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The Development of Resistance to Antibiotics by Bacteria

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Antibiotics are made by microbes, thus these microbes must have resistance mechanisms to prevent self-destruction. Antibiotic resistance mechanisms include modification of the binding site of the antibiotic, efflux of antibiotic, enzymatic modification of the antibiotic and change in permeability of the antibiotic. These resistance genes can be transferred to other microbes through vertical and horizontal gene transfer using plasmid (Silva Jesus. 1996). Gene transfer in bacterium occurs through transformation, transduction, conjugation and combination. This review focuses on resistance mechanisms and how they are transferred between bacteria. Bacteria resistance has led to the emergence of new therapeutic techniques such as bacteriotherapy.

Introduction

Antibiotics are usually made by microbes as a self-defense mechanism. Today evolution of antibiotic resistance has made most antibiotics such as penicillin and vancomycin ineffective in the present of some bacteria (Clardy et al. 2009). Resistance is mostly acquired through horizontal gene transfer from one bacterium to another. These gene transfer processes include transformation, transduction, conjugation and combination. The first antibiotic, penicillin, was produced by a fungus. Other antibiotics such as streptomycin, chloramphenicol, and tetracycline are produced from soil bacteria (Clardy et al. 2009).The dose of antibiotic produced by these microbes is too low to be toxic in their natural habitat. There is a trend in the discovery of antibiotics and the development of resistance by bacteria. Antibiotic resistance usually begins in places where antibiotics are overused such as hospitals and this resistance can then be transferred to the community. There are several mechanisms bacteria have developed to resist antimicrobial agents. These include enzymatic modification of the antibiotic, modification of the antibiotic target site through mutation, development of an efflux mechanism that physically removes the antibiotic before it get to its target site and changes in permeability of the antibiotic (Silva Jesus. 1996). The reason bacteria are winning the war against antibiotics is because they can transfer these resistance genes to other bacteria. Microbes colonize various habitats in the human body and they do not live in isolation. There are over 1000 species of microbes in the gastrointestinal (GI) tract; they can transfer useful genes to one another. Resistance of bacteria to antimicrobial agents has led to bacteriotherapy.

ACQUISITION OF ANTIBIOTIC RESISTANCE IN BACTERIA

Bacteria resistance to antibiotic can be natural or acquired through gene transfer. Natural resistance to an antibiotic may occur when a bacterium lacks the binding site of an antibiotic, lacks a transporting system to carry the antibiotic to its target site, or when the antibiotic is secreted by the bacterium for self-defense. Acquired resistance is obtained through modification of a gene during mutation, horizontal or vertical gene transfers (Kenneth Todar).

Vertical gene transfer is from parent to offspring while horizontal gene transfer is from one bacterial cell to another. Conformation is the importation of foreign DNA

into a bacterial cell. Transduction involves the transfer of DNA through a bacteriophage. Any gene can be transferred from a donor bacteriophage to a recipient bacterium in generalized transduction, while in specialized transduction only closely related genes can be transferred. Conjugation is the transfer of DNA that involves cell to cell contact through a pilus (Slonczewski & Foster). Examples include acquisition of the mecA genes encoding methicillin resistance in *Staphylococcus aureus* and the various van genes in *enterococci* encoding resistance to glycopeptides (Lambert Peter A. 2005).

Modes of Bacteria Resistance

There are various ways in which bacteria develop resistance to antibiotics. Non-inherited resistance to antibiotics usually causes bacterial persistence, phenotypic tolerance and adaptive resistance (Bruce R. Levin 2004). In bacterial persistence, the bacteria show little or no growth in the presence of an antibiotic, when the antimicrobial is removed, growth is resumed. Antibiotics are designed to kill rapidly growing cells. Bacteria fight for their survival through the following mechanisms.

1. Modification of target sites of antibiotic

This is a common mechanism most bacteria use to develop resistance to certain antibiotics. This is achieved through spontaneous mutation of a gene on the chromosome in the presence of an antibiotic. This can be seen in the mutation in RNA polymerase and DNA gyrase, which leads to resistance to rifamycins and quinolones respectively. The target site of antibiotics must be absent in mammalian cells, or if present, it must differ considerably to allow for selective inhibition of the bacterial target. Penicillin for example targets the peptidoglycan cell wall of bacteria, while mammalian cells lack a cell wall. DNA gyrase introduces supercoilings in DNA during replication or transcription. The antibiotic quinolones binds to DNA gyrase to stop replication or transcription. Mutations in DNA gyrase genes cause alterations in the binding site of the drug, making the antibiotic ineffective. (Lambert Peter A. 2005)

2. Antibiotic Efflux

Antibiotic is effluxed out of the bacteria cell through the cell membrane to reduce intracellular concentration of the antibiotic and also to prevent it from reaching its target site. Common efflux antibiotics include tetracycline, erythromycin and fluoroquinolones (Silva Jesus. 1996).

