Trends in Microbiology

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Review

RNA Regulators: Formidable Modulators of *Yersinia* Virulence

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A large repertoire of RNA-based regulatory mechanisms, including a plethora of *cis*- and *trans*-acting noncoding RNAs (ncRNAs), sensory RNA elements, regulatory RNA-binding proteins, and RNA-degrading enzymes have been uncovered lately as key players in the regulation of metabolism, stress responses, and virulence of the genus *Yersinia*. Many of them are strictly controlled in response to fluctuating environmental conditions sensed during the course of the infection, and certain riboregulators have already been shown to be crucial for virulence. Some of them are highly conserved among the family Enterobacteriaceae, while others are genus-, species-, or strain-specific and could contribute to the difference in *Yersinia* pathogenicity. Importantly, the analysis of *Yersinia* riboregulators has not only uncovered crucial elements and regulatory mechanisms governing host–pathogen interactions, it also revealed exciting new venues for the design of novel anti-infectives.

Pathogenicity and Virulence Factors in *Yersinia*

The three human pathogenic *Yersinia* species, *Y. enterocolitica, Y. pseudotuberculosis*, and *Y. pestis* possess an arsenal of conserved and species-specific virulence factors that promote efficient colonization and persistence of the bacteria in mammals (humans, rodents, pigs/boars, goats, deer, and hares) and insect vectors (fleas). This repertoire enables *Y. enterocolitica* and *Y. pseudotuberculosis* (with 60–70% genomic identity) to cause a range of similar, relatively benign, self-limiting intestinal diseases (yersiniosis). *Y. pestis*, which evolved clonally from *Y. pseudotuberculosis* 2000–10 000 years ago (>97% genomic identity), is the causative agent of plague [1,2]. Currently, the molecular mechanisms that determine the fundamental differences in the pathogenicity between both enteric *Yersinia* species and *Y. pestis* are unclear. Gene gain, loss, and rearrangements have been considered to play an important role [3,4]. Several virulence factors, such as the plasminogen activator Pla, the F1 capsular protein, and Ymt (*Yersinia* murine toxin), have been found exclusively in *Y. pestis*, whereas the crucial adhesion and invasion factors of the enteric pathogens, *invA* and *yadA*, are inactivated [4]. This could account for their distinct difference in pathogenicity. In addition, there are variations within the regulatory networks controlling expression of virulence-related genes.

Up to now a large repertoire of conserved and species-specific riboregulators, including numerous *cis*- and *trans*-acting ncRNAs, sensory RNA elements (RNA thermometers and riboswitches), regulatory RNA-binding proteins, and RNA-degrading enzymes, have been identified in pathogenic *yersiniae*, and many of these riboregulators are part of large regulatory networks. They adjust the expression of colonization factors, toxins, host defense processes, and virulence-related physiological and metabolic processes in response to fluctuating environmental conditions encountered during the course of an infection (Figure 1, Key Figure; Table 1). This review summarizes the current state of knowledge regarding RNA-mediated regulation in

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Numerous riboregulators, including regulatory/sensory RNAs, RNA-binding proteins, and RNA-degrading enzymes were discovered in *yersiniae* and several were found to be crucial for virulence.

The conserved RNAs CsrB and CsrC control expression of colonization factors, and they affect virulence-relevant activities in response to the pathogen's nutrient status.

The *Yersinia*-specific RNA Ysr29 contributes to resist stress from the host immune response, and Ysr141 modulates expression of the Ysc/Yop type III secretion system (T3SS).

The antisense RNA CopA decreases during infection. This induces replicase RepA, leading to a higher copy number of the *Yersinia* virulence plasmid encoding the T3SS.

Expression of the virulence regulator LcrF, the adhesin Ail, and the toxin CNF_Y is regulated by temperature-sensitive RNA structures. These RNA thermometers function as thermo-controlled RNA zippers that modulate translation.

