Systematic review of the *Listeria monocytogenes* σ^B regulon supports a role in stress response, virulence and metabolism

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Aim: Among the alternative sigma factors of *Listeria monocytogenes*, σ^B controls the largest regulon. The aim of this study was to perform a comprehensive review of σ^B -regulated genes, and the functions they confer. **Materials & methods:** A systematic search of PubMed and Web of Knowledge was carried out to identify members of the σ^B regulon based on experimental evidence of σ^B -dependent transcription and presence of a consensus σ^B -dependent promoter. **Results:** The literature review identified σ^B -dependent transcription units encompassing 304 genes encoding different functions including stress response and virulence. **Conclusion:** Our review supports the well-known roles of σ^B in virulence and stress response and provides new insight into novel roles for σ^B in metabolism and overall resilience of *L. monocytogenes*.

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Keywords: *Listeria monocytogenes* • regulon • SigB • stress response • virulence

Importance of *Listeria monocytogenes* as a foodborne pathogen & model organism

Listeria monocytogenes is a foodborne pathogen of concern for food safety and public health worldwide. This Gram-positive pathogen causes the serious infection, listeriosis, in susceptible populations, such as the immunocompromised, pregnant women, newborns and the elderly. This bacterium challenges food safety because it is commonly present in farm and food-processing environments and can utilize various food vehicles to transmit to a human host. *L. monocytogenes*' ability to rapidly adapt to changing environmental conditions enables it to survive harsh environments during food processing, as well as to adapt to intracellular growth and proliferation within a host. This bacterium is able to survive in a wide range of temperature and pH as well as high osmotic pressure and limited nutrient availability [1].

Several characteristics of *L. monocytogenes*' physiology have made it a unique model in infection biology, cell biology and fundamental microbiology. This successful intracellular pathogen can infect human and animal host cells, survive and grow under different conditions, and overcome important pathophysiological barriers, such as the intestinal epithelium, the blood–brain barrier and the placenta. Decades of studies have revealed important mechanisms of transmission, invasion, motility and resistance in *L. monocytogenes*; these findings support the consideration of this pathogen as a multifaceted model for the study of host–pathogen interactions, intracellular growth and pathogenic mechanisms (for a recent review, see [2]). *L. monocytogenes* is also an emerging model in prokaryotic transcriptomic studies and in environmental studies [3,4].

Importance of alternative sigma factor B in *L. monocytogenes*' gene regulation

Overview of the role of σ^B in *L. monocytogenes*' gene regulation

To overcome changing conditions, gene expression in *L. monocytogenes* is tightly regulated by transcriptional regulators including alternative sigma (σ) factors, transcriptional activators and repressors [5]. Among the alternative sigma factors, σ^B has the largest regulon in *L. monocytogenes* [6]. The complex and fine-tuned interplay between the regulatory circuits of σ^B , other transcriptional regulators and other sigma factors is the key for successful infection

Table 1. Medical Subject Heading terms used in this study.

Subheadings of ' <i>Listeria monocytogenes</i> '	SigB-related terms	Methods and approaches terms
'Genetics'	'SigB protein, bacteria (supplementary concept)'	'Sequence analysis, RNA'
'Growth and development'	'Sigma factor/genetics'	'RNA, untranslated/genetics'
'Metabolism'	'Gene expression regulation, bacterial'	'Genome-wide association study'
'Microbiology'	'Stress, physiological'	
'Pathogenicity'		

and survival under different conditions [7], including the transition from a saprophytic to a host-associated life stages of *L. monocytogenes* [8]. σ^B and other sigma factors such as σ^A and σ^H have overlapping regulons, which play important roles in metabolism and the transition to a pathogenic lifestyle [6]. In addition, σ^B and σ^B -regulated regulators, such as PrfA and Hfq, together coordinate the response to the stresses encountered during invasion and intracellular growth [9]. Deletion of *sigB* makes *L. monocytogenes* more susceptible to environmental stresses and attenuated in virulence [10–12], with transcriptomic and proteomic data showing significant changes in the gene expression profile of these mutants [9,13,14]. Based on these studies, σ^B is currently considered as the regulator of general stress response, virulence and resilience [7]. Reviewing studies on the σ^B regulon not only provides an overview of σ^B regulation in *L. monocytogenes* but also highlights the importance of future research on σ^B -dependent genes carrying out important functions for this pathogen.

*The σ^B regulon in *L. monocytogenes**

Several studies on the σ^B regulon in a single *L. monocytogenes* strain have suggested more than 200 genes to be directly regulated by σ^B [9,13,15,16]. However, as a pathogen with global distribution, multiple *L. monocytogenes* strains and isolates have been used in various studies worldwide. The most common lab strains of *L. monocytogenes* are 10403S (serotype 1/2a), EGDe (serotype 1/2a) and EGD (serotype 1/2a) [17]; other strains used less frequently include LO28 (serotype 1/2c), H7858 (serotype 4b) and clinical isolates [18,19]. Interestingly, even the commonly used lab strains have diverse genomic characteristics. While the names of EGD and EGDe imply a similar origin, these two strains are genetically highly distinct from each other with approximately 30,000 SNP differences [17]. Additionally, the commonly used *L. monocytogenes* strains do not share all genes, making it difficult to use the regulon of one strain to represent all. Previous studies have revealed that the σ^B regulon in *L. monocytogenes* can vary in different lineages and strains [16,20]. In this review, we searched for and summarized σ^B regulon members in different strains of *L. monocytogenes*.

