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Alternative Sigma Factors and Their Roles in Bacterial Virulence

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INTRODUCTION

Sigma factors are a class of proteins constituting essential dissociable subunits of prokaryotic RNA polymerase. The association of appropriate alternative sigma factors with core RNA polymerase provides a mechanism for cellular responses mediated through redirection of transcription initiation. Sigma factors provide promoter recognition specificity to the polymerase and contribute to DNA strand separation; they then dissociate from RNA polymerase core enzyme following transcription initiation (16). As the regulon of a single sigma factor can be comprised of hundreds of genes, sigma factors provide effective mechanisms for simultaneously regulating large numbers of prokaryotic genes. In some cases, the genes comprising a sigma factor regulon have a clearly defined primary function (e.g., genes regulated by the sporulation sigma factors in *Bacillus subtilis* [171]); in others, the genes comprising a regulon contribute to multiple functions (e.g., the stationary-phase and general stress response genes regulated by σ^B in *Listeria monocytogenes* [100]). One newly emerging field is identification of the specific roles of alternative sigma factors in regulating expression of virulence genes and virulence-associated genes in bacterial pathogens.

Virulence and virulence-associated genes are those that contribute to at least one aspect of bacterial disease transmission and infection processes. Specifically, virulence genes encode proteins whose functions are essential for the bacterium to effectively establish an infection in a host organism. Examples of virulence genes are *L. monocytogenes inlA*, which encodes the internalin-A protein important for invasion of nonprofessional phagocytes (129), and the *spv* gene cluster of *Salmonella enterica*, which allows for bacterial growth inside macrophages (128). In contrast, virulence-associated genes can contribute to bacterial survival in the environment (e.g., the *ica* operon of *Staphylococcus aureus*, which produces an adhesin important for biofilm formation on plastic surfaces such as those on indwelling medical devices [141]) or to survival in the host (such as *bsh* of *L. monocytogenes*, encoding bile salt hydrolase, which enhances bacterial survival in the intestinal environment prior to intracellular infection [48]). Therefore, activation of virulence-associated genes may enhance the capacity of the bacterium to spread to new individuals or to survive passage through a host organism. As alternative sigma factors have been shown to regulate expression of both virulence and viru-

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TABLE 1. Alternative sigma factors involved in virulence

Family, class, and sigma factor[a]	Bacterial species[b]
σ^{70} family	
Stress response	
σ^{B}	*B. anthracis*, *L. monocytogenes*, *M. tuberculosis*, *S. aureus*, *S. epidermidis*
σ^{S}	*E. coli*, *P. aeruginosa*, *S. enterica* serovar Typhimurium, *S. enterica* serovar Typhi
σ^{F}	*M. tuberculosis*
ECF	
RpoE	*H. influenzae*, *S. enterica* serovar Typhimurium, *V. cholerae*
AlgU	*P. aeruginosa*
PvdS, FpvI	*P. aeruginosa*
σ^{C}	*M. tuberculosis*
σ^{D}	*M. tuberculosis*
σ^{E}	*M. tuberculosis*
σ^{H}	*M. tuberculosis*
HrpL	*Erwinia* spp., *P. syringae*
σ^{28}	
FliA	*C. jejuni*, *H. pylori*, *S. enterica* serovar Typhimurium, *V. cholerae*, *Y. enterocolitica*
σ^{54} family	
σ^{N}	*C. jejuni*, *H. pylori*, *L. monocytogenes*, *P. aeruginosa*, *P. syringae*, *V. cholerae*, *V. parahaemolyticus*

[a] Sigma factors are grouped according to classes. The stress response, ECF, and σ^{28} classes are all members of the σ^{70} family of sigma factors.
[b] Species discussed in this review that contain the given sigma factors.

lence-associated genes, these sigma factors can contribute both directly and indirectly to bacterial virulence.

Virulence factor expression appears to be tightly regulated in bacterial pathogens. In some cases, pathogens have a "master regulator" of virulence gene expression, such as the positive regulatory factor A (PrfA) in *L. monocytogenes*. PrfA, a transcriptional activator, is required for expression of the majority of recognized *L. monocytogenes* virulence genes. Alternative sigma factors often function to regulate expression of virulence and virulence-associated genes in response to particular stimuli. Alternative sigma factors may regulate a small number of genes, each of which may be critical to infection (e.g., PvdS of *Pseudomonas aeruginosa* [discussed below] [147]), or they may regulate functions that contribute to virulence but also have additional physiological roles in the cell. For example, *Salmonella enterica* serovar Typhimurium σ^{E} regulates genes that provide resistance to oxidative stress, which also aids bacterial survival in macrophages (82). This review focuses on both direct and indirect roles of selected alternative sigma factors in regulating virulence of bacterial pathogens of plants and animals.

Sigma factors can be classified into two structurally unrelated families: the σ^{70} and the σ^{54} families. Table 1 lists sigma factors in both the σ^{70} and the σ^{54} families that are currently recognized as contributing, either directly or indirectly, to bacterial virulence. For several alternative sigma factors, nomenclature in the literature has been inconsistent. In this document, in general, we refer to sigma factor families by number (e.g., the σ^{54} family) and to specific sigma factors by letter (e.g., *P. aeruginosa* σ^{N}). For certain sigma factors, we use the predominant designation from the literature instead (e.g., FliA).

The σ^{70} family includes primary sigma factors (e.g., *Bacillus subtilis* σ^{A}) as well as related alternative sigma factors (145, 164). Alternative sigma factors within the σ^{70} family are further categorized by the physiological processes they control, e.g., stress response. In general, these groupings by function also correlate with phylogenetic relationships among the protein sequences (164). Within the σ^{70} family of sigma factors is a large, phylogenetically distinct subfamily called the extracytoplasmic function (ECF) factors. These sigma factors are responsible for regulating a wide range of functions, all involved in sensing and reacting to conditions in the membrane, periplasm, or extracellular environment (70). Structurally, σ^{70} family factors have four major regions, with the highest levels of conservation in regions 2 and 4. Subregions within region 2 are involved in promoter melting (region 2.3) and -10 sequence recognition (region 2.4). Region 4.2 is involved in -35 recognition. For a recent review on the σ^{70} family of sigma factors, see reference 164.

Although no sequence conservation exists between σ^{54} and σ^{70}-like family members, both types bind to core RNA polymerase. However, the holoenzyme formed with σ^{54} sigma factors has different properties than the σ^{70} holoenzyme. While the C terminus (region III) of σ^{54} enables DNA binding, all σ^{54} species require a separate activator protein along with the core RNA polymerase (RNAP) to form an open promoter complex. The σ^{54} N terminus, which inhibits isomerization in the absence of the appropriate activator, stimulates initiation upon activation (19). Further, promoter structures recognized by σ^{54}-RNAP differ from those recognized by σ^{70}-RNAP. σ^{54} promoters are highly conserved, short sequences that are located at positions -24 and -12 upstream of the transcription initiation site, whereas σ^{70} promoter sites are typically located at -35 and -10 upstream. σ^{54} promoters, which are called $-24/-12$ promoters, are almost completely invariant at the $-24/-12$ positions (GG and GC, respectively) and in their spacing in both gram-negative and gram-positive bacteria. For reviews on the structure-function relationships of σ^{54}, see references 19 and 142.

We present several examples of alternative sigma factors that have been shown to contribute to virulence in at least one organism. The text is organized by sigma factor to include the three subfamilies (stress response, σ^{28}, and ECF) within the σ^{70} family, as well as those within the σ^{54} family. For each sigma factor, when applicable, examples will be drawn from multiple bacterial species.

STRESS RESPONSE ALTERNATIVE SIGMA FACTORS

The ability to reproduce, or simply survive, under a wide variety of environmental conditions contributes to a microbial pathogen's potential for transmission by various routes. For example, to establish a food-borne infection in a human host, a bacterium first must survive transit in a contaminated food. Following ingestion, the bacterium then must survive exposure to rapid and dramatic changes in environmental conditions, including the acidic pH within the stomach, followed by vastly differing conditions during intestinal passage and/or infection (e.g., exposure to bile, vacuolar stresses, etc.) Survival under these extreme and rapidly changing

TABLE 2. Virulence genes and virulence-associated genes regulated by stress response sigma factors σ^B and σ^S and phenotypes of sigma factor null mutants in selected bacterial species

Sigma factor and species	Genes regulated by sigma factor[a] (reference[s])		Phenotype[b] (reference[s])
	Virulence associated	Virulence	
σ^B			
L. monocytogenes	*bsh* (100, 199, 200), *gadA* (100), *opuCA* (57, 100, 199, 200)	*inlA* (100, 103, 200), *prfA* (101, 151, 191)	Decreased invasion (103), decreased spread to spleen (151)
S. aureus	*cap* genes (14), *clfA* (14), *bbp* (14), *ebpS* (14), *icaA* (177)	*sarA* (13, 14, 44), *arlRS* (14)	No difference (22, 79, 152), caused more severe arthritis, weight loss, interleukin-6 production, and mortality (92)
σ^S			
S. enterica serovar Typhimurium	Unknown chromosomal factors (51, 153)	*spv* (51, 68, 112, 157)	Higher LD_{50} in mice (35, 51, 153)
P. aeruginosa	*rhl* (168, 218), *las* (168, 218)	Exotoxin A (201), alginate (196, 201), type IV pili (196, 201)	Higher LD_{50} in *G. mellonella* and mice (196)

[a] Virulence-associated genes and virulence genes directly regulated by σ^B or σ^S, as defined in the text.
[b] Virulence-related phenotypes observed in *sigB* or *rpoS* null mutants. Relative phenotypes are with respect to the wild type.

conditions requires timely and appropriate alterations in gene expression and protein activity that occur in a bacterial cell in response to stimuli signaling these new environmental conditions. At the transcriptional level, these alterations are often controlled by changes in associations between different alternative sigma factors and core RNA polymerase, which essentially reprogram promoter recognition specificities of the enzyme to allow expression of new sets of target genes.

