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MINIREVIEW

Role of RpoS in Virulence of Pathogens▽

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Understanding mechanisms of bacterial pathogenesis is critical for infectious disease control and treatment. Infection is a sophisticated process that requires the participation of global regulators to coordinate expression of not only genes coding for virulence factors but also those involved in other physiological processes, such as stress response and metabolic flux, to adapt to host environments. RpoS is a key response regulator to stress conditions in *Escherichia coli* and many other proteobacteria. In contrast to its conserved well-understood role in stress response, effects of RpoS on pathogenesis are highly variable and dependent on species. RpoS contributes to virulence through either enhancing survival against host defense systems or directly regulating expression of virulence factors in some pathogens, while RpoS is dispensable, or even inhibitory, to virulence in others. In this review, we focus on the distinct and niche-dependent role of RpoS in virulence by surveying recent findings in many pathogens.

RpoS is an alternative sigma factor of RNA polymerase primarily found in *Beta-* and *Gammaproteobacteria* (31, 59). RNA core polymerase requires a sigma factor for promoter recognition and transcription initiation. In addition to housekeeping sigma factors that control transcription of essential genes, bacteria also possess alternative sigma factors that recognize the promoters of a specific set of genes. There are seven known sigma factors in the Gram-negative model bacterium *Escherichia coli* (67) and 18 in the Gram-positive bacterium *Bacillus subtilis* (52). The contribution of alternative sigma factors to virulence can be direct through regulated expression of virulence genes or indirect by enhancing survival against host defense and other stress conditions (70).

Pathogenic bacteria experience many stresses during transmission and infection. For example, the enterohemorrhagic *E. coli* (EHEC) O157:H7 strain may face nutrient limitation and heat exposure in natural environments and acid stress and host defense after entry into human hosts. The ability to quickly adapt to changing environments is therefore critical for bacterial pathogens to successfully transmit and infect hosts. One of the most important adaptation factors in *E. coli* is RpoS (31, 59). The RpoS regulon, comprising 10% of *E. coli* genes (32, 33, 78, 108, 141), plays a critical role in survival of several stresses, including acid (124), heat (61), oxidative stress (116), starvation (79), and near-UV exposure (116). In *E. coli*, the levels of RpoS are low in exponential phase (32, 80), due to reduced transcription (80), attenuated translation (80), and, most importantly, rapid proteolysis mediated by RssB, a chaperone protein that binds to RpoS and directs the RssB-RpoS complex to the ClpXP protease (80, 93, 109, 150). The degradation of RpoS is suppressed in stationary phase (11, 150), resulting in increased RpoS levels (80). Expression of RpoS is sensitive to environmental changes and is under the control of many regulatory factors, such as acetate, ppGpp, and cyclic AMP (cAMP) (reviewed in references 31 and 59).

The RpoS-bearing bacteria have a broad host range, including human pathogens (e.g., *E. coli* and *Vibrio cholerae*), animal pathogens (e.g., *Citrobacter rodentium* and *Salmonella enterica* serovar Typhimurium), insect pathogens (e.g., *Serratia entomophila* and *Xenorhabdus nematophilus*), and plant pathogens (e.g., *Burkholderia plantarii*, *Erwinia carotovora*, and *Ralstonia solanacearum*). RpoS is required for resistance to many stresses in these bacteria (Table 1). However, the effect of RpoS on virulence is variable, differing even in closely related species. RpoS is required for virulence in some pathogens, including *Salmonella enterica*, *V. cholerae*, *B. plantarii*, and *S. entomophila*, but is less important in other species (Table 1). Despite the considerable accumulated information on RpoS control of virulence functions in specific bacteria, there is, as yet, no comprehensive review on this topic. Therefore, this review summarizes the involvement and contribution of RpoS in virulence of RpoS-bearing pathogens. We place special focus on studies that have tested *rpoS* in host (animal or plant) or cell culture models.

ENTERIC PATHOGENS

E. coli commensal strains are a common component of human intestinal flora, but there are many *E. coli* pathogens, including enteropathogenic *E. coli* (EPEC) and enterohemorrhagic *E. coli* (EHEC), which can cause severe gastrointestinal disease. Though the regulation of RpoS in gene expression is best studied in *E. coli*, RpoS involvement during enteropathogenesis is unresolved, probably due to the lack of effective animal models (97). Infection with *E. coli* in mice does not cause intestinal disease as it does in humans (97). However, several virulence traits are known to be controlled by RpoS. For example, the production of curli, important for coloniza-

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TABLE 1. Effects of RpoS on virulence of specific pathogens

