NEWS & VIEWS

MICROBIOLOGY

Loading the type III cannon

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Many pathogenic bacteria possess a secretion machine that shoots noxious proteins into host cells. But the ammunition is larger than the bore of the bacterial gun, so how is it fed into the machine?

Bacteria and the organisms they parasitize are engaged in a constant struggle. Each side possesses a veritable arsenal of weapons and defensive countermeasures. One of the most potent weapons systems that bacteria use is the type III secretion system, which injects certain bacterial proteins into adjacent host cells. The proteins selected by the secretion machinery often resemble the host's own proteins, so they can switch off defensive systems and turn the cells into puppets of a bacterial master. In this issue, Akeda and Galán (page 911)[1] give us a first peek into the loading mechanism of the bacterial type III secretion system.

The crystal structures of proteins that are transported by the type III secretion machine have been solved[2]. The diameter of the conduit these proteins must travel has also been ascertained[3]. A paradox emerges when these data are compared — the proteins are too large to travel through the secretory apparatus. So how do bacteria get the camel to pass through the eye of a needle? A solution suggested by Akeda and Galán implicates InvC, an essential component of the *Salmonella enterica* type III machinery.

InvC belongs to a class of enzymes called AAA ATPases that form a hexameric ring. These enzymes harness the energy released from ATP to unfold proteins and thread them through a channel at the centre of the ring[4]. Akeda and Galán reasoned that if InvC behaved like this at the breech of the type III secretion machine, secreted proteins would be of the correct calibre to pass through. Their careful *in vitro* examination of the SptP protein, which is transported by the *S. enterica* type III system, supports this idea. Before secretion, SptP is bound by a 'chaperone' called $SicP_2$, which is essential for its recognition by the secretion machinery. The authors found that InvC binds to the SptP–$SicP_2$ complex; that the consumption of energy by InvC releases $SicP_2$; and finally, that the SptP that is also liberated is in an unfolded state[1] (Fig. 1).

Akeda and Galán's hypothesis has several attractive features: InvC is associated with the cell membrane; it could therefore reside at the site where the pipeline into the host cell meets the bacterial cytoplasm, where there is a pool of substrate proteins to be secreted[5]. Moreover, because InvC can indirectly bind to secretion substrates through their cognate chaperones, it performs all the functions that are needed for the priming of proteins for type III travel: recognition, release of chaperones, and unfolding. Other secretion machines may indeed use similar mechanisms for substrate selection by chaperone binding, and these include *Escherichia coli* type III machines as well as the secretion of proteins that make up flagella (the whip-like 'tails' that propel some bacteria)[6,7].

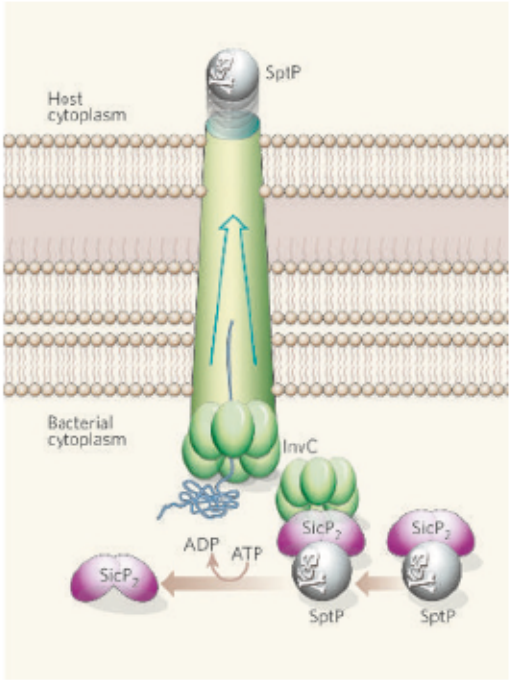

Figure 1 | Calibrating the ammunition. Bacteria shoot toxic proteins (such as SptP) into host cells through a type III secretion machine. In the bacterial cell, SptP is bound by a recognition factor ($SicP_2$) that docks at the InvC component of the secretory apparatus. InvC consumes energy (ATP) to dissociate SptP from $SicP_2$ and to unfold SptP — allowing it to fit through the narrow tube connecting the two cells. $SicP_2$ is released into the bacterial cell, and the toxic SptP is fired into the host cell.

This work may conveniently solve another puzzle: where does the energy for substrate travel come from? If InvC acts as the pumping station at the end of a pipeline, it is conceivable that the energy it invests in pushing substrates in one end is sufficient to shunt previously pumped substrates out of the other.

Given our current understanding of InvC, it is tempting to take the view that secretion substrates dock with InvC through their bound chaperones. Following chaperone displacement, a substrate would then be sucked in through the ring and unwound like a strand of spaghetti. The closely related flagellar assembly and secretion system has an InvC equivalent. In this system, the other components of the secretory machinery that face the interior of the bacterium can recognize not only substrates for secretion but also each other[8]. One of these proteins can even modulate the rate of ATP consumption of the InvC equivalent and another is part of the membrane-embedded secretion machinery[8,9]. So it seems likely that a complex web of interactions modulating InvC activity and specificity remains to be discovered, thereby providing even greater insight into the mechanisms by which bacteria load their type III weaponry. ■

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