The general stress-responsive alternative sigma factors σ^S (RpoS) and σ^B transcribe genes contributing to bacterial survival under conditions of environmental stress in gram-negative and in gram-positive bacteria, respectively (Table 2). σ^S was identified in both *Escherichia coli* and *S. enterica* serovar Typhimurium as an alternative sigma factor that activates the expression of numerous genes required to maintain cell viability during stationary phase (51, 119). σ^S also plays a key role in protecting *E. coli* and *S. enterica* serovar Typhimurium from different environmental stress conditions, including starvation, hyperosmolarity, oxidative damage, and reduced pH (51, 119). Since its initial discovery, the presence of σ^S and its role in the stress response has been confirmed in many gram-negative bacterial species, including *P. aeruginosa*, *Borrelia burgdorferi*, and *Vibrio cholerae* (49, 93, 227). Through enhancing environmental survival, as well as by directly activating virulence genes, σ^B and σ^S have both direct and indirect roles in bacterial pathogenesis.

Sigma B

σ^B (initially called σ^{37}) of *Bacillus subtilis* was among the first bacterial alternative sigma factors identified (65, 66). In *B. subtilis* and related species such as *L. monocytogenes* and *S. aureus*, σ^B activity increases in response to numerous environmental stresses, including exposure to acid, ethanol, and heat (12, 22, 53). The σ^B regulon in *B. subtilis* contains at least 127 genes, including those with functions in stress resistance, transcriptional regulation, and membrane transport (169, 174). In *B. subtilis* and *L. monocytogenes*, *sigB*, which encodes σ^B, is the seventh open reading frame in an operon containing eight genes involved in σ^B regulation (*rsbR*, *rsbS*, *rsbT*, *rsbU*, *rsbV*, *rsbW*, *sigB*, and *rsbX*) (Fig. 1A) (54, 223). All eight genes, including *sigB*, are cotranscribed from a housekeeping sigma factor (σ^A)-dependent promoter (P_A) located upstream of *rsbR*. A σ^B-dependent promoter (P_B), located upstream of *rsbV*, is responsible for enhanced transcription of the four downstream genes in the *sigB* operon (*rsbV*, *rsbW*, *sigB*, and *rsbX*) under conditions that stimulate σ^B activity (11, 12, 95).

While regulation of σ^B activity involves both transcriptional and posttranslational control, predominant regulation occurs via the Rsb proteins. Bacterial species differ in the numbers and identities of *rsb* genes carried in their genomes (Fig. 1A), suggesting divergent evolution of the *sigB* operon, both in its overall components and in the sequences of its individual proteins, even among closely related bacterial species (54). We hypothesize that differential evolution of the σ^B stress response system among various genera has enabled different bacteria to optimize cellular response and survival strategies that are appropriate for highly specific niches.

Although all seven Rsb proteins identified in *B. subtilis* and *L. monocytogenes* are not conserved among all bacterial species bearing σ^B, two key proteins (RsbV and RsbW) are conserved among all species examined to date and thus appear to be minimally essential for regulating σ^B activity (54). Specifically, in log phase, nonstressed *B. subtilis* cells, σ^B is inactivated by its association with the anti-σ^B protein, RsbW (i.e., the "anti-sigma factor"). In stressed cells, however, the unphosphorylated form of the anti-σ^B antagonist protein, RsbV, (i.e., the "anti-anti-sigma factor") competes for binding to RsbW. As the relative concentration of the RsbW-RsbV complex increases, the concentration of free σ^B also increases, thus allowing σ^B to bind to core RNA polymerase (47). In *B. subtilis*, both environmental and energy stress signals induce dephosphorylation of RsbV. Environmental stress signals specifically activate the *B. subtilis* RsbU serine phosphatase through involvement of RsbR, RsbS, RsbT, and RsbX (211, 212, 223). In addition to its role in partner-switching regulation under environmental stress, *B. subtilis* RsbX also functions as a feedback regulator for σ^B activity (Fig. 1B) (12). While both energy and environmental stresses have been

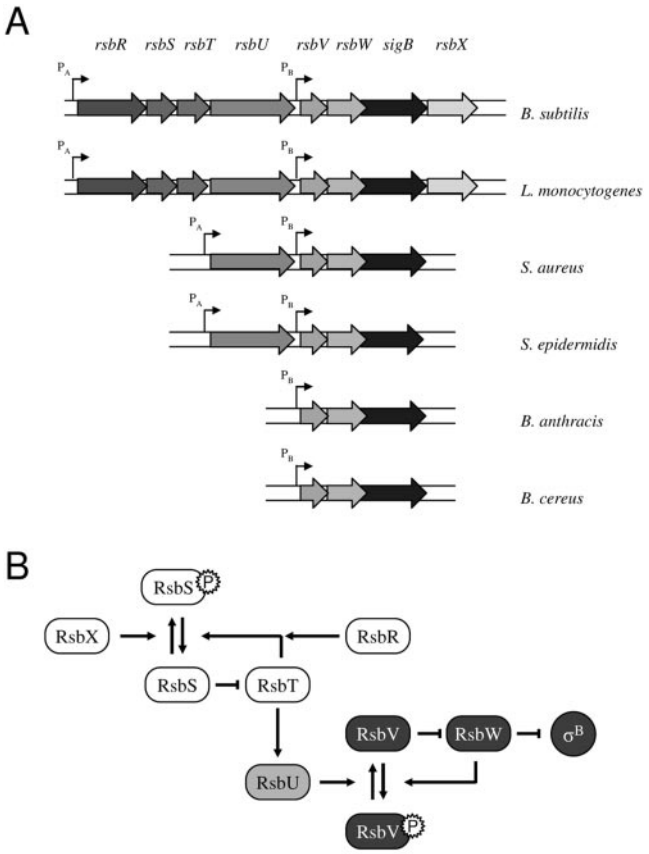

FIG. 1. (A) *sigB* operon structures in various gram-positive bacteria. Promoter sites are marked by arrows. P_A promoters are transcribed with RNAP-σ^A, and P_B promoters are transcribed with RNAP-σ^B. (B) Posttranslational regulation of σ^B activity via a partner-switching mechanism. Proteins shown are encoded by the *B. subtilis* and *L. monocytogenes sigB* operons depicted in panel A. Arrows indicate activation of protein activity, and T-bars indicate repression of protein activity. "P" represents a phosphate group. The proteins indicated by dark gray are encoded in all bacteria listed in panel A, whereas RsbU (light gray) is absent in the pathogenic *Bacillus* spp. and the proteins indicated by white are encoded only in *L. monocytogenes* and *B. subtilis*.

shown to activate *L. monocytogenes* σ^B (25), specific interactions among the Rsb proteins have not yet been investigated. To date, specific activation mechanisms have been most extensively reported for *B. subtilis* σ^B.

Pathogenic *Bacillus* species. At least two pathogenic species of *Bacillus* encode σ^B (55, 208). In *Bacillus anthracis*, only σ^B, RsbV, and RsbW are encoded in the *sigB* operon (Fig. 1A). A third *rsb* gene, *rsbY*, encodes a protein with low similarity to *B. subtilis* RsbP. *rsbY* is located in close proximity to, but not within, the *B. anthracis sigB* operon (55). As in *B. subtilis* and *L. monocytogenes*, the *sigB* operon is autoregulated by σ^B and is induced by heat shock and entry into stationary phase (55). A *B. anthracis sigB* mutant strain is virulence attenuated, producing less than half the mortality of the parent strain in the mouse model of anthrax (55). More-detailed studies are needed to determine if virulence attenuation is due to direct or indirect effects.