Organism	RpoS-dependent phenotype[a]						Virulence factor(s) controlled by RpoS	Role of RpoS in virulence	Model	Reference
	Starvation	Oxidative	Acid	Heat	Osmotic	Motility				
Escherichia coli										
K-12	+	+	+	+	+	−	NA[b]	NA	NA	33, 60, 108
BJ4	NA	+	NA	+	NA	NA	NA	Not required for competitive colonization	Female Ssc:CF1 mice (streptomycin treated)	75
CFT073	NA	NA	NA	+	+	NA	NA	Not required for colonization in murine urinary tract	Mice, transurethral inoculation	25
K-1	NA	NA	+	+	+	NA	NA	Important for BMEC[c] invasion	Cell culture, BMEC	140
O157:H7	+	NA	NA	NA	NA	NA	NA	Important for passage in mice and shedding in calves	ICR mice, calves	110
Borrelia burgdorferi	NA	−	+	−	+/−	NA	OspC, DbpA	Essential	Female C3H/HeJ, BALB/s, and SCID mice	18, 36, 64
Burkholderia plantarii	+	NA	NA	NA	NA	NA	NA	Important for rice seedling blight but not for colonization	Rice seedling leaves	126
Burkholderia pseudomallei	NA	+	+	−	−	NA	NA	Not required for intracellular survival	Cell culture with HEp-2 and RAW264.7 cells	129
Erwinia carotovora subsp. *carotovora*	+	+	+	NA	+	NA	Downregulates extracellular enzymes and Nip	*rpoS* mutants more virulent	Celery, tobacco, and potato	5, 89, 95
Legionella pneumophila	+	−	−	NA	+/−	+	Mip, FliA, Icm, ProA	With loss of *rpoS* impaired intracellular replication during early stage of infection in murine primary and human monocyte-derived macrophages	Cell culture, human macrophage-like cell U397, HL-60, and monocyte-derived macrophage, THP-1	3, 6, 7, 15, 55, 56, 152
								RpoS critical for growth in amoeba host and for pore-forming ability in erythrocytes	Murine bone marrow-derived macrophages	
								Not required for survival and cytotoxicity in macrophage-like cells	*Acanthamoeba castellanii* and *A. polyphaga* amoebae	
Pseudomonas aeruginosa	+	+	NA	+	+	+	Exotoxin A, alginate production	*rpoS* mutants more virulent in rat chronic lung infection, but moderate effect of RpoS on virulence in *Galleria mellonella*	Rat chronic lung infection with agar-bead-embedded bacteria placed in rat left lung; *Galleria mellonella* (wax moth)	127, 130
Ralstonia solanacearum	NA	−	+	−	−	NA	EPS 1, EGL, but downregulates PGL	Minor effect of RpoS on virulence	Tomato	45

Continued on following page

TABLE 1—*Continued*

Organism	RpoS-dependent phenotype[a]						Virulence factor(s) controlled by RpoS	Role of RpoS in virulence	Model	Reference
	Starvation	Oxidative	Acid	Heat	Osmotic	Motility				
Salmonella enterica serovar Typhimurium	+	+	+	NA	NA	NA	SpvR, SpvABCD, and chromosome genes	Essential (oral lethal dose 1,000-fold higher for *rpoS* mutants; CFU of wild-type-infected spleen 1,000-fold higher than that of mutants	Female BALB/c and C57BL/6 mice	40, 73
Serratia entomophila	NA	−	−	NA	NA	NA	AnfA1	Important for control of antifeeding effect	*Costelytra zealandica*, larval infection	49
Shigella flexneri	NA	+	+	NA	NA	NA	NA	Not required for invasion and plaque formation	Cell culture, Henle 407	92
Vibrio cholerae	+	+	NA	NA	+	+	HA/protease dependent on RpoS, but cholera toxin downregulated by RpoS	Mucosa escape response RpoS dependent; not required for intraintestinal survival in infant mice	Rabbit ileal loops, infant (4–5 days old) CFW mice	101, 149
	NA	NA	NA	NA	NA	NA	NA	Required for efficient colonization	5-day-old suckling CD1 mice	90
Xenorhabdus nematophilus	+	+	NA	NA	−	−	NA	Required for growth in mutualistic hosts; not required for virulence in insects	Mutualistic to *Steinernema carpocapsae*, pathogenic to *Manduca sexta*	139
Yersinia enterocolitica	+	+	+	+	+	NA	Yst (enterotoxin)	No effect in virulence and invasion; no difference in LD_{50}[d] in mice	Cell culture, Hep-2 cells, female BALB/c mice	8, 66

[a] +, positive effect; −, negative effect; +/−, either positive or negative depending on strain backgrounds or growth conditions.
[b] NA, information not available in the reference(s) cited.
[c] BMEC, brain microvascular endothelial cells.
[d] LD_{50}, 50% lethal dose.

