Institutionen för mikrobiologi, tumör- och cellbiologi

Caenorhabditis elegans as a Model to Elucidate Host-Pathogen Interactions for Human Bacterial Pathogens

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ABSTRACT

The soil nematode *Caenorhabditis elegans* is a popular host utilized to model bacterial virulence and microbial pathogenesis *in vivo*. This thesis explores the use of *C. elegans* for the study of host-pathogen interactions for two Gram-negative bacteria, *Burkholderia thailandensis* and *Salmonella enterica.*

We conducted a RNA interference screen to identify host genes capable of modulating the infection outcomes of *C. elegans* infected with *B. thailandensis*. We discovered that during infection, the cell junction protein LIN-7 appeared to modulate the evolutionarily conserved DAF-2 insulin/IGF-1 signalling pathway, culminating on both the FOXO transcription factor DAF-16 and the heat-shock factor 1. Moreover, LIN-7 regulated nematode survival during infection with other Gram-negative bacteria. Tissue-specific experiments also revealed that this interaction between LIN-7 and the DAF-2 signalling pathway operated mainly in nematode tissues outside the intestine (Paper I).

Through a forward genetics screen using ultraviolet light, we identified *pt1* as a novel allele of the *unc-7* innexin gene. We found that the *pt1* mutant exhibited enhanced survival only when infected with *Burkholderia* spp. We further defined a specific subclass of *unc-7* interacting genes, *unc-9* and *goa-1*, in a unique pathway which probably involves calcium dysregulation (Paper II).

Next we characterized a new aspect of *S. enterica* virulence. We observed that *S. enterica* provoked oxidative stress in the hypodermal tissues of infected *C. elegans* even though there was no apparent invasion beyond the intestinal epithelium. Via chemical and mutational interference, we found this phenomenon to be deleterious to the host. Genetic inactivation of the bacterial thioredoxin 1 strongly abrogated pathogenicity of *S. enterica* as well as the emergence of oxidative stress, thereby suggesting a novel role for this virulence factor (Paper III).

Finally, we investigated the combinatorial effects of the proton pump inhibitor omeprazole and the salicylidene acylhydrazide INP0010 during *S. enterica* infection. We observed disparate effects when they were used in combination and applied to different infection models including the epithelial and macrophage-like cell lines and *C. elegans*. The nematode can thus provide a platform for testing virulence inhibitors, allowing the elucidation of their mechanisms in the context of a whole organism (Paper IV).

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