The organization of the *Bacillus cereus sigB* operon is identical to that of *B. anthracis sigB*, and likewise, the *sigB* operon is autoregulated by σ^B and is induced by heat shock and entry into stationary phase (208). Through use of a combination of two-dimensional gels and Northern hybridizations, 15 *B. cereus* genes and proteins were determined to be σ^B dependent, including RsbV and the KatE catalase (209). The activity of currently recognized *B. cereus* virulence factors, including protease, lecithinase, and hemolytic activity, as well as production of nonhemolytic enterotoxin, was not affected by disruption of *sigB* (208), suggesting that σ^B does not directly contribute to *B. cereus* virulence.

***Staphylococcus* species.** *Staphylococcus aureus* was the first pathogenic bacterium in which *sigB* was identified. (115, 224) (Fig. 1A). In *S. aureus*, the *sigB* operon is comprised of four genes, which are homologous to *B. subtilis rsbU*, *rsbV*, *rsbW*, and *sigB*. As in *B. subtilis*, all genes in the operon are expressed during exponential growth, presumably from the σ^A-dependent promoter. The internal P_B promoter was confirmed as σ^B dependent through in vitro transcription analyses (44). Transcriptional regulation of the *S. aureus sigB* operon is complex, generating multiple transcripts that appear to include a bicistronic *sigB-rsbW* transcript as well as a *sigB* monocistronic transcript. In support of an autoregulatory role for *S. aureus* σ^B under conditions of environmental stress, an *rsbV-W-sigB* transcript was induced following exposure of cells to either 4% ethanol or a 48°C heat shock (115).

S. aureus σ^B activity is regulated posttranslationally by Rsb proteins. The open reading frame immediately upstream of *S. aureus sigB* encodes the anti-sigma factor, RsbW (146). As in *B. subtilis*, *S. aureus* σ^B also is activated via an RsbU pathway (62). An 11-bp deletion in *rsbU* in the NCTC8325 strain generated some phenotypic characteristics similar to those of a Δ*sigB* strain, (e.g., decreased H_2O_2 resistance [114]). Giachino et al. (62) confirmed that NCTC8325 does not produce a functional RsbU and that complementation of this strain with a complete *rsbU* allele restored phenotypes to those of the *rsbU*$^+$ Newman wild-type strain. However, some NCTC8325 phenotypes were identical to those of other *rsbU*$^+$ strains (e.g., lipase production [see below]), suggesting the existence of multiple *S. aureus* σ^B activation pathways, including at least one that is RsbU independent (114). As with RsbU, loss of RsbV results in a dramatic decrease, although not complete loss, of *S. aureus* σ^B activity (165).

Through application of full-genome microarray screens for σ^B-dependent genes in three *S. aureus* strains, as many as 251 genes have been identified as being σ^B regulated (14), including several genes encoding proteins involved in synthesis of capsular polysaccharides. A number of adhesins, which are involved in *Staphylococcus* virulence, are upregulated by σ^B. Multiple genes encoding exoenzymes and toxins (e.g., *hla* and *nuc*) are downregulated as σ^B is activated (14), which may reflect σ^B's role in controlling expression of *S. aureus* virulence gene regulators. For example, a number of the exoenzymes and toxins that are downregulated by σ^B depend on an effector RNA produced from the *agr* locus (RNAIII) for heightened expression (204). RNAIII levels are reduced when σ^B activity increases. The mechanism responsible for this phenomenon remains unclear (13, 14) but may involve the regulator SarA (8, 44, 79).

Multiple groups have described *S. aureus* Δ*sigB* mutants as having pigment loss and decreased peroxide resistance, but

higher α-hemolysin, coagulase, clumping factor, and lipase activity, compared to the wild type (27, 62, 79, 114, 152). These characteristics have all been associated with *S. aureus* virulence (61, 67, 98, 131, 150, 184). It is likely that optimal levels of virulence factor expression and activity are required for efficient *S. aureus* infection and that too much or too little activity or expression at the wrong time is detrimental for the infection process. These hypotheses remain to be rigorously tested. In various animal models, wild-type *S. aureus* and an otherwise isogenic Δ*sigB* strain showed no difference in virulence (22, 152). In additional, conflicting studies, Horsburgh et al. (79) found no difference in virulence between *rsbU*$^+$ and *rsbU* mutant strains in a murine skin abscess model, while Jonsson et al. (92) showed that both *rsbU* and *sigB* mutant strains displayed decreased virulence phenotypes compared to the wild-type strain in murine septic arthritis, including reduced mutant persistence in kidneys and reduced mouse mortality, weight loss, arthritis, and interleukin-6 production.

The contradictory evidence surrounding the role of σ^B in *S. aureus* virulence suggests that σ^B contributions to virulence may be indirect or not detectable in some model systems. For example, σ^B may contribute indirectly to *S. aureus* virulence through regulation of biofilm formation. Biofilm formation can be a prerequisite for establishing infection by staphylococci, and σ^B has been shown to enhance microcolony and biofilm formation in *Staphylococcus* species (5, 177). Two studies have shown induction of *S. aureus* biofilm formation in a σ^B-dependent fashion (5, 177), although another showed that a Δ*sigB* strain formed biofilms and produced PIA, the polysaccharide adhesin encoded by the *ica* operon, equally as well as the wild type (207). *S. aureus* σ^B contributions to biofilm formation likely occur through σ^B-dependent transcription of the *ica* operon, which encodes essential elements of biofilm biosynthesis (177).

Staphylococcus epidermidis also encodes σ^B. The *sigB* operon of *S. epidermidis* is similar to that of *S. aureus* (Fig. 1A); however, σ^B serves different functions in the two species. Processing of lipase, a virulence factor, is dependent on σ^B in *S. epidermidis* (102), while in *S. aureus*, lipase production is higher in a *sigB* mutant than in the wild-type strain (114). Multiple studies of σ^B and *S. epidermidis* virulence suggest that σ^B's effects are mediated primarily through its influence on biofilm formation in this organism (33, 106, 107). Stress induction of σ^B in *S. epidermidis* increases biofilm formation and synthesis of the adhesin PIA, but an *rsbU* mutant does not form biofilms or produce PIA (106). As in *S. aureus*, *S. epidermidis* σ^B contributes to biofilm formation via regulating expression of *ica* genes. By downregulating the *icaR* repressor, active σ^B causes an increase in *icaA* expression and a biofilm-positive phenotype (107).

***Listeria monocytogenes*.** σ^B has also been extensively studied in the gram-positive pathogen *Listeria monocytogenes*. While the *sigB* operon structures are identical in *L. monocytogenes* and in *B. subtilis* (11, 219) (Fig. 1A), signal transduction pathways differ in the two organisms. In *B. subtilis*, environmental and energy stresses are conveyed to σ^B through two interconnected but separate pathways. The environmental stimulus pathway is transmitted by regulatory proteins encoded in the *sigB* operon (RsbT, RsbU, RsbV, and RsbW). In addition to requiring RsbV and RsbW, the *B. subtilis* energy stress pathway also requires proteins encoded in a two-gene operon (*rsbQ-rsbP*) that is physically separate from the *sigB* operon (18). This operon is not present in *L. monocytogenes.* Instead, both energy stress and environmental stress activation of σ^B in *L. monocytogenes* occurs through a single pathway, which includes RsbT, RsbU, RsbV, and RsbW (25).

A genome-wide search for predicted σ^B-dependent promoters by using a hidden Markov model followed by application of a specialized, partial microarray identified 54 genes under positive control of σ^B in *L. monocytogenes*, although the full regulon is likely to be as large as that of *B. subtilis* (100). σ^B regulates expression of virulence and virulence-associated genes in *L. monocytogenes* (Fig. 2A; Table 2). *bsh* encodes a bile salt hydrolase that is important for virulence of *L. monocytogenes* (48) and is directly regulated by σ^B (100, 199). Another recently identified σ^B-dependent virulence-associated gene is *hfq*, which encodes an RNA-binding regulatory protein (29). Deletion of the σ^B-dependent *opuC* (57), which encodes an osmotransporter, also negatively affects *L. monocytogenes* virulence (194, 217).

As in *S. aureus*, *L. monocytogenes* σ^B also controls expression of virulence gene regulators (Fig. 2A). Of the two promoters directly upstream of the gene encoding positive regulatory factor A (PrfA), $P2_{prfA}$ is σ^B dependent. Dual deletion of *sigB* and the σ^A-dependent $P1_{prfA}$ promoter (leaving only the σ^B-dependent $P2_{prfA}$) reduced hemolytic activity and intracellular growth to the same low levels as deletion of both *prfA* promoters (151). σ^B activity at the $P2_{prfA}$ promoter was also directly confirmed, both by quantitative reverse transcription-PCR (101) and with β-glucuronidase reporter fusions of *prfA* promoters, which demonstrated σ^B- and growth phase-dependent expression from $P2_{prfA}$ (191).

