

*Introduction*

## Bacterial secretion comes of age

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Bacterial secretion systems play essential roles in pathogenesis and also in maintaining lines of communication between bacterial cells in the bacterial microflora or between commensal bacteria and their host. Recent breakthroughs in the field have yielded some novel insights into the mechanisms by which these systems operate. This issue of *Philosophical Transactions B* seeks to provide a detailed survey of the field, with an emphasis on mechanisms and how their unravelling might provide a new future for antibiotics research.

**Keywords:** secretion; system; membrane

Bacteriology is undergoing a revival and there are mostly two reasons for it: (i) to put it bluntly, we, humans, are 90 per cent bacterial, and indeed, 90 per cent of our cells are bacterial. Work pioneered by Jeff Gordon at Washington University Medical School in St Louis, demonstrating a link between the gut microflora and obesity, opened the flood gates and since then, the bacterial microflora has been associated with asthma, and other immunological and metabolic disorders [1–3]. The billions of bacteria in our body must therefore communicate not only with their hosts, but also with their bacterial colleagues. This constant flow of information is mediated at least in part by large macromolecular devices, bacterial secretion systems, embedded in the bacterial membrane, which control the secretion of signal molecules and DNAs.

Bacteria can also cause harm. It is not so long ago that humanity was scarred by the threat of bacterial infections. This threat had receded with the advent of antibiotics, but it is now being revived with the increased resistance to antibiotics and the lack of novel antibiotics reaching the marketplace [4]. Here again, bacterial secretion systems play a crucial role: (i) they are major virulent factors playing central roles in the execution of pathogenesis and (ii) they are themselves, in part, responsible for the propagation of antibiotic-resistance genes.

Because secretion systems are responsible for the secretion of virulence factors (toxins, lytic enzymes, transforming proteins or mimics of eukaryotic proteins interfering with host function), inhibiting these systems is a promising avenue in antibiotics research [5]. There are now overwhelming arguments that anti-virulent antibiotics have a viable future: (i) such antibiotics should be less prone to triggering resistance, as the bacteria are not killed, but simply

disarmed and then flushed out by the immune system; (ii) such antibiotics will keep the bacterial microflora intact and thus ‘good bacteria’ would continue to play their beneficial roles, as opposed to also being killed as the classical antibiotics presently do; and (iii) since the link between human diseases and the bacterial microflora is ever more apparent, it is becoming ever more evident that killing the bacteria that inhabit our bodies might trigger unintended consequences that have, so far, been underestimated.

This issue of the *Philosophical Transactions of the Royal Society B* focuses on bacterial secretion systems. The themes outlined above permeate most of the contributions to this issue. But perhaps more importantly, all these contributions highlight the spectacular revolution that has taken place in the past 5 years in the field of bacterial secretion. This revolution, led primarily by breakthroughs in the structural biology of membrane proteins and membrane-embedded macromolecular complexes, has led to the partial elucidation of many steps in the secretion pathways mediated by the various secretion systems that are used by bacteria.

There are broadly two classes of bacterial secretion systems: (i) the ‘one-step’ secretion systems and the ‘two-step’ secretion systems [6]. Gram-negative bacteria have two membranes, inner and outer membranes, and a ‘periplasmic’ space between the two membranes. Thus, substrates synthesized in the cytoplasm need to cross both membranes and the periplasm before being released in the extracellular milieu. In one-step Gram-negative secretion systems, substrate enters the secretion machinery from the cytoplasmic side and is released outside directly, without a periplasmic intermediate step. In two-step Gram-negative secretion systems, substrates will first cross the inner membrane, be released in the periplasm before being captured by an outer membrane transporter that releases them on the other side. In Gram-positive bacteria, there is only one membrane and the transporters operating in that membrane are the same as the ones operating in the inner membrane

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One contribution of 11 to a Theme Issue ‘Bacterial protein secretion comes of age’.

of Gram-negative bacteria. However, Gram-positive bacteria have a thick cell wall outside their membrane, made of complex peptidoglycan, and Gram-positive bacteria have developed mechanisms to anchor proteins or pili to this thick layer.

This issue follows a rather classical format, starting with the reviews by Driessen and colleagues [7] and Müller and colleagues [8] on the transporters that mediate substrate transfer through the inner membrane of Gram-negative bacteria or the single membrane of Gram-positive bacteria. Then follows a series of reviews describing secretion by double membrane-spanning secretion systems, from type I to type VI secretion systems [9–14], in Gram-negative bacteria. Also, in Gram-negative bacteria, we then focus on a specialized outer membrane transporter and assembly platform that assembles and secretes adhesive pili [15], and conclude this issue on bacterial secretion systems in Gram-positive bacteria [16].

Going through the entire issue, one will be astonished by the variety of structures and mechanisms that bacteria have evolved in order to transport substrate. Clearly, there are common themes. For example, outer membrane secretins are used by at least two secretion systems—type II and type III; a beta-barrel is the means of choice for two-step outer membrane transporters such as type V secretion systems and pilus biogenesis systems; chaperones maintaining substrates in semi-unfolded states are relatively commonly used to deal with substrates of large size; traffic ATPases appear commonly shared in type II, type III and type IV secretion systems. However, many of the various system components appear to be unrelated at least at the sequence level (we cannot yet exclude structural homology, a stronger marker of shared evolutionary history), suggesting a certain degree of evolutionary divergence and independent evolution.

Another striking theme emerging from this detailed survey of bacterial secretion systems is that each system is used to mediate processes that are sometimes very different. For example, a very similar architecture for type III secretion is used to produce flagellae; the type II secretion system framework is used to produce type IV pili (not to be confused with type IV secretion systems that also produce pili but in a very different way); type VI secretion systems appear to have evolved from phage baseplates and sheath; type IV secretion systems can transport both proteins or DNAs.

Finally, although ATPases are the most common way to power transport, they are not the only route. Type I secretion systems use a variety of ways to power transport including ATP and the proton motive force. Outer membrane transporter, of course, cannot use ATP (there is none in the periplasm) but instead use other means, the most common mechanism being folding (type V secretion systems) or folding and favourable thermodynamic and kinetic gradients (chaperone-usher pathway of pilus biogenesis).

I sincerely hope that the reader of this issue will marvel at the myriad of ingenious transmembrane devices that bacteria have evolved to communicate with their extremely varied environment. The distinct focus of modern bacteriology on extracting mechanistic details

will no doubt provide a needed springboard for the design of novel antibiotics, inhibiting virulent factors. In this respect, research on bacterial secretion systems has a very strong role to play and it is hoped that the detailed secretion mechanisms that it unravels will in the not-so-distant future yield selective inhibitor compounds able to jam secretion when needed.

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