

Table 1. *Yersinia* Virulence Riboregulators

Riboregulator	Type of regulator	Target	Function/ Mechanisms	Regulation	Virulence-associated process	Refs
ncRNAs						
CsrB/ Ysr179/sR003/YPTB_RNA_90 CsrC/ Ysr186/sR026/YPTB_RNA_113	trans-encoded ncRNAs	CsrA	structured RNAs with multiple GGA sequences that bind and sequester CsrB and CsrC	BarA/UvrY, PhoP/PhoQ, Crp, short chain fatty acids, acidic pH, antimicrobial peptides	RovM, RovA, InvA/PsaA adhesin, T3SS/Yops, host-adapted metabolism, motility, global carbon storage regulation, resistance against heat, osmolarity and antibiotics	[5, 8, 11, 13]
CyaR/ RyeE/Ysr159/sR012/ Yp-sR30	trans-encoded ncRNA	-	-	induced in the lung and spleen during infection with <i>Y. pestis</i> biovar microtus, regulated by Crp	-	[16, 23]
RyhB1/ RfrA RyhB2/R frB/IsrE Ysr146.2(KO)/Ysr187(BE)/sR024/RfrA	trans-encoded ncRNA	-	-	increased during iron starvation, induced in the lung and spleen during infection with <i>Y. pestis</i> biovar microtus, depends on growth phase, controlled by the regulator Fur, degraded by PNPase	important under iron starvation, single <i>ryhB1</i> and <i>ryhB2</i> mutants are not required for full virulence in <i>Y. pestis</i> biovar microtus	[23, 27, 34]
SsrA/ tmRNA/sR022/Yp-sR31	trans-encoded ncRNA	A-site of stalled ribosomes	binds together with SmpB to stalled ribosomes by mimicking a tRNA and mRNA, which replaces incomplete/truncated transcripts within stalled ribosomes	induced in the lung and spleen during infection with <i>Y. pestis</i> biovar microtus	rescues stalled ribosomes, holds the translation machinery in the operation mode	[23, 45, 49]
RybB/ Ysr48/sR023	trans-encoded ncRNA	-	-	induced in the lung and spleen during infection with <i>Y. pestis</i> biovar microtus, temperature and growth phase-dependent	-	[16, 19, 23]
sR039, sR035, sR055, sR084, sR088	trans-encoded ncRNAs	-	-	induced in the lung and spleen during infection with <i>Y. pestis</i> biovar microtus	not required for full virulence of <i>Y. pestis</i> biovar microtus in a mouse infection model, sR035/HmsB acts as a regulator for biofilm formation	[23, 67]

					and is important for pathogenesis of <i>Y. pestis</i> through the flea route	
Ysr29	<i>trans</i> -encoded ncRNA	general stress response (GroEL, DnaK, UreC, S/RpsA, Gst, AhpC, Rf)	-	temperature and growth phase-dependent	required for stress response and full virulence of <i>Y. pseudotuberculosis</i>	[19]
Ysr35	<i>trans</i> -encoded ncRNA	-	-	temperature-induced	required for full virulence of <i>Y. pseudotuberculosis</i> and <i>Y. pestis</i>	[19]
Ysr141	<i>trans</i> -encoded ncRNA	-	-	-	influences expression and secretion of T3SS/Yop components, the major regulator LcrF, host immune defense	[24]
Ysr285-303(NU)	antisense RNAs	complementary to the transcripts of the effector YpkA, YopD, V-antigen, T3SS components	repression of the translation of components of the T3S machinery	the majority is temperature- and growth phase controlled, and Crp-dependent	predicted to repress synthesis of T3SS components	[16]
CopA/ Yp-sR25	Antisense RNA	complementary to the replicase gene <i>repA</i> of the <i>Yersinia</i> virulence plasmid	repression of the replication of the virulence plasmid pYV	downregulated during colonization of the Peyer's patches	repression of <i>repA</i> mRNA translation/stability, reduces expression of the T3SS/Yop components	[21, 68]
asPla	antisense RNA	complementary to the transcript of the plasminogen activator protease Pla encoded on the <i>Y. pestis</i> plasmid pPCP1	repression of Pla expression	-	predicted to repress synthesis of Pla	[37]
RNA thermometer						
<i>ail</i>	5'-UTR of <i>ail</i>	RNAT of the Ail adhesin gene	stem-loop structure restricts access of ribosome to SD sequence at 25°C; but not at 37°C	temperature-induced	regulation of the expression of the cell attachment and invasion by Ail	[44]
<i>cnfY</i>	5'-UTR of <i>cnfY</i>	RNAT of the CNF _Y toxin gene	stem-loop structure restricts access of ribosome to SD sequence at 25°C; but not at	temperature-induced, controlled by <i>csrA</i> , <i>crp</i>	regulation of the expression of the cytonectinizing factor that enhances Yop translocation	[44, 69]