Several PrfA-regulated genes are also σ^B dependent, suggesting interplay between the two regulators (143) (Fig. 2A). For example, expression of the PrfA-regulated *inlA* gene, which encodes the cell surface protein internalin-A, is also at least partially σ^B dependent (100, 200). Internalins are cell wall-anchored proteins with important roles in the intracellular pathogenesis of *L. monocytogenes*, and several members of the internalin gene family show reduced expression in a *sigB* mutant compared to in the wild type (100). Internalin-A, specifically, is responsible for invasion of nonprofessional phagocytes (129). Loss of σ^B reduced invasiveness of the mutant strain compared to that of wild-type *L. monocytogenes* in two intestinal epithelial cell lines, Henle-407 and Caco-2 (103). In addition, *inlA* transcription was greatly reduced in the Δ*sigB* strain, and internalin-A was undetectable by Western blotting (103). None of the effects of the *sigB* deletion on *inlA* were mediated through loss of σ^B-dependent transcription of PrfA, however, as a $\Delta P2_{prfA}$ strain had the same levels of invasiveness, *inlA* transcription, and internalin-A concentration as the wild-type strain.

Wiedmann et al. (219) tested the effect of a *sigB* deletion on virulence in a mouse model and found a small, but significant, decrease in spread of the mutant strain to the liver compared with that of the wild-type strain. Mouse infection experiments have been widely used to evaluate virulence characteristics of *L. monocytogenes*, including the preliminary evaluations of the Δ*sigB* mutant (151, 219). In recent years, however, increasing evidence suggests that the murine model does not appropri-

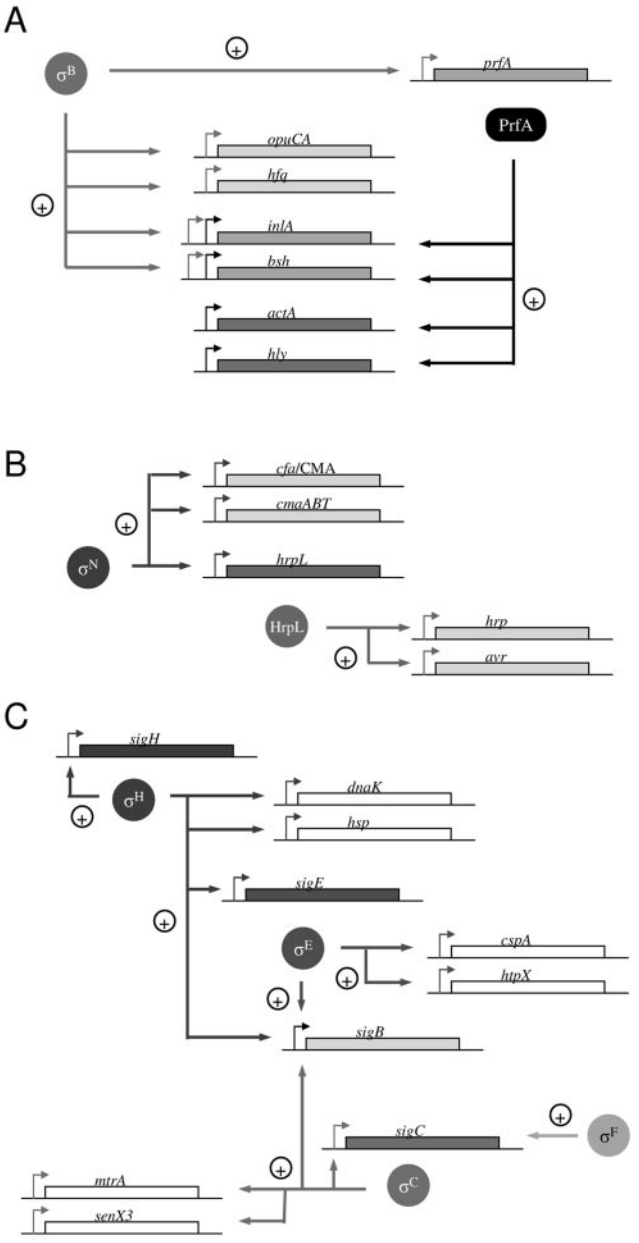

FIG. 2. Examples of regulatory networks involving sigma factors and other transcriptional regulators or multiple sigma factors. (A) The σ^B-PrfA network of *L. monocytogenes*. Some genes are activated solely by σ^B (e.g., *hfq* and *opuCA*), some solely by PrfA (e.g., *actA* and *hly*), and some by both factors (e.g., *inlA* and *bsh*). (B) The short sigma factor cascade regulating type III secretion in *P. syringae*. σ^N mediates transcription of *hrpL*, which encodes a sigma factor responsible for transcription of the *hrp* and *avr* genes of the type II secretion system, as well as other virulence genes. All transcription depicted in panels A and B is the result of direct activity by the sigma factor or regulator at the promoter sites. (C) The complex interaction of several sigma factors that affect virulence in *M. tuberculosis*. Multiple sigma factors activate expression of other sigma factors and of virulence-associated genes (white). The interactions depicted here were deduced from global expression profiles and may be the result of either direct or indirect regulation by the sigma factor(s).

ately represent human *L. monocytogenes* infection by the oral route (121, 122). The gastric pH of mice is higher than the pH of the human stomach (97); thus, the role of *L. monocytogenes* acid tolerance is likely to be less important in mouse infection than in human infection. More importantly, in the human, *L. monocytogenes* has the ability to cross the intestinal barrier, the blood-brain barrier, and the fetoplacental barrier. Human E-cadherin acts as an *L. monocytogenes* internalin-A receptor, and the interaction between the receptor and the internalin-A surface protein contributes to the ability of *L. monocytogenes* to target and cross human intestinal and placental barriers (123). Murine E-cadherin, which differs in amino acid sequence from human E-cadherin, does not interact effectively with *L. monocytogenes* internalin-A, and hence mice show limited susceptibility to intragastric *L. monocytogenes* infection (121). In fact, in the mouse, translocation of *L. monocytogenes* across the intestinal barrier is typically no greater than that of the nonpathogenic *Listeria innocua*. Further, *L. monocytogenes* also does not appear to target the murine brain stem or the fetoplacental unit, even following intravenous injection (121, 122). *L. monocytogenes* strains do vary in their ability to cause systemic infection in intragastrically infected mice (38), and some strains of mice (A/J) are also more susceptible than others (C57BL/6) to intragastric infection (39). However, as a consequence of the biological differences in murine and human *L. monocytogenes* translocation across the intestinal barrier, data from mouse infection experiments may underestimate a given strain's human virulence following oral infection.

The guinea pig has emerged as a more appropriate model than the mouse for studying oral *L. monocytogenes* infection (121, 122). Like humans, guinea pigs exhibit gastroenteritis following *L. monocytogenes* infection by the oral route (122). Cultured guinea pig epithelial cells allow internalin-A-dependent *L. monocytogenes* entry, and both guinea pig and human E-cadherins bear a proline at critical amino acid position 16. When guinea pigs were inoculated orally with *L. monocytogenes* strain EGD or an otherwise isogenic Δ*inlA* strain, significantly higher numbers of the wild type than of the Δ*inlA* strain were recovered from guinea pig liver and spleen. In contrast, in the mouse model, low, statistically indistinguishable wild-type and Δ*inlA* numbers were recovered from mouse organs (121). Lecuit et al. (121) also demonstrated that transgenic mice expressing human E-cadherin enable bacterial invasion of host cells. Taken together, these results illustrate the importance of appropriate internalin-A/E-cadherin interactions in the development of systemic listeriosis following oral infection with *L. monocytogenes*.

