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Antibiotic Development and Optimization Based on Bacterial Protection and Evolution

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Bacterial infections are the main component in the environment that plague humans in the sense of illness and health. There are thousands of bacterial pathogens identified and many more that we know little about. There is constant change in the susceptibility of these bacteria to our antibiotic armament that we posses due to evolution, mutation and the defense mechanisms these pathogens have. There is a diversity of problems because of these natural pathogenic defenses that must be overcome in order to continue on in successfully combating bacterial infection. These problems are identifying bacterial defenses and how they function, finding new alternatives to antibiotics that no longer work as well due to bacterial evolution and developing these new antibiotic's in ways that are effective cost wise and are applicable in the sense of experimental efficiency. New progress in this field has found important aspects of bacterial defense such as the role of indole as well as new antibiotic potentials like arylomycins and optimizing production of these antibiotics through secondary metabolic pathways. Many similar aspects are currently under research to combat problems of development and production of antibiotic agents.

Introduction

Antibiotics are organic products produced by bacterium in order to inhibit growth of competitive species of other bacteria. As humans we have utilized these products to prevent and fight bacterial infections. Through a process of research and understanding of what effects these antibiotic products have we have been able to formulate which antibiotics will affect certain organisms and thus kill and treat infections. Nearly one hundred years ago this field was revolutionized and many of the common broad spectrum antibiotics were found, creating a revolution in the health field and greatly reduced the death and illness correlated with bacteria. After almost a century these original broad-spectrum antibiotics are beginning to loose their effect through over use and general evolution of bacterial species. This lessening of effectiveness of antibiotics has led to a void of research needing to be done in order to develop new and effective combatants to bacterial pathogens. These areas of research include bacterial defense, new antibiotic pathways and effective ways of producing antibiotics. It is important to understand the processes of defense and evolution that bacterial pathogens go through in order to reformulate and create new ways to combat these infections. In (Catalin Chimerel) research has been done on the ways that *Escherichia Coli* responds to stress i.e. Competition or antibiotic inhibition and a key component of this is indole. Indole is produced by many species of bacteria from a very diverse background. This research has also show that indole is key factor in modulating the membrane potential of certain bacteria. This has many important aspects related to antibiotics because one of the key functions of antibiotics is to inhibit membranes of bacteria and break them down. In (Xuan Tan) research has been focused on new potential's for antibiotic agents and how they act. Arylomycins have been the focus of this research. Arylomycins are a natural antibiotic product that has been found to have a broad spectrum range and

are effective at inhibiting and killing many bacteria. In (Wolfgang Wohlleben) research has focused on the synthesizing of these natural antibiotics in an effective way. Producing antibiotics has it's own challenges and can be many times much more costly than the benefits that are produced. Once new effective antibiotics are found such as the Arylomycins possibly are the problem becomes how to create them. This research focuses on biological engineering so that these antibiotic products can be created more effectively through second metabolic pathways.

Recent Progress

There have been large amounts of progress in identifying the ways and methods that which antibiotics resist and cope with antibiotic treatment. The research of *Escherichia Coli* and how indole affects cell membranes is good example of this. This research showed that indole has a large effect on cell division of the bacterium. That is in significant amounts of indole Escherichia coli and many other bacteria cell division is stopped immediately. This research also identified indole as an ionophore that correlates to the inhibition of cell division. The significant amount of indole being 3-5 mMolar. At 5 mMolar growth inhibition is complete. Indole affects the cell membrane directly as an ionophore, which are usually known to be toxic. The indole that these bacteria produce benefits the host by producing a toxic substance to other cells. This benefit comes directly by either killing competitive cells or cells trying to attack the cell. Knowing that a key part of these bacteria defenses is indole can help antibiotic development by possibilities of indole in antibiotics, or indole resistant antibiotics so that the bacteria secreting these compounds cannot defeat the antibiotic.

