzymes (isolated biochemical target). Based on these targets, libraries of natural, recombinant and chemically synthesized compounds (called lead molecules) are screened for their binding or biological activity to a defined molecular target. The selected compounds may act by different mechanisms, e.g. inhibition of the *In vitro* catalytic activity of an enzyme, competition to the binding of the natural ligand to its receptor, and agonist/antagonist action at specific receptors. The identified hit molecules are further structurally modified through a multi-step process of synthesis followed by testing the obtained analogues series. From these series, medicinal chemists will select those molecules that have improved chemical characteristics and that may become potential drug candidates (called lead molecules). The lead molecules are further optimized by repeated chemical modifications in order to produce antibiotics with optimized properties needed for pre-clinical and clinical trials

The process of antibiotic drug discovery is similar to other therapeutic area, mainly following the target-based approach. This approach aims to identify compounds that interact with a bimolecular target and consequently to develop a structure-based design for the improvement of the activity and the selectivity of these antibacterial compounds.

A reconsideration of natural products research which has given excellent antibiotic drugs might lead to the discovery of novel encoded molecules as potential drug candidates. With this genomic and bioinformatics approach one can design novel therapeutic agent to treat bacterial infections (Walsh and Fischbach, 2010).

Insilico Approaches to identify the target:

The enhancement of Bioinformatics and Cheminformatics is paving the way for easy drug designing. Computational biology and Bioinformatics have the potential to speed up drug discovery processes, reducing the costs of the processes and changing the way the drugs are designed. Rational drug design facilitates and speeds up the drug designing processes that involves various method of identifying novel compounds. One advanced method is the docking of the drug molecule or ligand or inhibitor with the target. The site where the drug binds is known to the site of action, which is responsible for the pharmaceutical effect is the target. Docking is the method by which two molecules bind to each other in 3D space. In addition, regression based or knowledge based scoring functions can be useful to compute the free energy of ligand binding. There are various tools, softwares and servers meant for docking calculations. They may be rigid, flexible, and semi flexible docking. There are different databases store macromolecular 3D structure and ligand structure, which are extracted from NMR co-ordinates used for docking and simulations. Thus computational biology or *In Silico* approach is developing day by day with refinement. It is becoming a promising field and with the help of this the time and cost of biological work related to drug discovery, molecular interaction is reducing.

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In silico drug designing is a form of computer-based modeling whose technologies are applied in drug target identification or drug discovery processes. Unlike the historical method of drug discovery, by trial-and-error testing of chemical substances on animals, and matching the apparent effects to treatments, *In silico* drug design begins with knowledge of specific chemical responses in target organism, and tailoring combinations of these to fit a treatment profile.

In silico drug designing uses a variety of computational methods to identify novel compounds, design compounds for selectivity, efficacy and safety to develop compounds into clinical trial candidates. These methods fall into several natural categories, structure-based drug design, ligand-based drug design, *de novo* design and homology modeling depending on how much information is available about drug targets and potential drug compounds.

Summary

To treat MRSA and MDR (Multi drug resistance) *S. aureus* infections, there are several alternative methods are emerging, like phage theraphy, *In silico* drug designing approaches (To find alternative drugs) ete. In our studies *In silico* drug design with reference to structure based drug design is one in which one can address the real molecular interaction between drug and its target molecule. Due to the advancement in the field of Molecular biology, Structural biology, Bioinformatics and Computational Biology, there is a possibility to give insight into molecular interaction of drug with its target and to find better alternative for treatment of *S. aureus* and related infections. *In silico* drug designing is an emerging field in the area of pharmaceutical sector to design novel alternative drugs/altered antibiotics for the better treatment of infections. Keeping all above advanced technologies in mind we made an effort to find out an alternative drug (Modified antibiotic) for better treatment of *S. aureus* Infection.

Conclusion:

The *S. aureus* is a major problem in medical care, due to increased drug resistance to almost all the traditional antibiotics, including class of β-lactams (Methicillin antibiotic). The growing threat from resistance strains calls for development of accurate diagnostic methods and effective treatment strategies. Recent studies have focused on molecular mechanisms of antibiotic resistance to under stand spread of antibiotic resistance genes among the species. To treat *S. aureus* infections in convincing way there is a need of novel strategies/approaches to find better drug candidate in the field of pharmaceuticals. In recent years the pharmaceutical companies are looking towards alternative drugs instead of conventional antibiotics/drugs.

Bibliographic:

1. Adebayo O., Shittu Edet E., Udo and Johnson Lin. (2009). Phenotypic and molecular characterization of *Staphylococcus aureus* isolates expressing low and high-level mupirocin resistance in Nigeria and South Africa. *BMC Infectious Diseases*. 9 : 1-9

2. Adebola Onanuga., Avosuahi R., Oyi and Josiah A and Onaolapo (2005).Prevalence and susceptibility pattern of methicillinresistant *Staphylococcus aureus* isolates among healthy women in Zaria, Nigeria *African Journal of Biotechnology.* 4 (1): 1321-1324.

3. Akindele A. A., Adewuyi I. K., Adefioye O. A., Adedokun S. A and Olaolu A. O. (2010). Antibiogram and Beta-Lactamase Production of *Staphylococcus aureus* Isolates from Different Human Clinical Specimens in a Tertiary Health Institution in Ile-ife, Nigeria American-Eurasian Journal of Scientific Research. 5 (4): 230-233.

4. Altschul W., Gish W., Miller E. Myers W., and Lipman D. J. (1990) Basic local alignment search tool. *J. Mol. Biol.* 215: 403–410.

5. Aparicio P., Richardson J., Martin S., Vindel A., Marples R. R., Cookson B. D. (1992). An epidemic methicillin-resistant strain of *Staphylococcus aureus* in Spain. *Epidemiol Infect.* 108: 287–298.

6. Barski P., Piechowicz L., Galinski J. and Kur J. (1996). Rapid assay for detection of methicillin-resistant *Staphylococcus aureus* using multiplex PCR. *Mol. Cell. Probes.* 10 P: 471-475.

7. Aziz Japoni., Abdolvahab., Alborzi and Fatemech Orafa (2004). Distribution of Patterns of Methicillin Resistance Genes (*mecA*) in *Staphylococcus aureus* isolated from Clinical Specimens. Iran *Biomed. J.* 8: 173-178

8. Baker D Sali A. (2001). Protein structure prediction and structural genomics. *Science*. 294 (5540): 93–96.

9. Baldi A. (2010). Computational approaches for drug design and discovery Syst *Rev Pharm.* 1(1)**:** 99-105

10. Balkrishanan M., Srivastav R. C., and Mayank Pokhriyal. (2010). Homology modeling and docking studies between HIV-1 protease and carbimic acid. *Indiam Journal of Biotechnology*. 9: 96-100.