***Mycobacterium tuberculosis* σ^B and σ^F.** *Mycobacterium tuberculosis*, a high-GC-content bacterium, has 13 sigma factors (for a review, see reference 137). Two of these 13, σ^B and σ^F, appear to share an evolutionary origin (54). *M. tuberculosis* σ^F appears more similar to σ^B of the low-GC gram-positive bacteria than to σ^F of *B. subtilis*, which is a sporulation factor. Specifically, *M. tuberculosis* σ^F is antigenically closer to *B. subtilis* σ^B (43) and has the same consensus promoter recognition sequence (10, 60), and expression patterns for its encoding gene are similar to those of *B. subtilis sigB* (42, 133). As with *B. subtilis* σ^B, *M. tuberculosis* σ^F is regulated posttranslationally by an anti-sigma factor and anti-anti-sigma factor partner-switching mechanism (10). The gene encoding *M. tuberculosis* σ^F is immediately

TABLE 3. Genes regulated by mycobacterial alternative sigma factors and phenotypes of sigma factor null mutants

Sigma factor	Genes regulated by sigma factor (reference[s])		Phenotype[b] (reference[s])
	Virulence[a]	Regulatory	
σ^C	*hspX*, *mtrA*, *senX3* (202)	*sigB* (202)	Nonlethal (202)
σ^D	None identified	Rv1816 (possible *tetR* family transcriptional regulator) (179)	Delayed time to death (20, 179), decreased lung tissue damage and granuloma formation (179)
σ^E	*sodA*, *hsp*, *htpX* (134)	*sigB*, *cspA*, Rv0287 (possible transcriptional regulator) (134)	Decreased survival in macrophages (134), delayed time to death (2, 136)
σ^F	*ahpC* (60)	*sigC* (60)	Delayed time to death (26), decreased numbers in lungs, milder histopathology (60)
σ^H	MT1516-7, MT4032-3, MT0838 (possible thioredoxins) (99); MT2541, MT2063 (possible oxidative stress response) (99); MT0265, *dnaK* (99); *hsp*, *clpB* (135)	MT3938 (possible *tetR* family regulator) (99), *sigE* (99, 135), *sigB* (99, 135), Rv0142 (possible transcriptional regulator) (135)	Nonlethal (99)

[a] Includes virulence-associated genes and virulence genes directly or indirectly regulated by the respective sigma factors, as defined in the text.
[b] Virulence-related phenotypes observed in the respective sigma factor null mutants. Relative phenotypes are with respect to the wild type. All animal infections were done in mice.

downstream of the gene encoding its anti-sigma factor, UsfX, as is the case with *B. subtilis* σ^B and its anti-sigma factor, RsbW. *M. tuberculosis sigB*, on the other hand, is located 3 kb downstream of the gene for the primary sigma factor, σ^A, and is not flanked by genes encoding sigma factor regulatory proteins (45). The *sigB* genes in *M. tuberculosis* and in *L. monocytogenes* also share some characteristics. For example, expression of *M. tuberculosis sigB* is growth phase dependent, as is expression of *sigB* in other species (42, 80). The same studies also showed that *sigB* transcription is induced under a variety of stresses, including peroxide stress, heat shock, and cold shock. In spite of these observations on σ^B stress induction, no studies on contributions of this protein to either *M. tuberculosis* stress resistance or virulence have been reported.

Microarray analysis of the *M. tuberculosis* σ^F regulon identified *ahpC*, a gene implicated in virulence, as greatly reduced in expression in a Δ*sigF* mutant (60). In addition, another sigma factor, *sigC*, which is required for *M. tuberculosis* lethality in mice (202), is also σ^F dependent (Table 3). Several studies have linked *M. tuberculosis* σ^F with virulence. Mice infected with a Δ*sigF* strain displayed a longer time to death than mice infected with the wild-type strain, and the weight loss caused by wild-type *M. tuberculosis* did not occur in mice infected with the mutant strain (26). In a separate study, CFU counts recovered from the lungs and spleens of infected mice were approximately 40 times higher for the wild type than for the Δ*sigF* strain. Histopathological analyses showed that the Δ*sigF* mutant caused fewer, smaller granulomas and less inflammation than the wild type (60) after 12 weeks. In summary, multiple lines of evidence support direct and indirect roles for σ^F in *M. tuberculosis* virulence.

Sigma S (RpoS)

In gram-negative bacteria, RpoS (σ^S) is functionally similar to σ^B in that it is responsible for stationary-phase and stress response gene expression. The chromosomal organizations of the *rpoS* and *sigB* loci, as well as the transcriptional and posttranscriptional regulatory mechanisms for these genes and proteins, are distinctly different, however. Regulation of σ^S expression and activity is extremely complex, relying on transcriptional, translational, and posttranslational mechanisms (for a thorough review, see reference 75). Further, a sequence comparison of 31 σ^{70} family sigma factors groups *Escherichia coli* σ^S separately from *B. subtilis* σ^B, indicating that while σ^B and σ^S may have similar functions, they are not highly homologous proteins (132).

***Escherichia coli*.** A few reports have examined associations between σ^S and *E. coli* virulence, but little direct evidence of a link exists. Wang and Kim (214) demonstrated that *E. coli* K1 invasion of brain microvascular endothelial cells was higher for stationary-phase cells than for exponentially growing cells, possibly due to stationary-phase activity of σ^S. Indeed, complementation of *rpoS* into an *rpoS* mutant significantly increased invasion for one *E. coli* isolate but not for another (214). σ^S is not essential for murine urinary tract colonization (37) and actually appeared to be detrimental during competitive colonization experiments in the mouse intestine (113). It is also possible that the lack of an appropriate animal model for investigating all aspects of *E. coli* pathogenesis (e.g., the absence of an appropriate model for studying hemolytic uremic syndrome infections caused by enterohemorrhagic *E. coli* [193]) has impeded identification of a direct role for σ^S in *E. coli* pathogenesis.

It is likely that σ^S contributes indirectly to *E. coli* pathogenesis. *E. coli* O161:H7 strains tend to be acid resistant, and *rpoS* mutants show decreased acid resistance and fecal shedding in mice and cattle (175). Several studies have shown that *rpoS* transcription and σ^S activity are induced under stress conditions such as osmotic shock, heat, and low pH and that survival of *rpoS* mutants is reduced under these same conditions (3, 37, 59, 74, 215). Thus, in addition to enabling survival in high-acid

and high-salt foods, σ^S may enhance *E. coli* host survival and transmission.

***Salmonella* species.** *S. enterica* serovar Typhimurium σ^S is highly similar to *E. coli* σ^S, in both function and regulation. In contrast with *E. coli*, however, numerous studies have shown the unequivocal dependence on σ^S for full virulence of *S. enterica* serovar Typhimurium. For example, the plasmid-borne *spv* gene cluster is required for *S. enterica* serovar Typhimurium virulence, and several studies have demonstrated that transcription of this gene cluster is σ^S dependent (51, 68, 112, 157) (Table 2). In fact, an *rpoS* mutant is up to 10-fold less virulent than an *rpoS*$^+$, plasmid cured (*spv*-negative) strain, and the levels of plasmid-cured *rpoS*$^+$ bacteria in the intestine were significantly higher than those of plasmid-cured *rpoS* mutants (51, 153), indicating that the effect of σ^S on virulence is likely due to its role in regulating expression of chromosomal genes in addition to its effects on the plasmid-borne *spv* locus. In addition, mouse-based virulence assays show that in comparison to the wild-type strain, the *rpoS* mutant has a 3- to 4.5-log-unit higher 50% lethal dose (LD_{50}) (35, 51, 153). Similarly, an *rpoS aroA* strain was more virulence attenuated than an *aroA* strain, which has been used in vaccine candidate trials, as determined by spleen bacterial counts and time-to-death analyses (35). σ^S does not contribute to levels of *S. enterica* serovar Typhimurium adherence, invasion, or intracellular survival, however (153).

Further evidence for the role of σ^S in *Salmonella* virulence was obtained through analysis of *rpoS* alleles from recognized avirulent or virulence-attenuated strains. For example, the *Salmonella enterica* serovar Typhi vaccine strain Ty21a contains an *rpoS* sequence that generates a nonfunctional σ^S (181). Virulence attenuation in the *Salmonella enterica* serovar Typhimurium LT2 strain may be a consequence of low levels of *rpoS* mRNA translation due to the presence of a rare UUG start codon on the transcript (124, 203). As in laboratory-generated *rpoS* mutants, the LT2 strain is greatly decreased in its ability to reach the spleen and liver of mice (221).

***Pseudomonas aeruginosa*.** *P. aeruginosa* produces many exotoxins that contribute to its pathogenesis. σ^S appears to have multiple regulatory roles in *P. aeruginosa*. In some cases, σ^S positively regulates *P. aeruginosa* toxin expression; in others, it negatively regulates expression; and in still others, it appears to have no effect at all. For example, in an *rpoS* mutant, both exotoxin A and alginate production are approximately 50% of that of the wild type (196, 201) (Table 2). However, both reduced *rpoS* expression (109) and loss of σ^S (196, 201) resulted in increased expression of pyocyanin, an antibiotic that also inhibits lymphocyte proliferation. In two studies, loss of σ^S was shown to have little to no effect on production of elastase or LasA protease (196, 201). Some of the phenotypic effects on *P. aeruginosa* virulence factor production that are associated with loss of σ^S may be indirect, for example, resulting from reduced expression of quorum-sensing systems (Table 2). σ^S contributes to expression of members of the *P. aeruginosa rhl* and *las* quorum-sensing systems (168, 218). These quorum-sensing gene products are responsible for regulating production of several virulence factors, including lectins (190, 222); aminopeptidase, endoproteinase, and lipase (158); and rhamnolipid (166, 232). Several studies have shown quorum-sensing mutants to be avirulent or less virulent than the wild-type strain in mouse (167, 185, 195, 232), amoeba (34), and rat models (126). Finally, the role of σ^S in *P. aeruginosa* virulence is highly dependent on the model system in which it is assessed. For example, while an *rpoS* mutant was as virulent as the wild type in a rat chronic lung model (201), it was approximately half as virulent as the wild-type strain in a *Galleria mellonella* (silk moth) larva model (196).

