**Horizontal Gene Transfer and Antibiotic Resistance**

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Antibiotic resistance has become a significant issue in global health. This issue is complex, and a multi-pronged approach is necessary to fix the problem. One important component of this approach is understanding not only how antibiotic resistance develops, but how it could possibly spread not only among harmful bacteria, but among the commensal bacteria living in the human gut microbiome. The reconstruction of the bifidobacteria pan-genome allows for the identification of the bacterial resistome as well as providing a reference to compare to that of other commensal bacteria to see if they contain the same antibiotic resistant genes. Knowing if antibiotic resistance is being shared via horizontal gene transfer can provide more knowledge in the fight against antibiotic resistant bacteria. It could also allow for a more complete understanding of the role of bifidobacteria in antibiotic resistance in the human gut microbiome.

**Introduction**

Antibiotic resistance is a growing problem worldwide. In the simplest terms, antibiotic resistance is when bacteria are able to resist and survive the medications used to treat them. If bacteria survive treatment with antibiotics, they are able to continue reproducing and the infection worsens. Though antibiotic use is being curbed in agriculture, antibiotics have been used both prophylactically and for production enhancement in the past. (National Research Council, Committee on Drug Use in Food Animals, 1999). This means that there was, at one point, higher levels of antibiotics present in meat and other animal byproducts. The general public were then exposed to these antibiotics when they consumed those products. This, combined with medical antibiotic treatment courses, leads to disruption of gut microbiota homeostasis and selection of antibiotic resistant bacteria.

Another bacterial response to the use of antibiotics is the development of a resistome, or genes used specifically to inactivate or remove antibiotics. This resistome is mainly found in the chromosomal DNA, but can also be present in cytoplasmic DNA, such as plasmids and phages. These extrachromosomal replicons can be shared with other gut microbiota via horizontal gene transfer. Genes that encode the antibiotic target are susceptible to mutation, also resulting in antibiotic resistance.

Bifidobacteria are abundant in human infants, and play an important role in the long-term health of humans as a member of the gut microbiome (Young, 2012; Turroni, 2012). They are also known to be susceptible to antibiotic treatment courses (Francino, 2016). As members of the gut microbiome, bifidobacteria are exposed to antibiotics every time the host takes a treatment, and as such have a higher exposure to antibiotics than common human pathogens. There is a concern that exposure could lead to selection for antibiotic resistant strains of bifidobacteria, which could then be passed to other bacteria via horizontal gene transfer. This would allow both common members of the gut microbiome and pathogens passing through the digestive tract to develop antibiotic resistance. Using the recently reconstructed pan-genome of bifidobacteria to identify its resistome, a prediction can then be made for genetic mobility of antibiotic resistant genes to other genomes of gut bacteria.

Resistance to eight different antibiotics, including ampicillin, vancomycin, gentamicin, streptomycin, erythromycin, clindamycin, tetracycline, and chloramphenicol, was determined. The proteome of 93 *Bifidobacterium* strains was then screened for enzymes that act as antibiotic inactivators. Once these enzymes were identified, the strains were analyzed to find genomic islands and evaluate the genes flanking them. Mobile elements were then predicted through homology searches against in house databases. This analysis allowed researchers to evaluate the bifidobacterial resistome contribution to overall bifidobacterial gene sequences.

**Recent Progress**

Certain enteric pathogens in India appear to be responsible for spreading antimicrobial resistance via horizontal gene transfer (Kumar, 2017). The resistance diversity of pathogens was compared across multiple genera, as well as resistance trends for different antibiotics, and associations were made between the two indicating resistance traits linked to acquired mobile genetic elements. Though antibiotic resistance cannot be prevented, the diagnosis of resistant traits makes it possible to adapt treatment courses to counteract said traits.

It has also been theorized that continuous switching of antibiotics may potentially control the development of antibiotic resistance by modulating antibiotic selection stresses (Yoshida, 2017). In laboratory studies, drug type and concentration were changed or varied according to bacterial culture size. When the drugs were switched and varied, the bacterial colonies only developed resistance to one type, meaning the other remained effective. If applied correctly, this could allow for continued general use of antibiotics in healthcare while minimizing the risk of future infections being untreatable by antibiotics.

An unexpected area of progress comes in the form of government regulation, specifically in the United States. There has been progress on this front, including the GAIN act. This allows extended exclusivity for new antibiotics, giving pharmaceutical companies more time to recoup investments made in drug development. It also gives fast track and priority status to new antibiotics (Generating Antibiotic Incentive Now act, 2012).

**Discussion**

The looming threat of antibacterial resistance cannot be discounted. In 2013 alone, at least 23,000 people died as a direct result of antibiotic resistant infections in the United States (Centers for Disease Control, 2013). As more bacterial strains become resistant to common antibiotics, options for treatments become fewer and fewer. If antibiotics are no longer a viable treatment for bacterial infection, medical intervention for infections could be set back by nearly a century. The relative ease of treating infections could be replaced with the real concern of death from a simple cut.

One of the best ways to combat antibiotic resistance is to simply develop new antibiotics the bacteria have not encountered before. There are a few major hurdles to new development, though. One of the biggest is financial incentive. Antibiotics are generally used in shorter treatment courses for acute conditions. Also, the majority of antibiotics currently prescribed have been in use for years, and are relatively inexpensive. This means patients and insurance companies are not willing to spend more money for a new antibiotic unless it is absolutely necessary, such as in cases of antibiotic resistant infections. Simply put, there is little financial incentive to create a last option drug which would be used short term in very specific situations (Kuehn, 2011).

An understanding of how antibiotic resistance can spread through the human gut microbiome and even to passing pathogens could provide a key to understanding how to slow antibiotic resistance, or augment current therapies to make them more effective. This study assessed genetic traits that support antibiotic resistance, as well as establishing a trend of bifidobacteria resistome comprising a substantial portion of the mobilome of the genus *Bifidobacterium*. It has also allowed for an improved understanding of the role of bifidobacteria in overall gut microbiome antibiotic resistance. Though this is an advancement in understanding the development and transmission of antibiotic resistance in the gut microbiome, this study offers no direct applications for the discovery, nor do they propose a next step for research in this subject.

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