How a bacterial virulence factor promotes its own secretion

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In adhering to body cells, many bacteria cause disease. Antibiotics are the usual means for treating infection, but decades of use have led to increasing bacterial resistance. Therefore, scientists are looking at other strategies.

"If we can block the bacteria's mechanism for attaching to our cells, we can disarm them instead of killing them," says Jack Leo, a post-doc at the Department of Biosciences at the University of Oslo.

He and his team have been studying the protein Intimin, which is an essential adhesin of certain diarrhoea-causing bacteria such as enteropathogenic E. coli. Intimin is a so-called autotransporter, which means it mediates its own secretion to the bacterial surface. Once there, Intimin causes the bacteria to attach to the cells of the intestinal lining, which leads to disease symptoms. If you can block the function of Intimin, then you also block the bacterial adhesion.

Until now, it has been a mystery how Intimin actually transports itself outside the cell. Intimin is found in Gram-negative bacteria, which, unlike our own cells, have two membranes covering the cell. This means that transporting something across these two barriers requires extra energy. Bernstein and co-workers have argued that protein folding alone cannot provide enough free energy in order to secrete a protein.

"In this study, we prove that it is, indeed, the protein folding that provides energy for the secretion, at least in the case of Intimin and

related proteins," concludes Leo.

However, the study has not found which energy source initiates the transport. The way intimin works is via the folding of part of the protein already outside the cell, which literally pulls the rest of the protein across the outer membrane. But without initiation, nothing happens. Intimin folds domain by domain, pulling the rest of the protein through. A protein domain is defined as part of a protein chain that can fold independently to produce a stable three-dimensional structure.

"When we introduced a 'tag' at the first domain in Intimin, the protein folding was disrupted," says Leo.

More research is needed to fully understand the process, but it is one small step closer to targeting the weaknesses in the way bacteria adhere to cells.

More information: Jack C. Leo et al. Secretion of the Intimin Passenger Domain Is Driven by Protein Folding, *Journal of Biological Chemistry* (2016). DOI: 10.1074/jbc.M116.731497

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