tion, is dependent on RpoS (105). RpoS also controls the expression of the *ehxCABD* operon, encoding enterohemolysin, in *E. coli* O157:H7 (83). A common characteristic of EPEC and EHEC infection is the formation of attaching and effacing (A/E) lesions, which requires expression of genes on a pathogenicity island, the locus of enterocyte effacement (LEE) (37). The LEE island harbors five polycistronic operons, which encode a type III secretion system (T3SS) and secreted proteins essential for virulence (27). The effect of RpoS on the expression of LEE genes has been studied by several independent groups, and variable results have been reported. Expression of *lacZ* fusions to promoters of LEE3 and EspA is higher in the wild-type K-12 strain than in isogenic *rpoS* mutants (13, 128). However, other studies report that RpoS is a negative regulator of LEE genes (34, 68, 77, 133). It is known that expression of LEE genes varies among *E. coli* species (35, 114), although the basis for this is not yet fully understood. One likely contributing factor is the sequence variation in the *pch* prophage adjacent genomic regions that affects expression of LEE genes in *E. coli* O157:H7 subpopulations (148). Expression of LEE genes is also dependent on environmental conditions (2, 71). We recently found that RpoS positively regulates expression of Ler, a LEE-encoded regulator, in stationary phase in LB media (a noninducing condition for LEE expression), but negatively regulates expression of Ler and other LEE genes under LEE induction conditions (34). Interestingly, mutations in Hfq, a small RNA chaperone protein that is required for effective RpoS translation (94), also result in elevated expression of LEE genes through posttranscriptional control (57). However, this effect is RpoS independent (57).

Because of its importance in the bacterial stress responses, RpoS may be required for *E. coli* to survive passage through the gastrointestinal tract. When *rpoS* mutants and the wild type of *E. coli* O157:H7 are fed to mice and calves, the recovery of the wild type in feces is much higher that that of *rpoS* mutants, probably due to the RpoS-regulated acid resistance response (110). RpoS also plays a role in intestinal colonization of *E. coli* strain BJ4 in streptomycin-treated mice (75). Colonization in mice by *rpoS* mutants is as high as that of wild type in separate infection (75). However, *rpoS* mutants can outcompete the wild type in mouse colon during coinfection, suggesting that *rpoS* mutants may be

able to better utilize a specific limiting nutrient in colon (75).

In nonenteric *E. coli* pathogens, RpoS also controls expression of virulence traits. In *E. coli* K-1 strains that can cause neonatal meningitis, RpoS is important for invasion of brain microvascular endothelial cells, although the mechanism has yet to be identified (140). RpoS also positively controls motility and biofilm formation in uropathogenic *E. coli* (UPEC) strain UTI89 (76). However, mutations in *rpoS* have little effect on biofilm formation in UPEC strain 536 (12) or on colonization of urethra, bladder, and kidney in UPEC strain CFT073 (25).

Citrobacter rodentium is a natural murine enteropathogen closely related to *E. coli*, and, similar to EPEC and EHEC strains, it utilizes the LEE-encoded type III secretion system for delivery of virulence factors (97). Infection of mice using *C. rodentium* provides a promising alternative model to study enteropathogenesis in natural hosts (97, 143). The *rpoS* mutant of *C. rodentium* is more sensitive to heat and oxidative stress than the wild type, indicating a conserved RpoS function (30). Colonization and virulence of *C. rodentium* are attenuated in *rpoS* mutants during infection in mice (30). However, *rpoS* mutants outcompete the wild type during coinfection in mouse colon (30). In contrast to the negative regulation of LEE genes by RpoS in *E. coli*, RpoS has a moderate yet positive effect on expression of LEE genes in *C. rodentium* (30).

Salmonella serovars can cause severe systemic infection (typhoid fever) or nonsystemic gastroenteritis, depending on the serotypes (103). The systemic infection of *S. enterica* serovar Typhimurium in mice resembles the severe infection of *S. enterica* serovar Typhi in humans causing typhoid fever (103). RpoS plays a critical role in *Salmonella* virulence (40). Specifically, RpoS is important for persistence in lymphoid organs, such as the spleen (24, 73) and liver (24), and for initial stages of infection in murine Peyer's patches (24, 100). RpoS acts primarily through positive regulation of expression of the plasmid-borne *spvR* and *spvABCD* genes, which are required for intracellular growth and systemic infection in mice and humans (40, 102). RpoS positively regulates the expression of SpvR, a LysR family regulator, which accounts for the RpoS dependence of *spvABCD* (1, 21, 58, 73). Interestingly, *rpoS* mutants are also less virulent than the plasmid-cured wild type in mouse infections, suggesting that RpoS regulates chromosomal virulence determinants as well (40). Identified chromosomal virulence factors in *Salmonella* include YedI, SodCII, and genes for curli synthesis. The *yedI* gene is RpoS dependent and is important for persistence during infection in mice by *S.* Typhimurium (38). The *yedI* mutants are impaired in competition with the wild type during oral infection and are sensitive to polymyxin B, a cationic antimicrobial peptide (38). Genes coding for curli production, *csgD* and *csgAB*, are positively regulated by RpoS in *Salmonella* (115). There are two *sodC* alleles, *sodCI* and *sodCII*, encoding superoxide dismutase in *Salmonella*. Most *Salmonella* serotypes possess *sodCII* (39). SodCII is controlled by RpoS and is important for virulence, likely by protecting bacteria against superoxide-dependent host defense (39, 117, 123). However, other studies show that only SodCI, but not SodCII, contributes to virulence (74, 138). The small RNA chaperone protein Hfq, an important RpoS regulator, also plays an essential role in virulence in *Salmonella* through posttranscriptional regulation of many virulence genes (122). This virulence effect, however, is largely independent of RpoS (122).