SIGMA 28 SUBFAMILY

σ^{28} is a subfamily of the σ^{70}-like sigma factors. Members of this subfamily are structurally and functionally related and span many genera of both gram-positive and gram-negative bacteria. While the primary regulatory role of σ^{28} in many bacterial species is to transcribe genes required for flagellar synthesis and bacterial motility (69, 144), it also contributes to other functions. For example, in the nonmotile *Streptomyces coelicolor*, σ^{28} contributes to expression of a diverse set of genes, including those responsible for sporulation and agarase production (96). Examples of σ^{28} factors are FliA of enteric bacteria and σ^D of *B. subtilis*.

FliA

***Salmonella enterica* serovar Typhimurium.** As in many enteric bacteria, the genes for flagellar biosynthesis and function in *S. enterica* serovar Typhimurium are divided into three hierarchical classes based on their temporal order of transcription (116). One operon, *flhDC*, is categorized into class I. The *flhDC* operon encodes activators required for transcription of the class II operons, including *fliA*, which encodes the σ^{28} subfamily sigma factor responsible for expression of the class III genes (84, 161), and *flgM*, which encodes the FlgM anti-sigma factor that regulates activity of FliA (63, 162). The remaining class II genes encode proteins responsible for formation of the flagellar basal body and hook apparatus. Through an additional posttranslational regulatory mechanism, following formation of the flagellar structure, FlgM is secreted through the basal body/hook assembly, which enables derepression of FliA and allows subsequent transcription of the class III genes (81, 117). Inactivation of any of the class II genes interrupts complete formation of the flagellum, and the accumulated FlgM prevents further flagellar filament formation. Loss of FlgM results in an approximately sixfold increase in transcription of the FliA-dependent class III genes (118). Interestingly, while *flgM* mutants are virulence attenuated, an additional mutation that inactivates FliA function restores virulence to the strain (187). The mechanism for this phenomenon is still unknown. Many studies have shown the importance of flagella for virulence of *S. enterica* serovars (87, 182, 188, 197), although the specific aspect of flagellar function that contributes to virulence remains unclear.

Other species. Regulation of flagellar gene expression in *Yersinia enterocolitica* is similar to that in *S. enterica* serovar Typhimurium. *fliA* encodes a σ^{28} factor responsible for motility of the bacterium, and the master regulators FlhC and FlhD are required for expression of all genes encoding proteins active in subsequent flagellar synthesis (85). Motility is also required for full *Y. enterocolitica* invasion efficiency (228). However, another group of enteric bacteria has a different strategy for regulating

flagellar gene expression. *Helicobacter pylori*, *Campylobacter jejuni*, and *Vibrio cholerae* do not have the *flhDC* master operon. Instead, early flagellar gene expression is carried out via a σ^{54} factor, while later genes are transcribed by FliA (89, 105, 154). These species also encode one or more σ^{54} activator proteins, such as FlgR. Virulence in these species is linked to production of flagella. In *C. jejuni*, virulence proteins are secreted through the flagella, and full virulence requires a complete flagellar export apparatus (110). Multiple studies have shown *H. pylori* virulence to be dependent both on expression of flagellin proteins and on flagellar motility (94, 140).

ECF SIGMA FACTORS

Members of the extracytoplasmic function subfamily of σ^{70} sigma factors regulate functions related to sensing and responding to changes in the bacterial periplasm and extracellular environment. These sigma factors are conserved in both gram-positive and gram-negative species. The first ECF sigma factor identified was *E. coli* σ^{E}, which was recognized as a second heat shock sigma factor in this organism (213). Although σ^{E} does not appear to affect virulence in *E. coli*, other ECF sigma factors contribute to regulation of virulence genes and virulence-associated genes in a number of bacteria, including *S. enterica* serovar Typhimurium, *Pseudomonas aeruginosa*, and *Mycobacterium tuberculosis*. A recent review covers some aspects of ECF sigma factors and their involvement in pathogenesis (4).

Sigma E (RpoE)

rpoE contributes to oxidative stress resistance in *S. enterica* serovar Typhimurium. To illustrate, inactivation of *rpoE* diminishes bacterial survival and growth inside host macrophages (21, 82). Further, while an *rpoE* mutant is severely attenuated in virulence in a mouse model of infection (82, 205), an *rpoE* mutant strain appears to be fully virulent in gp91*phox*$^{-/-}$ mice, which are defective in phagocyte oxidative burst (205). Expression of *htrA*, a gene required for oxidative stress resistance, macrophage survival, and *S. enterica* serovar Typhimurium virulence (7, 23, 91), is dependent on σ^{E} (50, 130). However, the survival and virulence defects in *rpoE* mutants are not entirely due to loss of *htrA* expression, because the attenuated virulence phenotype of an *htrA* mutant is less severe than that of the *rpoE* mutant (82).

σ^{E} also appears to contribute to oxidative stress resistance in other gram-negative pathogens. In *Haemophilus influenzae*, *rpoE* expression was discovered to increase 102-fold inside macrophages, and survival of an *rpoE* mutant was reduced relative to that of the wild type in the macrophage (36). *Vibrio cholerae rpoE* mutants are virulence attenuated, exhibiting a reduced ability to colonize the mouse intestine and an LD_{50} that is 3 log units higher than that of the wild type (111). Although σ^{E} is not essential for growth in *H. influenzae* or *V. cholerae*, interestingly, it is essential for growth in *Yersinia enterocolitica* (76). σ^{E} in *Y. enterocolitica* also appears to regulate *htrA*, which is important for virulence in this bacterium as well (77, 127).

AlgU of *P. aeruginosa* (also called AlgT) is homologous and functionally equivalent to σ^{E} of *E. coli* (139, 229). As in the pathogens mentioned above, *P. aeruginosa algU* mutants have increased sensitivity to oxidative stress (139) and reduced survival in macrophages and neutrophils (230). Additionally, AlgU regulates biosynthesis of alginate, a major virulence factor in *P. aeruginosa* infections of cystic fibrosis patients. Expression of the major alginate biosynthesis gene *algD* and production of alginate are dependent on *algU* (138, 189). Thus, while regulation of oxidative stress resistance is functionally conserved between *P. aeruginosa* AlgU and σ^{E} in multiple bacterial species, AlgU also has an additional role in *P. aeruginosa* virulence through the regulation of alginate production.

PvdS and FpvI

In *P. aeruginosa*, secretion of the siderophore pyoverdine, a virulence factor, is required for in vivo growth and virulence. Pyoverdine is released when cells experience iron-limiting conditions, which is common during host infection. Pyoverdine enables *P. aeruginosa* to sequester iron from the environment. The secreted pyoverdine chelates extracellular iron, and the resulting ferri-pyoverdine complex is transported back into the bacterial cell (210), as described below.

The genes involved in pyoverdine synthesis are located in three clusters on the *P. aeruginosa* chromosome, with the major genes comprising the *pvd* locus. Among these genes is *pvdS*, which encodes an alternative sigma factor. PvdS appears to be predominantly responsible for regulating genes in the *pvd* locus as well as other pyoverdine synthesis genes (147, 160, 198). The binding of iron by pyoverdine, which occurs outside of the cell, initiates a signaling cascade that leads to enhanced expression of *pvd* genes and additional secretion of pyoverdine and other virulence factors. Upon forming a complex with iron, pyoverdine binds to the FpvA cell surface receptor protein. FpvA is responsible for transporting the pyoverdine into the cell, but it also triggers a signal cascade to the membrane-bound anti-sigma factor, FpvR, which releases PvdS and allows it to transcribe the *pvd* genes. FpvR also controls the activity of another sigma factor, FpvI (9). The signal from bound pyoverdine also results in release (and hence activation) of this factor, which is responsible for expression of *fpvA*.

In addition to increasing pyoverdine synthesis and secretion, free PvdS also activates transcription of genes encoding two more virulence factors, those encoding exotoxin A and PrpL endoprotease. Expression of genes responsible for pyoverdine, exotoxin A, and PrpL production is also controlled by the regulator PtxR; expression of *ptxR* is also controlled by PvdS. A *pvdS* deletion mutant generates less PrpL (220) and only 5% of the exotoxin A produced by a wild-type strain (159).

Loss of PvdS results in decreased *P. aeruginosa* virulence in a rabbit aortic endocarditis model (226). The PrpL endoprotease contributes to the ability of *P. aeruginosa* to persist in a rat chronic pulmonary infection model (220). PvdS is required for virulence and appears to regulate only virulence-related genes.

