How bacterial predators evolved to kill other bacteria without harming themselves

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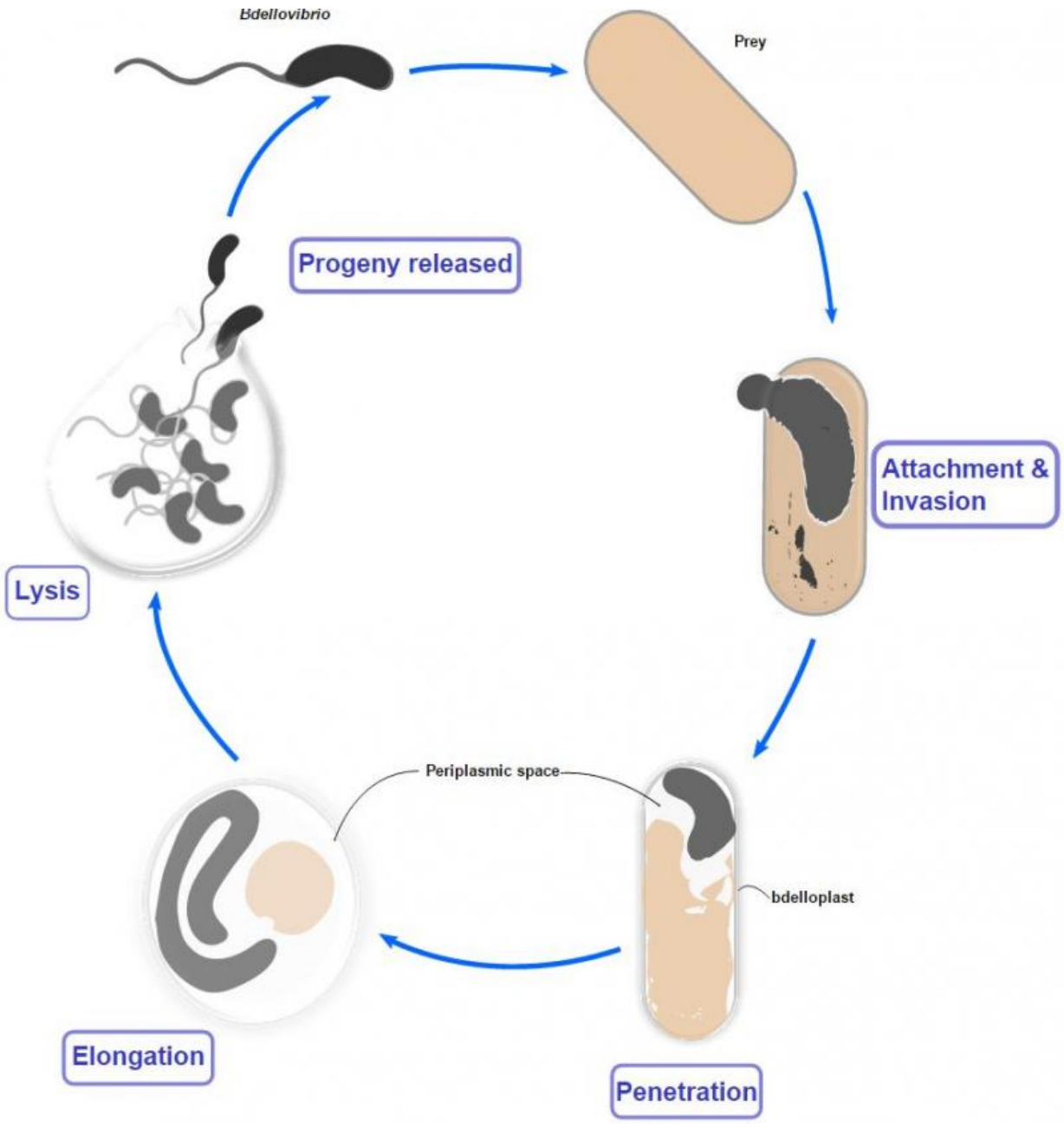

Bdellovibrio Life Cycle. The Bdellovibrio attaches to a gram-negative bacterium after contact, and penetrates into the prey's periplasmic space. Once inside, elongation occurs and progeny cells are released within 4 hours. Credit: Estevezj/Wikipeida

A joint study by the labs of Dr Andrew Lovering and Prof Liz Sockett, at the Universities of Birmingham and Nottingham, has shown how predatory bacteria protect themselves from the weapons they use in their bacterial killing pathway.

The research, published in *Nature Communications*, offers insights into early steps in the evolution of bacterial predators and will help to inform new ways of combatting antimicrobial resistance.

A useful predatory bacterium called Bdellovibrio bacteriovorus eats other bacteria (including important pathogens of humans, animals and crops).

It attacks them from inside out using enzymes (called DD-endopeptidases) that first loosen the cell walls of prey bacteria and then cause them to round up like a pufferfish, providing space as a temporary home for the predator.

However, Bdellovibrio also have similar cell walls so why don't they fall victim of their own attack?

The project, funded by the Biotechnology and Biological Sciences Research Council (BBSRC), found that the bacterium uses an ankyrin-type protein called Bd3460 as a shield. It binds to the tip of the enzyme

weapons, nullifying their action until they are safely secreted out of the Bdellovibrio and into the prey bacteria.

Dr. Andrew Lovering and Ian Cadby at the University of Birmingham determined the structure of the ankyrin protein using X-ray crystallography and found that that it attaches to two DD-endopeptidase weapons to temporarily deactivate them.

"When I first showed this to Liz, she hit the nail on the head by describing it as a decorative "quiff" on top of the endopeptidase" said Dr Lovering. "This covers up the active site of the enzymes that are used to cut cell walls and offers protection to the Bdellovibrio until these weapons are excreted into the prey."

Carey Lambert, Rob Till and Prof Liz Sockett at The University of Nottingham confirmed the antidote protein's use when the gene responsible for its production was deleted.

Prof Liz Sockett said: "When the Bd3460 gene responsible for antidote production was deleted, the Bdellovibrio had no way of protecting itself from its own weapons. When it attacked harmful bacteria with its cell-wall-damaging enzymes it also felt the effects.

"The Bdellovibrio bacteria lacking the Bd3460 gene tried to invade the bacteria but suddenly rounded up like pufferfish and couldn't complete the invasion—the fatter predator cell could not enter the prey cell."

This is the first paper to discover a 'self-protection' protein in predatory bacteria.

Prof Liz Sockett added, "Most bacteria are not predatory and so understanding these mechanisms gives us a glimpse of how predation evolved. In this case it seems that the Bd3460 gene was transferred into

ancestors of Bdellovibrio, probably when they were beginning to develop as predators."

Commenting on the potential impact of the study, Dr Andrew Lovering added: "If we are to use Bdellovibrio as a therapeutic in the future, we need to understand the mechanisms underpinning prey killing and be sure that any self-protective genes couldn't be acquired by pathogens, causing resistance. Brilliantly, Liz and Carey have demonstrated this did not happen with the bd3460 antidote protein, and Ian and I showed how the mechanism works on predator enzymes only - this is a great inter-university collaboration."

More information: Ankyrin-Mediated Self-Protection During Cell Invasion by the Bacterial Predator Bdellovibrio bacteriovorus, *Nature Communications*. DOI: 10.1038/NCOMMS9884

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