In addition to regulating virulence functions, RpoS is essential for survival against stresses, such as oxidative stress, starvation, DNA damage, and low pH, which *Salmonella* likely encounters during intracellular growth in host macrophages (40). In *S.* Typhimurium, RpoS and RpoS-regulated genes, including *katE* and *spv*, are induced after invasion of epithelial cells and macrophages (22). RpoS is also important for survival of *S.* Typhi in mouse peritoneal macrophages through protection from nitric oxide produced by macrophages (4). Although not required for survival of *S.* Typhi in the human promonocytic macrophage THP-1, RpoS is required for the effective induction of macrophage apoptosis by *S.* Typhi during intracellular infection (72).

Interestingly, *Salmonella* cells infect and grow intracellularly in cultured epithelial and macrophage cells but not fibroblasts and other nonphagocytic cells (88). Using a random mutagenesis strategy, Cano and colleagues have found that mutations in genes *phoP*/*Q*, *rpoS*, *spvR*, and *spvB* can allow for growth in fibroblasts (NRK-49F rat kidney cell line) (20). This growth repression in fibroblasts by these genes is likely restricted to specific cell lines, since mutations in *phoP*/*Q* result in enhanced growth in the 3T3 mouse fibroblast cell line, but not in HeLa cells (20). The viable but not growing intracellular state in fibroblasts could conceivably aid in bacterial persistence within infected nonphagocytic cells (20).

Because of the virulence deficiency of *rpoS* mutants, these mutants are potential candidate vaccine agents (24, 26). However, the potential of using *rpoS* mutants as a vaccine is serotype dependent (23). Protection from infection of wild-type *S. enterica* serovar Dublin can be achieved with preinoculation of *rpoS* mutants of *S.* Dublin but not with a heterologous preparation made from *S.* Typhimurium (23).

During outbreaks, *Salmonella* spreads through contaminated food sources, including vegetables. In an alfalfa sprout model, the *S. enterica* serovar Newport wild-type strain colonizes the plant tissue much better than *rpoS* mutants by 24 h, although the number of cells reaches a similar level after 48 h (9). Interestingly, studies with the plant pathogens *Erwinia carotovora* (5) and *Pseudomonas putida* (91) have shown that RpoS is important for colonization on tobacco, bean, and cucumber.

Vibrio cholerae is another major food-borne human pathogen. During infection, *V. cholerae* adheres to the epithelial cells in the small intestine and secretes enterotoxins to disrupt ion transport of attached cells, resulting in severe diarrhea (42). RpoS mutants are impaired in survival under starvation, osmotic shock, and oxidative stress in *V. cholerae* (149). The hemagglutinin (HA)/protease that processes cholera enterotoxins is positively controlled by RpoS (149). Though HA/protease is not required for colonization and virulence in infant rabbits, it may allow *V. cholerae* to detach from epithelial cells to be released into the environment (44).

RpoS is required for efficient colonization of *V. cholerae* in suckling CD1 mice (90). However, another study reports that, after coinfection with wild-type *V. cholerae* in infant mice, the proportion of *rpoS* mutants remains stable by 20 h, indicating that RpoS is not required for intestinal survival (149). This

difference has been attributed to strain variation within *V. cholerae*, which will require further study (90).

The last phase of *Vibrio* infection when cells detach from epithelial layers is termed the "mucosa escape response," and this phase requires the expression of RpoS (101). The expression of genes required for motility and chemotaxis is upregulated by RpoS in the mucosa escape response and in stationary phase (101). Under *in vitro* virulence-inducing conditions, production of cholera toxin is 10- to 100-fold higher in the *rpoS* mutants than in the wild type, and virulence genes, including *aphA*, *toxT*, and *vpsA*, are expressed significantly higher in the *rpoS* mutants (101). Thus, it is likely that, during the last phase of infection, RpoS represses virulence gene expression and stimulates motility to facilitate transmission (101).

