Deadly Images: how electron microscopy helps to prevent antibiotic resistance

A century ago, a paper cut could have been a death sentence. This was the reality of the pre-antibiotic era, and there is chance it could be returning, but new research into key bacterial proteins offers a way to circumvent this outcome.

We have become used to the idea that if you are sick, you will be prescribed antibacterial drugs. Usually, they take just few days to fight off otherwise dangerous bacterial infections. Normal daily life, surgeries, transplantations and cancer treatments all depend on the availability of these miraculous drugs. Unfortunately, their overuse has led to the rise of resistance – selection and amplification of those otherwise rare bacteria which can thrive in the presence of antibiotics. This problem has become particularly serious in hospitals where people can spend many weeks with weakened immune systems. Traditionally new antibiotics have been developed to replace of the ones that lost their effectiveness, but it becomes increasingly difficult and expensive to develop entirely new antibacterial drugs. One good strategy to solve this issue is to make old drugs, which have already proven their safety, effective again. An example of this is the famous antibiotic penicillin, which is destroyed in resistant bacteria by enzyme called beta-lactamase. To restore penicillin's activity, it is now administered together with clavulonic acid, an inhibitor of beta-lactamase (for example, in Augmentin pills). This combination is highly effective.

A very important target in the fight against bacterial diseases is the enzyme DNA gyrase. This enzyme, found in all bacteria, is a fascinating molecular machine able to alter the twisting of DNA, which is essential for bacterial survival. In doing so, gyrase takes the risky step of temporarily cutting the DNA strands before stitching them back together again. The fluoroquinolones, a very successful class of antibacterials, work as gyrase poisons which cause the premature release of the cleaved DNA, eventually leading to cell. Bacteria have evolved resistance to fluoroquinolones, notably genes which bacteria can easily acquire from each other (this is called "transmissible resistance"). These fluoroquinolone resistance genes encode a small protein Qnr, which protects gyrase by displacing the bound drug molecules.

Noting the success of clavulonic acid in addressing penicillin resistance, we propose to use a similar strategy to restore the activity of fluoroquinolones. We will use cryo-electron microscopy, the Nobel prize-winning technique where proteins are flash-frozen in very thin ice to preserve them intact, to look at the molecular details of how Qnr proteins bind and rescue their targets from antibiotics. With this information we will firstly understand much more about how gyrase works. We will also use computer modelling to find molecules which can prevent the interaction between gyrase and resistance proteins. Such molecules will restore the potency of fluoroquinolones allowing their widespread clinical application again. We will also look at the possibilities to design new a generation of drugs not affected by transmissible resistance.

In summary, our efforts will lead both to new scientific breakthroughs in our understanding of DNA gyrase and will provide a quicker way towards better and safer antimicrobial therapies for everyone