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Key Figure

Regulatory Network of Virulence Factors Controlled by Small ncRNAs in *Yersinia*

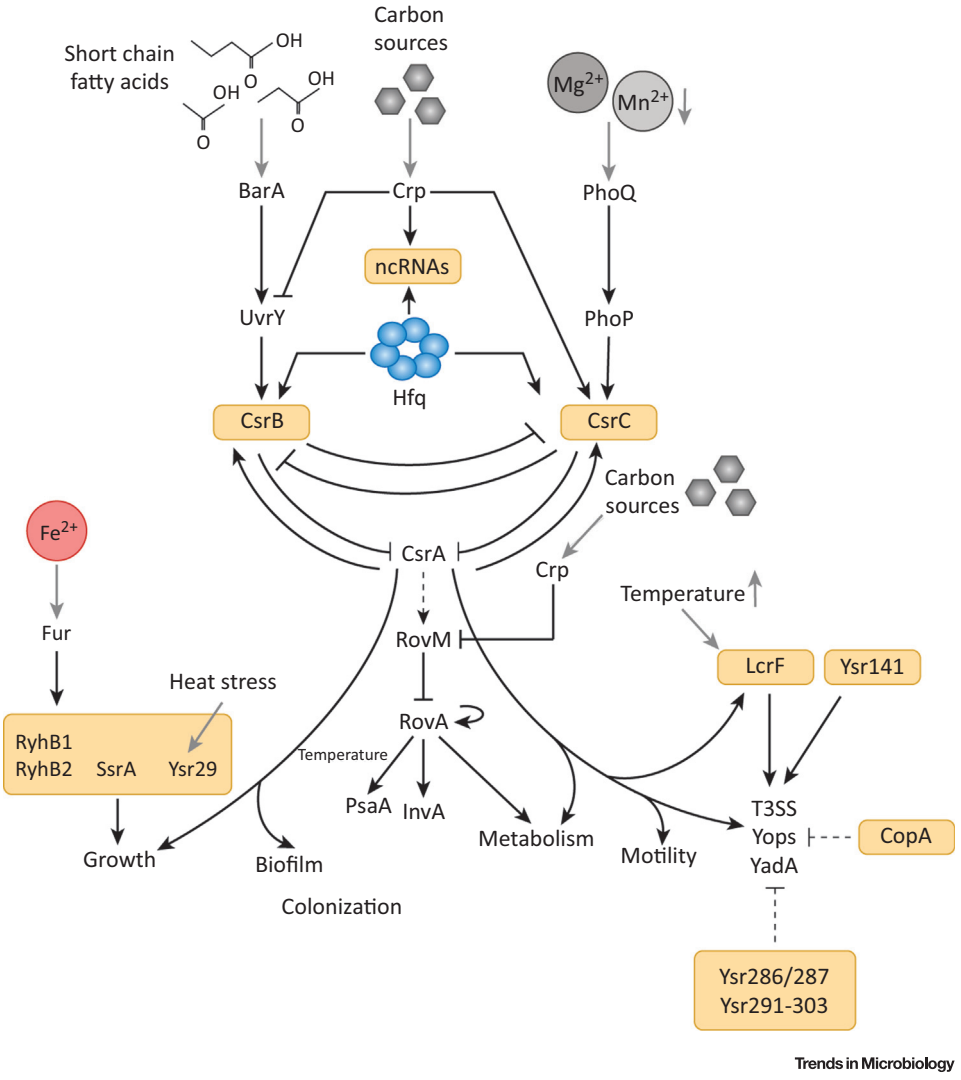

Figure 1. Overview of regulatory and environmental factors that control expression of virulence-associated traits in *Yersinia*, including host colonization, host-adapted metabolism, and immune defense. Transcriptional and post-transcriptional effects and involved ncRNAs (in yellow) are listed.

Yersinia. It describes the characteristics, function, and regulation of all classes of *Yersinia* riboregulators with special emphasis on their role in pathogenesis.

The Regulatory Noncoding RNA Repertoire of *Yersinia* Which Impacts Virulence

Regulatory ncRNAs are important players of the post-transcriptional regulation of virulence genes. They can interact with ribosomal binding sites or other 'complementary' sites within the