Vibrio vulnificus is a human pathogen that can cause wound infections and septicemia. RpoS protects cells from many stress conditions, except for heat shock (65). RpoS positively regulates the production of extracellular enzymes, such as albuminase, caseinase, and elastase, which may be required for survival of bacteria under many environmental conditions and for host adaptation (65). RpoS is also required for full motility (65). Interestingly, the catalase HPI is controlled by RpoS in *V. vulnificus*, while the gene encoding catalase HPII, which is highly RpoS dependent in *E. coli*, is not expressed (107).

Vibrio anguillarum is the causative agent of vibriosis in fish (84). A gene encoding the essential virulence factor EmpA metalloprotease is positively regulated by RpoS (28). The virulence of *rpoS* mutants is severely reduced in zebra fish (87). Similar to *V. vulnificus*, the *V. anguillarum rpoS* mutants are also impaired in production of extracellular enzymes, including phospholipase, diastase, lipase, caseinase, hemolysin, catalase, and protease (87).

Yersinia enterocolitica is an invasive enteropathogen that causes gastroenteritis in humans. Adherence and invasion of *Y. enterocolitica* initiate at the terminal ileum. RpoS positively regulates the expression of Yst enterotoxin (66), but does not control the expression of *inv* and *ail*, two virulence genes that are also required for invasion (8). RpoS has little effect in invasion in cell culture and in virulence of *Y. enterocolitica* in mouse models (8, 66).

Shigella flexneri infection causes severe dysentery in humans (118). After adherence and invasion of the colon mucous epithelial layer, *S. flexneri* is engulfed in phagocytic vacuoles (118). Following the lysis of these vacuoles, *S. flexneri* replicates and spreads to adjacent cells (118). As expected, RpoS is critical for resistance to acidic and oxidative stress in *S. flexneri* (92). When an *rpoS* mutant allele of *E. coli* was introduced to *S. flexneri* by P1 transduction, the resultant mutant exhibited no defect in invasion and formation of plaques on cultured Henle 407 cell monolayers, indicating that RpoS is not required for intercellular proliferation and spreading (92). However, the invasive ability of *S. flexneri rpoS* mutants has yet to be tested in animal models.

Overall, RpoS and its regulated genes are important for stress resistance and adaptation in enteric pathogens. Although RpoS plays an unequivocal role in the virulence of *Salmonella* species, the requirement for RpoS in the virulence and/or host adaptation in other species remains elusive. Nevertheless, given the importance of RpoS in adaptation, mutants of RpoS may be impaired in transmission to hosts due to reduced survival under adverse conditions. However, this has yet to be confirmed in animal models.

RESPIRATORY PATHOGENS

Pseudomonas aeruginosa is an opportunistic pathogen that causes chronic lung infection (104). RpoS is highly expressed in *P. aeruginosa* isolated from sputum samples of cystic fibrosis (CF) patients with chronic lung infection (46). As is the case in *E. coli*, RpoS is critical for survival of *P. aeruginosa* under osmotic shock, heat shock, and oxidative stress conditions (130). The effect of RpoS on expression of known virulence factors varies. For example, RpoS positively regulates the production of exotoxin A, which inhibits eukaryotic protein synthesis, and alginate, an important factor in the persistence of *P. aeruginosa* in CF lung and evasion of phagocytosis (127, 130). The secreted protease activities of elastase and LasA are also reduced in *rpoS* mutants (130). However, the production of pyocyanin, a virulence secondary metabolite that interferes with host immune defense response (136), is enhanced in *rpoS* mutants (130). In a rat chronic-infection model that specifically assesses the effect of extracellular secreted virulence proteins, *rpoS* mutants survive as well as the wild type but cause more damage to lung tissues, which may be attributable to excess pyocyanin production (130). RpoS is required for full motility of *Pseudomonas* and thus has been suggested to be important for colonization (130).

The RpoS translational regulator Hfq is critical for virulence of *P. aeruginosa* O1 in the wax moth *Gelleria mellonella* and in mice (127), while RpoS only has a moderate virulence effect in *G. mellonella* (127). Production of pyocyanin is negatively controlled by Hfq and RpoS (127). RpoS has little effect on motility of *P. aeruginosa* (127), which differs from previous results (130), probably due to differences in testing conditions.

The role of RpoS in quorum sensing of *P. aeruginosa* remains elusive. It has been shown that transcription of *rpoS* is controlled by quorum-sensing regulators, LasR and RhlR (81), while another study reports that quorum sensing has little effect on expression of RpoS and is in fact repressed by RpoS (142). The basis for these conflicting effects is unknown. Nonetheless, there certainly is overlapping regulation between regulons of quorum sensing and RpoS in *P. aeruginosa*. For example, the production of cytotoxic lectins is controlled by both RpoS and the quorum-sensing regulator RhlR (144).

