Shigella bacterium exploits a physical force called 'endocytosis' in the membrane of cells

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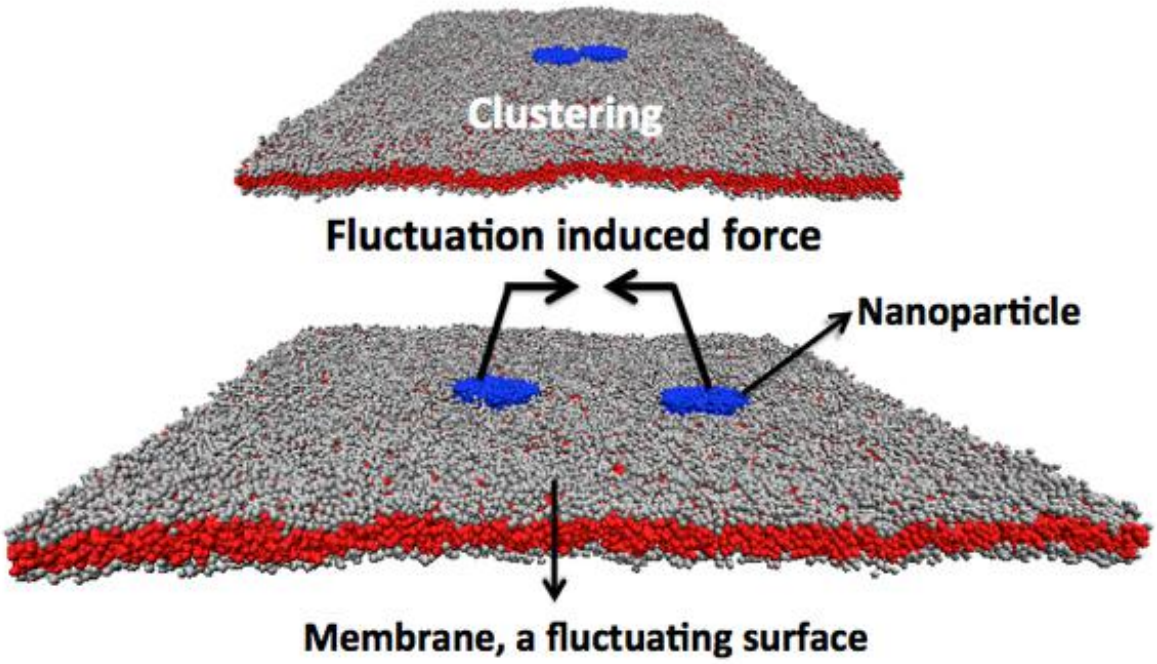

Illustration of a dissipative particle dynamics simulation showing two tightly bound toxins bound together by the Casimir-like force. Credit: Julian Shillcock/EPFL

The study found that Shiga toxin particles bind tightly to certain lipids, or fats, on the membrane surface of the cell to be invaded. They then begin to form clusters on the membrane, which cause the membrane to

curve inwards, creating tube-shaped invaginations, through which the toxin particles enter the cell. Once inside, the Shiga toxins modify the cell's genetic mechanism, and infection has begun.

But the major discovery was that the toxin actually exploits a generic, physical force in the cell's membrane to produce the invaginations. This is called the "Casimir force" and was first described as a theoretical force acting between two charged, parallel, conducting surfaces.

In terms of biology, the Casimir force is thought to act between membrane-bound proteins in cells, existing on all fluid biological cell membranes and arising only when the pathogen binds tightly to the membrane surface.

The researchers propose that Shigella bacteria, and other pathogens, have evolved to take advantage of the Casimir force arising from the fluctuating plasma membrane to infect cells. In addition, because the fats that the toxin binds to are used by the cell for its own operations, the Shiga toxin cannot be blocked from entering without disabling or modifying the normal functions of the cell.

Nanoparticles for drug delivery

But because the Casimir force is thought to arise for any tightly bound nanoparticles on the surface of the cell's membrane, there is the potential for producing a novel, nanoparticle-based pathway for drug delivery. First, we would have to bind nanoparticles tightly to the surface of the cell where they will cluster. Second, the nanoparticles must also slightly increase the cell membrane's curvature to exploit the Casimir force and gain entry into the cell. Once inside, they can begin making beneficial, defensive changes in the cell's behavior.

"Where Nature has led in devising a means for pathogens to infect cells,

manufactured nanoparticles can follow to treat cellular dysfunction," says Julian Shillcock.

More information: Weria Pezeshkian et al. Mechanism of Shiga Toxin Clustering on Membranes, *ACS Nano* (2016). DOI: 10.1021/acsnano.6b05706

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