3. Modification of antibiotic

Bacteria produce enzymes that chemically change antibiotics. Resistance to beta-lactm antibiotic is caused by the enzyme beta-lactamase. This enzyme splits the amide bond of the beta-lactam ring there by rendering the antibiotic inactive. The lactone ring of erythromycin is hydrolyzed by erythromycin esterase thus preventing this antibiotic from binding on the 50s subunit of ribosomes. This is common in *Staphylococcus aureus*, *streptococcus* and *enterococcus* species.

Enterobacteriaceae, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* have the enzyme chloramphenicol acetyl transferase that catalyzes the acetylation in the two hydroxyl groups of chloramphenicol (Silva Jesus. 1996).

4. Change in membrane permeability

In *Salmonella typhimurium*, a transport protein (porin) with a larger diameter can be substituted for another porin with a smaller diameter. This substitution prevents the entry of larger antibiotics such as carbenicillin (Silva Jesus. 1996).

Recent Progress

Bacteriotherapy is becoming more common and research in many regions of US and other country is showing positive results from the use of probiotics to regulate the virulence of certain bacteria. Opportunist infections usually complicate antibiotic treatments; an example of such infection is pseudomembranous colitis which is caused by a pathogen that is allowed to grow uncontrolled in an antibiotic-suppressed flora of the distal gut (Khoruts & Sadowsky 2011). To treat such an infection, a team of surgeons at the University of Colorado and the Veterans Administration Hospital thought of a very easy but unpopular therapeutic method to re-establish the normal microbiota of the distal gut. This was done through transplantation; not the transplantation of intestines or parts of the GI tract but transplantation of feces obtained from a healthy donor to the colon of the patients. Patients described in this research were 45-65 years. The patients had symptoms of pseudomembranous colitis after being exposed to multiple antibiotics. Three out of four patients were in a critical condition that continued to worsen despite use of hydration, vasopressors, hydrocortisone, and even probiotics such as “acidophilus milk” containing *Lactobacillus acidophilus*. Because the patients’ symptoms continued to worsen, the physicians used feces collected from healthy donors without recent antibiotic exposure. Surprisingly all patients experienced immediate recovery and were discharged within days from the hospital after the transplantation.

In 2008, a patient crippled by constant diarrhea was brought to Dr. Khoruts, a gastroenterologist at the University of Minnesota. After the resistance of various antibiotics to treat this diarrhea caused by *Clostridium defficile*, Dr. Khorut was left with only one option; to revisit the 1958 fecal transplantation (bacteriotherapy) technique. He transplanted stool obtained from the patient’s husband to the patient’s colon. The diarrhea disappeared within a day and *Clostridium defficile* infection vanished ((Khoruts & Sadowsky 2011)

What is really happening? Do pharmaceutical industries have to start obtaining feces from healthy individual with no recent antibiotic exposure to make a pill that can treat gastrointestinal infections, or do they have to collect mucus from the lungs of healthy individual to make a pill that can treat respiratory infections? There is still a lot of research going on in bacteriotherapy.

Probiotics are live microorganisms added to food to improve microbiota balance. Since they are added to food, they need to undergo mechanical and chemical digestion. These organisms are made up of biomolecules such as proteins, carbohydrates, lipids and nucleic acids. The GI tract has enzymes that can digest these microbes before they reach to their destination. Gastric juice contains HCl which is a very strong acid that can kill these microbes and denature their proteins. The GI tract also has a fluctuating pH, the stomach is acidic while the small intestine is basic and this pH fluctuation can kill many of the microbes before they reach their destination. For example insulin-dependent diabetic patients can't take insulin orally because insulin is a protein and it will be digested in the GI tract, therefore it must be administered intravenously for it to be effective.

Discussion

Bacteria continually evolve mechanisms of resistance to antibiotics. One of the most interesting evolutions of bacteria is that they don't need to transfer gene only through vertical gene transfer as is the case with humans. Useful genes such as resistance genes can be transferred from one bacterial cell to another through the various horizontal gene transfer processes such as transduction, transformation and conjugation. In the course of evolution, bacteria also modified genes for better adaptation and survival in an antibiotic environment by modifying antibiotics target sites, changing antibiotics permeability, modifying antibiotics and by developing efflux mechanisms.

Bacteriotherapy is a more promising approach to replace both antibiotics and probiotics, but a lot of research is still needed in this therapeutic technique to determine specific microorganism(s) that can kill the virulent bacteria and have no effect in the normal microbiota flora.

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