Legionella pneumophila is a facultative intracellular pathogen that can cause severe pneumonia, named "Legionnaires' disease" (131). A natural reservoir for *L. pneumophila* is a wide range of amoebae living in soil and water sources (43). *L. pneumophila* is transmitted to the human respiratory tract through contaminated water aerosols (131). During phagocytosis, *L. pneumophila* engulfed in phagosomes initially suppresses virulence traits until entry into stationary phase, when virulence and transmission traits are activated to stimulate transmission to adjacent cells (131).

RpoS plays a critical role in regulation of transmission and virulence of *L. pneumophila* (3, 7). Transcription of *rpoS* peaks in exponential phase, while the protein level of RpoS reaches maximum in postexponential phase (7). RpoS is important for survival in osmotic shock but not other stress conditions in

exponential phase (55). In stationary phase, though cells become more stress resistant, RpoS is dispensable (55).

In exponential phase, RpoS downregulates the transcription of *L. pneumophila* virulence genes *csrA*, *letE*, *fliA*, and *flaA* and represses motility, infectivity, and cytotoxicity (6, 7). However, in postexponential phase, RpoS is critical for the transcription of flagellar genes *fliA* and *flaA* (7). The repression of traits for transmission and cytotoxicity by RpoS in exponential phase may be important to allow cell replication to a high level, while in stationary phase, RpoS repression is relieved and the transmission traits are upregulated by RpoS (7).

The pathogenesis of *L. pneumophila* requires the virulence factor Mip, a peptidyl-prolyl isomerase, for invasion and replication within both amoebae and macrophages (7). The transcription of *mip* is severely impaired in postexponential phase *rpoS* mutants (7). Production of phospholipase and lipophospholipase, two virulence factors, is also under positive control of RpoS (15). In addition, RpoS positively regulates expression of ProA, a secreted virulence protease that is cytotoxic to macrophages and is important for virulence in a guinea pig model (15). RpoS also regulates the expression of the ankyrin genes that play a critical role in intracellular growth within amoeba hosts and human macrophages (54). A pleiotropic regulator, LqsR, is RpoS dependent (132). LqsR-regulated genes are involved in virulence, motility, and cell division, and mutations in *lqsR* result in attenuated growth in macrophages and the protozoan hosts *Acanthamoeba castellanii* and *Dictyostelium discoideum* (132). RpoS may also contribute to blocking phagolysosome formation by preventing the accumulation of LAMP-1, a phagolysomal protein (6). RpoS is crucial for the pore-forming activity of *L. pneumophila* and adaptation to phagosomal intracellular environments during infection (3).

The expression of the *icm* and *dot* genes, encoding the Icm/Dot type IV secretion system in *L. pneumophila*, is required for cytotoxicity and intracellular replication within macrophages and for intracellular growth in the protozoan host *Acanthamoeba castellanii* (152). RpoS only has a minor effect on the expression of the Icm/Dot genes (63, 152). However, many genes encoding Icm/Dot secreted proteins require RpoS for full expression (63).

The potential involvement of RpoS in invasion of cell cultures likely depends on the characteristics of macrophages (6). The intracellular environment is likely more deleterious to bacteria in primary macrophages than that in macrophage-like cells (6). *L. pneumophila* requires RpoS for efficient replication in the protozoan hosts *A. castellanii* (55) and *Acanthamoeba polyphaga* (3) and in murine bone marrow-derived macrophages (6) and human monocyte-derived macrophages (3). However, RpoS is not required for replication in cultured human macrophage-like HL-60 and THP-1-derived cells (55). In murine bone marrow-derived macrophages, most *rpoS* mutants, except for a small subpopulation (~5%), cannot replicate within infected vacuoles during initial infection in the first 48 h (6). However, *rpoS* mutants can grow to wild-type levels after 72 h (6).

Burkholderia pseudomallei, a member of the *Betaproteobacteria*, is the causative agent of melioidosis. *B. pseudomallei* can invade host cells and induce the formation of a multinucleated giant cell (MNGC) by cell fusion (137). *B. pseudomallei* requires RpoS for resistance to stresses including starvation, oxidative stress, and acidic conditions, but not to osmotic shock and heat exposure (129). RpoS is not involved in invasion of cultured human epithelial cells HEp-2 and murine macrophage RAW264.7 (129). However, another study reports that RpoS is important in invasion of RAW264.7 cells but not required for intracellular replication after invasion (137). The reason for this difference is not known. Survival of *rpoS* mutants in gamma interferon (IFN-γ)-activated macrophages is severely impaired in comparison to that of wild-type cells (137). RpoS mutants cannot induce MNGC formation that is important for *B. pseudomallei* to spread to neighboring cells (137).