Mycobacterial ECF Sigma Factors

Mycobacterium tuberculosis has 13 recognized sigma factors; among these, 10 are ECF sigma factors. At least six *M. tuberculosis* sigma factors affect virulence, including the primary sigma factor (31), σ^{F}, and four ECF sigma factors, σ^{C}, σ^{D}, σ^{E},

and σ^H (Table 3). The regulons of many of these sigma factors (σ^C, σ^D, σ^E, σ^F, and σ^H) have been identified through application of *M. tuberculosis* genome arrays (20, 60, 99, 134, 135, 179, 202). *M. tuberculosis* ECF sigma factors do not appear to control many currently characterized virulence genes. For example, σ^D does not appear to directly regulate any virulence-associated genes (20, 179), although it does control the putative transcriptional regulator Rv1856. It is possible that this putative regulator is responsible for direct control of virulence gene expression, but no evidence currently exists to support this hypothesis (179). σ^C, σ^E, and σ^H each control a relatively small number of virulence or virulence-associated genes, as well as some regulatory genes that may influence expression of other virulence genes. Several other ECF sigma factors also regulate a number of known or putative regulatory genes (Table 3). Interestingly, in some cases, this group of sigma factors contributes to regulation of other sigma factors within the group. For example, *sigB* expression is affected by σ^C, σ^E, and σ^H (99, 134, 135, 202). σ^C activates expression of *hspX*, *mtrA*, and *senX3* (202), three genes shown to be required for virulence. *mtrA* and *senX3* are examples of two-component system response regulators. Other virulence-associated genes regulated by *M. tuberculosis* ECF sigma factors include genes for heat shock proteins and oxidative stress response proteins. For example, the heat shock genes *hsp* and *htpX* are σ^E dependent (134), and *hsp*, *dnaK*, and *clpB* are regulated by σ^H (99, 135). A number of putative thioredoxins and other oxidative stress genes are controlled by σ^H (99) (Table 3), and *sodA*, encoding the superoxide dismutase, is regulated by σ^E (134). The contributions of these ECF sigma factors to expression of oxidative stress resistance genes may explain reduced survival of the respective null mutant strains under oxidative stress conditions or inside macrophages (134, 135).

Recently, deletion of *sigC* was shown to render *M. tuberculosis* unable to cause death in infected mice (202). Deletion of another sigma factor gene, *sigH*, also produced a nonlethal strain (99). Interestingly, despite the inability to cause fatalities, both *sigC* and *sigH* mutants grew to wild-type numbers in macrophages and murine tissues (99, 135, 202). Although the reasons for the similar phenotypes in the two different mutant strains are unknown, it is possible that a subset of virulence-associated genes are regulated by both factors. Alternatively, σ^C and σ^H may provide similar contributions to *M. tuberculosis*, but through different mechanisms. σ^E appears to affect *M. tuberculosis* virulence differently than σ^C and σ^H. As with *sigH*, *sigE* expression is induced inside macrophages (64, 90). Loss of σ^E, however, does result in decreased strain survival in macrophages and a greater susceptibility to killing by activated macrophages (134). In mouse infection models, the *sigE* mutant is delayed in its ability to cause lethality but is not completely compromised, as with the *sigC* and *sigH* mutant strains (2, 136). Manganelli et al. (136) reported a lower number of *sigE* mutants in the lungs compared to the wild type, while Ando et al. (2) reported no difference. This discrepancy may be due to differences in mouse strains used in the two studies.

Multiple studies suggest that σ^D also contributes to *M. tuberculosis* virulence. Deletion studies of *sigD* show the mutant to be less virulent than the wild type in BALB/c and C3H:HeJ mouse infections, allowing substantially longer mouse survival (20, 179). The Δ*sigD* strain did not show a difference in time to death in SCID mice, which lack T and B cells (20), suggesting that σ^D regulates pathogenicity in a manner that is dependent on cell-mediated immunity. In addition, loss of σ^D resulted in much milder tissue damage and granuloma formation in lung tissue histopathology in BALB/c mice (179).

Several alternative sigma factors present in *M. tuberculosis* affect virulence, whether through direct, indirect, or both types of strategies. In addition, some alternative sigma factors of *M. tuberculosis* autoregulate transcription of their own genes. Many sigma factors also activate transcription of other alternative sigma factors (Fig. 2C). In all, *M. tuberculosis* appears to have control over expression of its virulence genes via a complex network of multiple alternative sigma factors.

HrpL

Pseudomonas syringae is a plant pathogen with several pathovars that display selective host specificity. Infection of a plant by a specific pathovar will cause disease in susceptible host species, while eliciting a programmed cell death termed the hypersensitive response (HR) in resistant plants. The groups of genes responsible for both of these reactions have been termed *hrp* and *avr*. These gene products encode either the type III secretion machinery that translocates proteins into host plant cells or the effector proteins that are delivered and that interact with host elements. Most of the *hrp* genes are regulated by the alternative sigma factor HrpL, which has been shown by microarray analysis to be almost exclusively responsible for virulence functions (56). Strains with mutations in *hrp* genes cannot elicit disease or HR in plants (for a review, see reference 120). Likewise, inactivation of HrpL decreases *P. syringae* pv. Phaseolicola growth in leaves (178).

Another important phytopathogen, *Erwinia amylovora*, also utilizes an *hrp*-encoded type III secretion system. As in *P. syringae*, *E. amylovora* HrpL is an alternative sigma factor that directs transcription of several *hrp* genes (104). Inactivation of HrpL prevents *E. amylovora* from causing disease in susceptible plant species or HR in resistant plants (216). *E. amylovora* also has a *dsp*, or "disease-specific," gene cluster which is homologous to the *avr* genes of *P. syringae* (15). *dspA* is dependent on HrpL for expression and is required for virulence (58). In addition to *E. amylovora*, several other members of the *Erwinia* genus carry *hrpL* and other *hrp* genes, including the tumorigenic pathogen *Erwinia herbicola* (149, 155, 156) and the soft-rot pathogens *Erwinia carotovora* (24, 125, 180) and *Erwinia chrysanthemi* (6). The *hrp*-encoded type III secretion system is thus a common virulence mechanism among plant pathogens and is widespread among several types of pathogens, including tumorigenic, macerating, and soft-rot-causing species.

SIGMA 54

σ^{54} forms a distinct subfamily of sigma factors, apart from the σ^{70}-like family. In almost all species, the σ^{54} factor is called σ^N. σ^N has been identified in many species, spanning a diverse phylogeny, including *Legionella pneumophila* (88), *Pseudomonas* spp. (72, 86, 108), *Enterococcus faecalis* (40), *Campylobacter jejuni* (89), and *Listeria monocytogenes* (183). A physiological theme for σ^N-dependent genes has not yet emerged, as the regulated genes described to date control a wide diver-

TABLE 4. Virulence genes regulated by σ^N in multiple bacterial species

Species	Virulence mechanism[a]	Gene(s)[b] (reference[s])
H. pylori, *C. jejuni*, *V. cholerae*	Flagella	Class II flagellar genes (*fliA* and structural) (89, 154, 176)
P. syringae, *E. carotovora*	Type III secretion	*hrpL* (24, 83)
P. aeruginosa	Flagella	Class II flagellar genes (regulatory and structural) (41)
	Alginate	*algD*, *algC* (17, 233)
	Pili	*pilA* (206)

[a] Virulence systems regulated by σ^N-dependent genes.
[b] Specific genes or types of genes within a virulence system that are regulated by σ^N.

sity of processes (Table 4). Often nitrogen metabolism is controlled by σ^N, but other functions of σ^N-dependent genes can be found in several organisms.

Sigma N

***Pseudomonas aeruginosa*.** Evidence of σ^N involvement in bacterial pathogenesis and virulence is well documented for *P. aeruginosa*. Alginate has been identified as a virulence factor that is important in strains colonizing cystic fibrosis patient lungs. *algD* and *algC*, two important genes for the biosynthesis of alginate, are controlled by σ^N (17, 233). In addition, through gene fusion and microarray studies, expression of a large number of flagellar structural genes was shown to be dependent on σ^N (41).

Flagellar motility and pilus-mediated attachment are established virulence factors in *P. aeruginosa* (148, 186). Pili are external structures that are responsible for adhesion to host cells and interactions such as internalization. *P. aeruginosa rpoN* mutants do not produce pilin or form pili (206), and they demonstrate drastic loss of adhesion to multiple cell types (28, 32, 172). Wild-type *P. aeruginosa* also is internalized by host cells more efficiently than an *rpoN* mutant (172), suggesting an enhanced capacity of the wild-type strain to invade host cells. Reduced virulence due to loss of flagellar motility is also possible in *rpoN*-disrupted strains, as mutants are decidedly nonmotile (73, 206). *rpoN* mutants also do not produce the proteinaceous flagellin subunit or form flagella (206). Several studies have shown that *P. aeruginosa* strains lacking flagella are severely virulence attenuated (46, 52, 148).

