Scientists gain first glimpse of one of nature's measuring 'rulers'

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An international team of scientists, led by researchers from the University of St Andrews in the UK and Guelph in Canada, have used cutting edge X-ray and ultraviolet light studies to reveal the workings of the molecular ruler that helps bacteria to survive and outsmart the human immune system.

The research findings, published today in *Nature Structural & Molecular Biology*, represent a significant step forward in our fundamental understanding of biology. While the concept that biology can control the length of polymer chains using a molecular ruler dates back to the early 1970s, the ruler itself has never been visualized by scientists at the molecular level.

These careful control mechanisms are commonly found in nature. Prof James Naismith from the University of St Andrews explains the significance of this work, "The molecular ruler, which we've shown to be a rigid coiled-coil protein/protein complex, is critical as without it bacteria have no idea when to stop producing the long polymers that are attached to their outer membranes. The length of these sugar polymers are controlled in the same way as curtain makers pull and measure their rolls of fabric before deciding where to make their cut. It is a beautiful and elegant demonstration of form and function."

When humans or animals are invaded by bacteria, the body does its best to go on the counter attack and provide a natural immune response that will make us well again. If this doesn't work, we turn to the medical

profession for drugs.

Combating infection and disease is a tricky business, as the invaders invariably have a host of tricks up their sleeve to thwart us. One of these tricks involves using these sugar polymers to protect themselves against us.

Prof Naismith continues, "This project involved scientists from St Andrews, along with collaborators from Germany, Canada and Diamond Light Source. We used a combination of experimental techniques at Diamond, the UK's national synchrotron science facility, and the European Molecular Biology Laboratory (EMBL) in Germany, to piece together the structure of this molecular ruler, and crucially to prove that it is possible to change the length of it and, in doing so, change the length of the polymer. This opens up a new avenue of research whereby we can look to design drugs that interfere with the ruler. The work gives chemists something to aim for, the elegant solution to controlling polymerisation: a problem in many industrial processes."

Dr Rohanah Hussain, Senior Beamline Scientist on Diamond's Circular Dichroism beamline adds, "This project demonstrates how important it is for scientists to draw on a variety of techniques. In this case, the team carried out structural studies with crystallography and X-ray scattering, before turning to the capabilities of intense ultraviolet light to confirm that the ruler manipulation was ocuring in the manner they predicted; a crucial test of the idea."

Scientists are in a race against antimicrobial resistance, which currently threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, viruses, parasites and fungi, including HIV, infections caused by E. coli, tuberculosis, influenza and malaria.

Professor Naismith concludes, "The work is part of my long term link with Chris Whitfield's lab in Canada; the real credit belongs to Drs Gregor Hageluken, Brad Clarke and Hexian Huang, the lead scientists in our labs, who did the vast bulk of the experiments. It is their skilful experimental work alongside our collaborators from Germany and Diamond that made this insight possible. I want to thank the Wellcome Trust who funded this work as well as Diamond and EMBL at DESY, Hamburg for access to their facilities"

Insights into nature's molecular ruler and how it can be engineered and modified to help in the fight against disease opens up a new avenue of research for scientists with exciting potential for novel drug design development in the future.

More information: A coiled-coil domain acts as a molecular ruler to regulate O-antigen chain length in lipopolysaccharide, *Nature Structural and Molecular Biology*, DOI: 10.1038/nsmb.2935

Provided by Diamond Light Source