To summarize, in the respiratory pathogens *L. pneumophila* and *B. pseudomallei*, RpoS-regulated genes are important for survival within the intracellular environment, although this appears to be also dependent on cell lines. In *P. aeruginosa*, the virulence effect of RpoS is not conclusive. RpoS positively regulates expression of extracellular enzymes but negatively affects production of the virulence factor pyocyanin. Whether RpoS controls colonization and virulence needs to be further tested in animal models.

LYME DISEASE SPIROCHETE

Borrelia burgdorferi, the Lyme-disease-causing bacterium, is readily transmitted between arthropod and mammalian hosts. In contrast to proteobacteria, RpoS in *B. burgdorferi* is not important for resistance under most stress conditions, except for hyperosmolarity (36) and low pH (18). RpoS is induced in stationary phase, low pH, and during temperature shift from 23°C to 37°C (18, 146). The induction of RpoS is controlled by RpoN and an associated activator, Rrp2 (16, 64, 125, 147). Two-dimensional gel analysis reveals that RpoS controls the expression of a group of proteins in stationary phase (36). RpoS is essential for virulence of *B. burgdorferi* in mouse models (18). RpoS positively regulates expression of the *ospC* gene (50, 64), encoding an outer surface lipoprotein critical for virulence (120). The expression of RpoS regulon *in vivo* is modulated by mammalian host signals, since transcriptome analysis shows that many genes regulated by RpoS are only expressed *in vivo* within dialysis chambers (19).

INSECT PATHOGENS

Serratia entomophila is a soilborne pathogen that causes amber disease and general septicemia lethal to the grass grub, *Costelytra zealandica* (49). *S. entomophila* appears to have only one catalase, whose expression is RpoS independent (49). Both the wild type and *rpoS* mutants are sensitive to acid conditions (49). RpoS positively regulates the expression of *anfA1*, which codes for an important virulence factor during the development of larval infection (49).

Xenorhabdus nematophilus, a member of the *Gammaproteobacteria*, is mutualistic to *Steinernema carpocapsae* nematodes but pathogenic to many insects (e.g., *Manduca sexta*). RpoS is important for survival upon exposure to H_2O_2 but not to osmotic stress (139). In addition, *rpoS* mutants survive longer than the wild type in long-term batch cultures. The *rpoS* gene is required for colonization in the mutualistic host, *S. carpocapsae* nematodes, but not for virulence in insects (139).

PLANT PATHOGENS

The plant pathogen *Erwinia carotovora* requires RpoS for survival under stresses including starvation, acidic pH, and exposure to H_2O_2 (95). RpoS mutants are more virulent during infection in celery and tobacco but not potato (5, 95). The expression of a virulence factor, Nip (*n*ecrosis-*i*nducing *p*rotein), is enhanced in *rpoS* mutants (89, 95). RpoS also negatively regulates the production of extracellular enzymes, pectate lyase, polygalacturonase, and cellulase, which are important for degradation of plant cell wall during infection (89, 95). This negative regulation is probably mediated through the RpoS-dependent gene *rsmA*, encoding a repressor for extracellular enzymes (95). A competition study shows that *rpoS* mutants cannot outcompete the wild type *in vitro* or *in planta* in tobacco (5).

Burkholderia plantarii is a plant pathogen that can cause rice seedling blight, and its *rpoS* mutants show a severe defect in pathogenesis (126). Since RpoS mutants colonize rice leaves as well as wild-type cells, this virulence defect is likely due to control of virulence traits by RpoS (126). However, these RpoS-regulated virulence traits have not been identified.

Ralstonia (previously *Pseudomonas*) *solanacearum* is a soilborne phytopathogen that can cause lethal vascular wilt disease in plants, with a wide host range (47). Survival of *rpoS* mutants is impaired in acid and starvation but not in heat, oxidative, or high-osmolarity conditions (45). The production of extracellular polysaccharide and activity of endogluconase, two known virulence factors (69, 113), are attenuated in *rpoS* mutants, while the polygalacturonase (PGL) activity is elevated in *rpoS* mutants (45). Tomatoes infected with *rpoS* mutants show delayed wilting of leaves compared with plants infected with wild-type *P. solanacearum*, indicating an attenuation in virulence (45). RpoS is also important for the production of the quorum-sensing autoinducer acylhomoserine lactone (45).