In the sense of developing new antibiotics (Xuan Tan) is right on par. This research has taken a previously researched topic of Arylomycins and expanded on it. Arylomycins are natural product antibiotics that inhibit bacterial type I signaling. They were previously thought of as narrow spectrum antibiotic products but new research has found that modified arylomycins have broad-spectrum potential that is limited by specific mechanism of resistance. The arylomycins work on Spase (type I signaling peptidase), a binding site that is very essential to most bacteria. This makes this type of antibiotic action very popular because of its potential targets large range. The previous idea that this product was narrow spectrum was in part to the binding sights and the placement of the active sight within the binding sight of this Spase. The Spase has a strong correlation to virulence because many of the factors rely on the Spase directly through direct secretion. The arylomycins were considered broad spectrum when derivatives with different areas of active sights were formulated and allowed for much better active sight binding in many cases resulting in the completion of action of the antibiotic. Arylomycins are latent antibiotics as they are natural products of bacteria. As latent antibiotics the researchers suggest that these are highly optimization, which is they can be modified easier than some other therapeutic antibiotics.

The optimization aspect of arylomycins correlates with the third research article examined in that optimization of antibiotic's and their metabolic pathways can create an easier way to produce antibiotics. This research focuses on the best ways to produce antibiotics. It focuses on the Actinomycetales because these are the most prolific producers of microbial secondary metabolites. Antibiotics are products of bacteria and therefore must be derived from bacteria in order to harness their therapeutic potential. Many bottleneck restrictions come in to place when trying to "farm" therapeutic products that can hurt the production process. To overcome this problem things such as repeating rounds of mutations and downstream processing technologies are incorporated to provide maximum yield of the generation of these novel (natural) antibiotics and even further potentiating them through optimization of their yield. Through adding extra precursors, such as amino acids supply, to these metabolic pathways the products (antibiotics) come out in greater quantity. It being the products that are needed for the antibacterial agents this creates a higher yield for useable therapeutics. It was found by increasing precursors in the primary metabolic pathway glycopeptide antibiotic products were increased by three times.

Discussion

Identifying methods that bacteria fight and protect themselves is an essential part of antibiotic research. It leads to new types of antibiotics and also increasing overall production. In the indole research that this paper reviews a key factor of bacteria defense has been identified that will possibly help development of new antibiotics. It definitely identifies a new possible mechanism in which to deal with infection. This type of research opens up other questions as to what are the other defenses that bacterial pathogens posses in order to defeat treatment, and as a way to decrease competition. Understanding other possibilities will allow for new ways to treat dieses and provide critical information that will advance medical techniques and treatments. Further research should be done in a similar manner for organisms that do not create indole but do posses defenses to combat treatment. Also research that applies indole to medicines that fight bacteria mimicking the natural action of indole in bacteria to fight competition should be conducted in order to create possibilities for medicines.

The understanding of Arylomycins as possible broad-spectrum antibiotics is a great leap when compared to the previous thought that these have a small range of effectiveness. This information dictates that continued research should be conducted. It is a complete turnaround when it was found that the Arylomycins target an essential component of bacteria. If no further research were done Arlomycins could have been tossed out and a valuable new antibiotic possibility could have never been realized. This evidence provides a whole new idea for research that previously low effective antibiotics should be reevaluated as to find their true affectability on bacteria. If many antibiotics that have been deemed unfit for treatment purposes were found to have beneficial properties a whole new armament of antibiotics could be produced in order to combat the growing ineffectiveness and resistance that bacteria have to current antibiotics. These not often used compounds could provide a plug to fill the gap in the antibiotic spectrum. The article does not go in to detail of clinical trials on humans; it has only been preformed in lab. Further research should do these clinical human trials to actually see the effects these Arylomycins have.

The optimization of antibiotics and production of them is very important to antibiotic science. Research in this area has shown that it is possibly to increase yield of costly antibiotic production making it a better more effective process. Questions arose as to what other methods could increase antibiotic productivity and effectiveness. Further research should be done in order to identify other possibilities for greater potentiation of the effectiveness in producing antibiotics. The research done is on one type of antibiotic pathway that is of the Actinomycetales; further families of antibiotics should be explored in the possibility of similarly increasing their productive factors.

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