			37°C,		into immune cells	
<i>lcrF</i>	<i>ysw-lcrF</i> intergenic region	FourU RNAT	two-stem loop structure restricts access of ribosome to SD sequence at 25°C; but not at 37°C, proper function required for virulence	temperature-induced, iron limitation and oxidative stress, controlled by the transcription factors YmoA, RcsB, IscR	regulation of the <i>ysc/yop</i> T3SS system	[42-44, 70]
<i>trxA</i>	5'-UTR of <i>trxA</i>	RNAT of the <i>trxA</i> gene	thermally induced structural changes liberate the SD sequence, also predicted as a putative riboswitch	temperature-induced, induced upon oxidative stress	regulates thioredoxin, resistance against oxidative and nitrosative stress, , also predicted as a putative riboswitch	[16, 44]
<i>katA</i>	5'-UTR of <i>katA</i>	RNAT of the <i>katA</i> gene	thermally induced structural changes liberate the SD sequence	temperature-induced, induced upon oxidative stress	regulates a katalase, resistance against oxidative stress	[44]
<i>sodA</i>	5'-UTR of <i>sodA</i>	RNAT of the <i>sodA</i> gene	thermally induced structural changes liberate the SD sequence	temperature-induced, induced upon oxidative stress	regulates a superoxide dismutase, resistance against oxidative stress	[44]
<i>sodB</i>	5'-UTR of <i>sodB</i>	RNAT of the <i>sodB</i> gene	thermally induced structural changes liberate the SD sequence	temperature-induced, induced upon oxidative stress	regulates a superoxide dismutase, resistance against oxidative stress	[44]
<i>sodC</i>	5'-UTR of <i>sodC</i>	RNAT of the <i>sodC</i> gene	thermally induced structural changes liberate the SD sequence	temperature-induced, induced upon oxidative stress	regulates a superoxide dismutase, resistance against oxidative stress	[44]
Riboswitch						
<i>mgtA</i>	Mg ²⁺ -binding RNA structure	5'-UTRs of <i>mgtA</i>	Mg ²⁺ binding leads to early Rho-dependent termination of <i>mgtA</i> transcription through conformational change in the RNA;	high Mg ²⁺ concentration	regulates magnesium transporter production, important for survival and replication in macrophages	[39], [16]
<i>crp</i>	Predicted riboswitch-like element	5'-UTR of <i>crp</i>	post-transcriptional activation of Crp synthesis in <i>Y. pestis</i>	-	regulates many virulence-related genes and ncRNAs in response to nutrient availability, essential for virulence	[16-18, 63]

RNA Binding proteins						
CsrA	RNA binding protein	ANGGA motifs in 5'-UTRs or early coding region of mRNAs	CsrA interaction modulates translation efficiency and in many cases also stability of the target mRNAs	controlled by CsrB, CsrC, autoregulated, stationary phase-induced	RovM, RovA, InvA/PsaA adhesin, T3SS/Yops, host-adapted metabolism, motility, global carbon storage regulation, resistance against heat, osmolarity and antibiotics, promotes biofilm formation	[5, 8, 11, 13, 14]
Hfq	RNA binding protein	AU-rich motifs, multiple ncRNA and mRNA targets	Hfq acts as an RNA chaperone, which enhances and stabilizes interaction of ncRNAs with their target mRNAs	regulated in response to growth phase and temperature	pleiotropic influence on virulence-related traits, e.g. expression of multiple adhesins, regulates cyclic-di-GMP levels and subsequently biofilm formation, <i>hfq</i> mutants of all human pathogenic <i>Yersinia</i> are attenuated	[16, 28-31, 71]
SmpB	RNA binding protein	interacts with A site of ribosomes together with SsrA	assists SsrA interaction with stalled ribosomes to rescue the translation machinery on mRNAs without a stop codon (truncated transcripts)	-	pleiotropic, upregulated in the lung and spleen during infection with <i>Y. pestis</i> biovar microtus, affects <i>yop/ycs</i> expression and T3SS, motility, resistance towards oxidative, acidic and nitroactive stresses	[45, 49]
YopD	RNA binding protein	5'-UTR of <i>yop/ycs</i> mRNAs, RNA binding mechanism unknown	acts most likely together in complex with the chaperone LcrH and LcrQ (YscM1/YscM2 in <i>Y. enterocolitica</i>)	repression of protein expression by interference with ribosome binding	deregulation of <i>yop/ycs</i> gene expression, Ca ²⁺ independent T3SS	[50-52, 72]
RNases						
Rne RNase E	RNA decay, endonuclease	cleaves RNA substrates in single-stranded regions that	is part of the RNA degradosome, cooperates with PNPase	-	inhibits secretion of T3SS effector proteins	[57]

		are usually proceeded or followed by a stable stem \pm loop structure				
Pnp Polynucleotide Phosphorylase (PNPase)	RNA decay, exonuclease	cleaves from the 5'- and 3'-end	is part of the RNA degradosome, cooperates with RNase E	-	inhibits secretion of T3SS effector proteins, oxidative stress and growth in the cold	[58-61]
YbeY RNase Y	RNA decay	single-strand specific, processes the 3'-ends of the 16S rRNA	responsible for the late-stage 70S ribosome quality control	-	pleiotropic, controls many virulence-related features, including acid stress resistance, cell adhesion/-invasion properties and T3SS, regulates the ncRNAs CsrB and CsrC	[62]
Rnc Rnase III	RNA decay	binds to and cleaves double-stranded RNA	processing of ribosomal RNA precursors and of some mRNAs	-	affects abundance of the RyhB2 transcript	[34]