RpoS AS A NICHE-ADAPTATION REGULATOR

Given that RpoS is found in bacteria that occupy very different environments, a natural question arising is "Are there common requirements for gene expression among bacteria that invade different hosts?" Common factors during host adaptation include slow growth as the pathogen adapts to new nutrient sources and possible exposure to host defense mechanisms, including oxidative and acid stress components. These factors are controlled by RpoS regardless of the nature of the host. However, there are also many specific functions that may only be required on an episodic basis for host adaptation and colonization that are not required in other environments. Thus, adhesion factors, extracellular enzymes including lipases, proteases, and sugar-metabolizing functions also may be dependent on RpoS when bacteria are experiencing suboptimal growth conditions. While RpoS is conserved across several genera of the *Proteobacteria*, the species-specific nature of the regulon can vary considerably. RpoS-controlled genes, although important for full virulence in specific cases, are invariably nonessential genes and thus likely do not have to be expressed under conditions in which RpoS itself is at basal levels, as is the case during exponential growth in nutrient-rich environments. As a result, the regulatory environment in which RpoS-controlled genes exist is fairly permissive. It is possible that horizontally transferred genes, which may enhance host adaptation, might easily integrate into the suboptimally expressed regulon controlled by RpoS. Phylogenetic studies examining the evolutionary relationship of RpoS to the broad class of genes that it controls will be necessary to resolve this question.

CONCLUDING REMARKS

Bacterial pathogenesis is a multifaceted process that requires concerted expression of not only specific virulence factors but also genes encoding other cellular functions, including metabolism and adaptation. As a transcription regulator, RpoS can mediate virulence either directly by controlling expression of virulence factors or indirectly by stimulating the general adaptation response to enhance survival of pathogens in hostile host environments. Since expression of RpoS is tightly controlled by environmental signals, including those specific to infection (e.g., intracellular infection of *Salmonella* and *Legionella*), RpoS may be viewed as a transient regulator that allows expression of specific genes to quickly respond to environmental stimuli. The RpoS regulons identified in different bacteria also vary substantially (33, 34, 63, 119, 141). It is possible that, from an evolutionary point of view, RpoS has evolved to modulate temporal expression of specific genes whose expression is only transiently required, such as those genes for host adaptation or genes for adaptation to episodic environmental stresses (e.g., high osmolarity and oxidative stress).

The interaction between a pathogen and its host is complex, having discrete infection stages, including entry, attachment, colonization, and dispersal. Regulators may have roles in one or more of these steps, and each of these must be considered in a complete evaluation of RpoS as a potential virulence factor. In addition, choice of animal models to study regulatory factors may markedly affect the results observed.

Given that RpoS expression and activity are regulated at multiple levels by a number of other regulatory factors (60), expression of genes under the control of RpoS should be considered not as an isolated event but rather a result of complex regulatory interaction between RpoS and other regulators, including H-NS (10), ppGpp (10, 48), and Hfq (94). For instance, H-NS, a nucleoid-associated DNA-binding protein (41, 98), controls the expression of a large number of genes in *Salmonella* (86, 99) and *E. coli* (51, 62, 106). By direct binding to AT-rich regions, H-NS represses expression of virulence genes, including the plasmid-borne *spv* virulence region and all five chromosomal pathogenicity islands in *Salmonella* (41, 99), the LEE pathogenicity island in enteropathogenic *E. coli* (17, 53), and all major virulence regions in uropathogenic *E. coli* (96). Interestingly, H-NS-controlled genes can be derepressed and transcribed by RpoS-associated RNA polymerase (10, 41, 98, 105, 121). Therefore, the episodic functions of RpoS may be required to allow transcription of genes repressed by H-NS or H-NS homologs, such as Ler (134) and StpA (85). In *Salmonella*, a third of StpA-repressed genes are under positive control of RpoS for expression (85). In addition to the functional antirepression relationship, H-NS and StpA also negatively control RpoS translation and stability (10, 85, 145, 151).

Recent insights from genomic expression profiling studies

has expanded our understanding of RpoS from a particular stress regulator to a second vegetative sigma factor that has a much broader physiological function (29, 33, 111, 141). Nevertheless, we still do not know the function of a large number of RpoS-regulated genes, even in the well-studied model organism *E. coli*. In many pathogens known to require RpoS for full virulence, the exact mechanism has not been identified. Characterization of the RpoS regulon in these pathogens may provide valuable insights. The RpoS regulon varies substantially between even closely related pathogens, which may reflect modulation by other regulatory factors. One example of a known factor is the Crl protein, which regulates RpoS activity by direct interaction in both *E. coli* and *Salmonella* (14, 82, 112, 135). How Crl and similar regulatory factors may interact in other RpoS-expressing pathogens has not been examined. Therefore, both genomic and functional approaches are required to advance our understanding of the role that RpoS plays in bacterial pathogenesis and related cellular functions.

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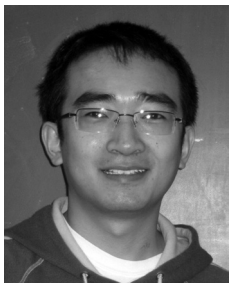

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