Scientists unearth secrets of Sir Alexander Fleming's medical breakthroughs

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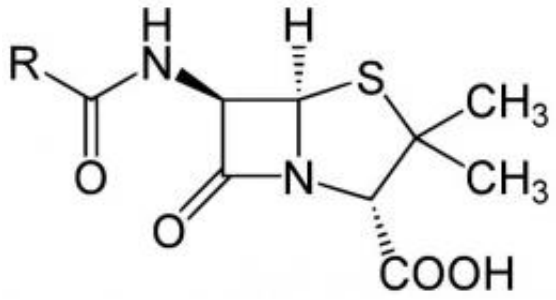

Penicillin, the first natural antibiotic discovered by Alexander Fleming in 1928

A century after Sir Alexander Fleming made two of the most important medical breakthroughs, scientists have unlocked the secret of how his discoveries may contribute to recurrent patient infections.

Fleming's best-known findings are the enzyme lysozyme—found in tears and many body secretions—and penicillin, perhaps the most significant medical revelation of all time.

Now, for the first time, experts at Newcastle University, UK, whose study is published online today in *Cell*, have identified how lysozyme and penicillin could work in combination to cause recurrent infections.

It is hoped that this study will prompt a re-evaluation of looking at why some patients with health complaints, such as urinary tract or

streptococcus infections, can become resistant to antibiotics.

New understanding

Both penicillin and lysozyme work on bacteria cell walls. Penicillin weakens the cell walls of dividing bacteria, so that they burst and die due to osmotic pressure.

Lysozyme is a small enzyme that attacks the same protective cell wall of a bacterium, causing it to degrade.

The study from the Errington Lab, based at Newcastle University's Centre for Bacterial Cell Biology, has revealed exciting new features of both agents and how they can act in patients.

It is a development from previous work done in the Errington Lab on bacterial variants—called L-forms—which lack a cell wall and can grow if they have some protection, which human tissue allows.

The lab found that when bacteria are exposed to penicillin under conditions mimicking human tissue fluids they do not explode but slowly die because they are trapped in their own solidified wall.

If penicillin-treated cells in tissue fluid are exposed to lysozyme—found in places in the body where infections occur—the enzyme degrades the cell wall, allowing the bacterium to turn into a wall free L-form, which penicillin can't kill.

The formation of these antibiotic tolerant bacteria in patients could be a very important factor in allowing infection to recur.

Important implications

Professor Jeff Errington, lead author of the study, said: "Given Sir Alexander Fleming made his two major discoveries 80 or 90 years ago, you would expect that we knew pretty well how they worked.

"But our study has unearthed completely unexpected findings and significantly enhances our understanding of why some patients may find their infections relapse.

"The results of our study have important implications because they suggest that the L-form transition may be occurring frequently during infection.

"Although L-forms are much more fragile than walled cells, because they are completely resistant to penicillins and related antibiotics, they may be contributing substantially to problems of persistence or recurrence of infection, which is a frequent clinical problem.

"L-forms have been implicated in a range of chronic diseases but experts remain unconvinced as to how prevalent they are—our findings give clear evidence of their potential importance."

More information: Yoshikazu Kawai et al, Lysozyme Counteracts β-Lactam Antibiotics by Promoting the Emergence of L-Form Bacteria, *Cell* (2018). DOI: 10.1016/j.cell.2018.01.021

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