Efflux Pumps in Antibiotic Resistance

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ABSTRACT

Efflux pumps are a microorganism's way of regulating their internal environment by making it possible to pump out toxic substances. Drug efflux is a significant mechanism of antibiotic resistance. The ongoing progress of efflux pumps in microorganisms raises obstacles for clinicians and professionals of the healthcare world. This is relevant because low-level resistance within microorganisms can develop into clinical resistance. A clinical microbiology laboratory determines a minimal inhibitory concentration (MIC) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) determines the clinical breaking point. The MIC is the lowest concentration of an antibiotic required to inhibit bacterial growth; the clinical breaking point is whether a said organism is susceptible or resistant to an antibiotic. If the MIC is lower than or equal to the breaking point, the bacterium is susceptible. If the MIC is higher than the breaking point, the bacterium is considered resistant. More and more attention is being brought to efflux pumps and the possibility of the increasing clinical resistance. With increasing clinical resistance, effective drugs against bacterium rapidly decreases.

Introduction

As stated in the article, "Antibiotic resistance is one of the biggest public health challenges of our time." (The Role of Efflux Pumps.., 1) The increasing resistance of antibiotics plays a role in the decreasing amount of effective antibiotics that can be used for different diseases, infections, etc. Along with the increasing amount of not only low-level resistant bacterium, but also more and more clinically resistant bacterium, the production of new drugs is becoming slow. The reason for slowing drug production is the cost of production itself is on the rise. Even with the demand being high for new and improved drugs for different infections and such, once the drugs are produced and used often in a clinical setting, resistance begins. Once resistance is in the way, it's onto the next drug option looking for effectiveness.

An example of this being, as shown in the referenced text, chronic lung disease. When a patient first presents this disease and it is treated with an antibiotic, the patient may show some progress in getting better. This is because the MIC as mentioned above, is lower than the clinical breakpoint. Once the treatment is continued, the antibiotics have a chance to not be evenly disseminated. Once this happens, it leaves bacteria untreated to begin developing mutations. Once this happens, resistance may begin to occur due to the MIC now being above the clinical breakpoint. As the antibiotic is continued to be used, the resistance can continue to develop.

Recent Progress

The way that the transition from low-level to clinical resistance works is that a drug can be presented to a patient with an infection and when the bacteria are sensitive to said antibiotic, it is effective. But once the antibiotic is not distributed evenly throughout the infection site, the bacteria in the niches that receive minimal antibiotics and have active efflux pumps can develop a low-level resistance. Once overexpression of the efflux pump is present, that bacteria has the opportunity to survive in the infection area even with antibiotics being administered and evolve to a high-level resistance leading to treatment failure and reaching a clinical breakpoint. One way that is being focused on reducing the progress of low-level resistance to clinical resistance is the use of efflux pump inhibitors. When these inhibitors are used, it is a likely result that the bacteria are resensitized to a certain antibiotic or even that the multidrug resistant (MDR) phenotype is reversed. There have been multiple bacteria that this has proven to be effective with and prevented the transition from low-level to clinical resistance. Two examples of this treatment being successful is inhibitors that were administered against both P. *aeruginosa* and S. *aureus.* The inhibitors used were reserpine for S. *aureus* and phenylalanine arginyl β-naphthylamide (PaβN) for P. *aeruginosa* (The Role of Effluc Pumps…, 5). Both of these inhibitors suppressed the emergence of high-level fluoroquinolone resistance causing the bacteria to then be susceptible. It is suspected that not only would these inhibitors cause sensitivity again to said antibiotics, but also restore mutation rates and decrease persisters formation. Doing these things would cause lead to an better-quality treatment than before the inhibitor. Efflux pump inhibitors have not yet been used clinically though due to the fear of side effects and in vivo toxicity.

Discussion

The issue of efflux pumps is more widespread than recognized. It is becoming a much more common problem in the healthcare world and making it harder for clinicians to find effective treatments for disease, infection, etc. Patients who gain a clinical resistance to an antibiotic have few choices of alternate routes. Not all infections have multiple possible routes of treatment to begin with. Efflux pump inhibitors are a seemingly effective way to counteract this problem in the healthcare industry. With, as stated above, antibiotic production being at a low and not seeming to pick back up very soon, a different solution should be sought out and used in a clinical setting. Once the inhibitor shows any effectiveness, the clinicians could “rapid fire”, so to speak, the antibiotic to fight the resistance while the efflux pump is inhibited and fight the infection. Without the use of inhibitors, the commonness of antibiotic resistance due to efflux pumps is only going to increase.

References

2020, The Role of Efflux Pumps in the Transition from Low-Level to Clinical Antibiotic Resistance, *Antibiotics*, Iss: 9, Pgs 1-7