P. aeruginosa rpoN mutants are also less virulent than wild-type strains in multiple infection models. An *rpoN* mutant strain showed diminished cytotoxicity to Madin-Darby canine kidney (MDCK) cells (32) and reduced virulence in several mouse models specifically developed to study *P. aeruginosa* pathogenicity; compared to the wild type, *rpoN* mutants cause lower mortality rates in infected mice (32, 73) and reduced fecal carriage and recovery from gastrointestinal tissues (170). In addition, no pathology was observed following infection with an *rpoN* mutant in a murine corneal scratch model (173). Cohn et al. (30) reported that *rpoN* mutants did not readily colonize human tracheal epithelium xenografts implanted in mice, although the difference in bacterial numbers of the mutant and wild-type strains was not statistically significant. In general, the defects associated with the *rpoN* mutation were greater than with strains that were specifically pilin negative, indicating the existence of an additional, pilus-independent mechanism through which σ^N also contributes to virulence (28, 32, 170, 172).

***Pseudomonas syringae*.** σ^N of *P. syringae* controls *hrp* gene expression and influences virulence. Regulation occurs via a short regulatory cascade, wherein σ^N and its enhancer-binding proteins HrpR and HrpS direct transcription of *hrpL*, the product of which is the alternative sigma factor required for expression of the *hrp* and *avr* genes (83) (Fig. 2B). Xiao et al. (225) showed that while expression of *hrpL* and HrpL-dependent genes requires *hrpR* and *hrpS*, constitutive expression of *hrpL* can provide full expression of HrpL-dependent genes with or without *hrpR* and *hrpS*. In addition, *avrD*, which is transcribed from an HrpL-dependent promoter, requires *rpoN*, *hrpL*, and *hrpS* for its expression (192). Characterization of *P. syringae* pv. Maculicola *rpoN* mutants identified a more severe phenotype than in *hrpL* mutants, however (72). *rpoN* mutants were nonmotile, displayed nitrogen utilization defects, and were unable to produce the phytotoxin coronatine, cause disease or HR, or induce host defense mRNAs. Complementation of *hrpL* into this strain partially restored some phenotypes but did not restore coronatine production. Other studies have also shown that σ^N is required for production of coronatine biosynthetic intermediates (synthesized by the *cfl*/CMA and *cmaABT* gene products) as well as *hrpL* transcription and HrpL-dependent gene expression (1, 71). Thus, σ^N regulates a range of virulence factors in *P. syringae*, some via *hrpL* activation and others by HrpL-independent mechanisms.

***Vibrio* species.** The contributions of σ^N to virulence in *Vibrio* species are similar to its contributions in *P. aeruginosa*. *V. cholerae rpoN* mutants lack flagella and are completely nonmotile (105). In a competitive infant mouse colonization trial, an *rpoN* mutant was 10- to 20-fold less able to colonize the intestine than the wild type (105). This defect is not entirely due to lack of flagella, because a *flaA* mutant, while inhibited in intestinal colonization, was still superior to the *rpoN* mutant in colonization. Prouty et al. (176) also demonstrated the involvement of σ^N in expression of several *V. cholerae* flagellar structural genes. σ^N is required for flagellin production and motility in the fish pathogen *Vibrio anguillarum* as well. A mutant lacking σ^N was also severely impaired in its ability to infect fish immersed in contaminated water but was not virulence attenuated in an intraperitoneal injection model (163).

Other species. σ^N contributes to virulence in a number of gram-negative pathogens. In addition to the examples provided above, the uropathogen *Proteus mirabilis* is 1,020-fold less virulent than the wild type when σ^N is inactivated but remains identical to the wild type with respect to growth, glu-

tamine synthesis, and fimbria production (231). σ^N does not share a common role among all pathogens, however. For example, the plant pathogens, *Pseudomonas syringae*, *Erwinia carotovora*, and *Xanthomonas campestris* all use type III secretion systems to cause disease in host organisms, and σ^N has a substantial effect on virulence and *hrp* gene expression in *P. syringae* and *E. carotovora* (24) but is not required for expression of *hrp* genes or for virulence in *X. campestris* (78). As with the low-GC bacterial σ^B, σ^N appears to be an alternative sigma factor that has evolved to regulate virulence determinants in some species but not in others.

CONCLUSIONS

Bacteria utilize alternative sigma factors to regulate a wide range of physiological processes. In pathogenic bacteria, alternative sigma factors often affect virulence. Virulence effects can be mediated either through direct virulence gene regulation or indirectly, by regulating genes that increase fitness of the bacterium during transmission and infection. Direct effects on virulence genes include σ^B activation of the *L. monocytogenes* virulence genes *inlA* and *prfA* and σ^S-dependent expression of the *S. enterica* serovar Typhimurium *spv* genes. Indirect effects of sigma factors on virulence may be more difficult to identify, but alternative sigma factors frequently have roles in virulence by regulating virulence-associated genes that aid in a bacterium's survival during infection. For example, σ^E enhances survival of oxidative stress and hence aids in bacterial survival of the oxidative burst within macrophages. The stress response sigma factors σ^B and σ^S contribute to survival of multiple stresses (e.g., acid and osmotic stresses) important for bacterial survival of passage through a host stomach and gastrointestinal tract. In addition, σ^B and σ^S contribute to environmental survival, and thus transmission, of food-borne pathogens in foods and food-processing environments. Another alternative sigma factor role that contributes to environmental survival, and has virulence implications, is regulation of biofilm formation, e.g., by σ^B in *S. aureus* and *S. epidermidis*.

Functional roles for alternative sigma factors can be clearly defined and highly specific (e.g., sporulation sigma factors) or multifunctional. While *Pseudomonas syringae* HrpL's role is predominantly virulence related, most alternative sigma factors contribute to multiple, diverse functions in a cell. In some cases, sigma factors are conserved across pathogenic and nonpathogenic species, with virulence genes constituting a relatively small subset of the total regulon in the pathogenic species. For example, σ^B is present and contributes to stress resistance in the nonpathogenic *B. subtilis* and *Listeria innocua* (S. Raengpradub, unpublished data), both of which are closely related to the pathogenic *L. monocytogenes*. It is possible that virulence gene incorporation into the *L. monocytogenes* σ^B regulon is a relatively recent evolutionary event. Likewise, as no evidence currently supports a direct role for σ^S in *E. coli* virulence gene regulation, the inclusion of virulence genes in the regulatory network of *S. enterica* serovar Typhimurium σ^S may have occurred after the species divergence of *S. enterica* serovar Typhimurium and *E. coli*.

A comparison of homologous sigma factor functions among different bacterial genera reveals that the roles of sigma factors vary greatly among bacterial species, even for closely related species such as *E. coli* and *S. enterica* serovar Typhimurium. In some cases, as with *M. tuberculosis* σ^F, distinct virulence-related phenotypes have been observed in alternative sigma factor null mutants. For others, such as *S. aureus* σ^B, while virulence genes are directly transcribed by the sigma factor, Δ*sigB* strains are not severely virulence attenuated. Even more apparent are the different roles for σ^S. σ^S is required for virulence in *S. enterica* serovar Typhimurium and yet does not demonstrate a pronounced role in *E. coli* pathogenesis.

A common mechanism of virulence regulation by alternative sigma factors involves coordinated networks of sigma factors along with other transcriptional regulators. Alternative sigma factors may regulate not only individual genes involved in virulence but also other sigma factors or transcriptional regulators that in turn regulate virulence genes and virulence-associated genes (Fig. 2). For example, σ^B of *L. monocytogenes* not only directly regulates *bsh* and *inlA* but also contributes to expression of PrfA, which is required for transcription of almost all of the currently recognized *L. monocytogenes* virulence genes. σ^B of *S. aureus* also affects expression of a virulence gene regulator, RNAIII. σ^N and HrpL of *P. syringae* present a different type of regulatory network, in which one sigma factor controls expression of another. HrpL also controls expression of the HrpR and HrpS two-component system regulators. Regulatory networks can be very complex, as in the multiple sigma factor interactions of *M. tuberculosis*.

Finally, to extrapolate bacterial pathogen research findings to ensure relevance in human infection, the importance of identifying and applying suitable model systems that accurately mimic interactions between pathogen and humans is essential. This point is illustrated by the significantly reduced traversal of the intestinal barrier by *L. monocytogenes* in wild-type versus (human) E-cadherin transgenic mice (121). In addition, pathogens such as *P. aeruginosa* that can infect a multitude of different hosts are likely to respond differently and to have different virulence requirements depending on the host species. Significant efforts are still needed to identify or develop appropriate model systems for exploration of virulence mechanisms that are important in human infection.

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