Methods

Systematic review of literature on σ^B in *L. monocytogenes*

A systematic literature search was performed guided by preferred reporting items for systematic reviews and meta-analyses (PRISMA) [21] (Figure 1).

Search strategy

PubMed and Web of Knowledge databases were searched for relevant articles. Broad search terms for *Listeria monocytogenes*, σ^B regulation, stress response and transcriptional studies were used. Specifically, the Medical Subject Headings (MeSHs) in PubMed search as well as the text-word searching was employed. MeSH terms covered the ones linked to *L. monocytogenes*, σ^B and methods (Table 1). Text-words included '*Listeria monocytogenes*', 'listeriosis', 'SigB', 'Sigma B', 'SigmaB', 'stress response' and 'virulence gene'. The final search was conducted on 29 October 2017. A list of 291 publications was generated through the search.

Inclusion & exclusion criteria

Articles were reviewed through an abstract screen and a subsequent full-text screen. The inclusion criteria for abstract screen were that the abstract: mentioned σ^B -dependent promoter, σ^B regulon, σ^B -dependent genes with transcriptional or translational evidence in *L. monocytogenes*; or was a transcriptional/proteomic study with transcription start site and/or promoter region prediction. The exclusion criteria for abstract screen were that the abstract was: not a study in *L. monocytogenes* (e.g., *Bacillus*); not focusing on the genes regulated by σ^B (e.g., growth of $\Delta sigB$ mutant under stress condition); on regulation of other regulators except σ^B (e.g., PrfA); on phylogenetic

Figure 1. Selection process for inclusion of articles in the review.

studies using *sigB* to subtype *Listeria*; a study of the mechanism of σ^B activation. Abstracts meeting the inclusion criteria were then screened through full-text screening.

The inclusion criteria for full-text screen were that: the article identified σ^B -dependent genes that showed evidence for higher expression levels in the presence of σ^B as compared with an isogenic null mutant; or the article identifies σ^B -dependent promoters or transcription units (TUs). Only papers with full text in English were included. No further restrictions were placed on study design, lineages and strains, study location or technique methods (e.g., transcriptomic or proteomic).

With these inclusion and exclusion criteria, 42 publications that reported σ^B regulon members in *L. monocytogenes* or reported TUs by genome-wide analyses were identified (Figure 1). An additional dataset [22], which was unpublished at the time of the search, was also included as it consisted of a transcriptomic study in wild-type and isogenic $\Delta sigB$ mutants of *L. monocytogenes* under stress. Data were extracted from these 43 publications (Supplementary Table 1) to summarize the σ^B regulon in *L. monocytogenes*.

Compilation of the *L. monocytogenes* σ^B regulon

Summary of the σ^B regulon in *L. monocytogenes* strains

A recent study identified 127 TUs, which had upstream σ^B -dependent consensus promoters and encompassed 240 genes, as the σ^B regulon in *L. monocytogenes* strain 10403S [15]. The systematic literature review described above was used to: verify and expand this regulon for strain 10403S and identify additional TUs with upstream σ^B -dependent consensus promoters in other strains, including EGDe, EGD, H7858, LO28 and others. Overall, these efforts identified 171 TUs that encompassed 304 genes (Table 2).

Table 2. σ^B regulon members in *Listeria monocytogenes*.

TU no. [†]	Gene locus	Coordinates for the gene [‡]	Gene	Strand	Strain [§]	Ref [¶]	Gene locus in EGD ^e	Putative σ^B promoter sequence [#]
1	LMRG.02442	16,220	<i>qoxA</i>	+	10403S	1	Imo0013	tGTTTcggtattccaatctaGGGAATa
1	LMRG.02443	17,345	<i>qoxB</i>	+	10403S	1	Imo0014	
1	LMRG.02444	19,312	<i>qoxC</i>	+	10403S	1	Imo0015	
1	LMRG.02445	19,925	<i>qoxD</i>	+	10403S	1	Imo0016	
2	LMRG.02448	23,133	LMRG.02448	-	10403S	1	Imo0019	tCTTTtatttttcaaaataGGGTATa
3	LMRG.02472	48,076	<i>arcA</i>	+	10403S	1	Imo0043	cGCATacatgacaaacttttgGGGTAAc
4	LMRG.02382	133,269	LMRG.02382	+	10403S	1	Imo0133	cGTTTcttttggtgatgagTGGAAATa
4	LMRG.02383	133,514	LMRG.02383	+	10403S	1	Imo0134	
5	LMRG.02414	161,540	LMRG.02414	+	10403S	1	Imo0169	gGAATgatttcagaggaaaGGGTATa
5	LMRG.02415	162,459	LMRG.02415	+	10403S	1	Imo0170	
6	LMRG.02622	198,099	<i>prfA</i>	-	10403S	1	Imo0200	tGTTAgtcctaattgttttaGGGTATt
7	LMRG.02632	208,946	<i>ldh</i>	-	10403S	1	Imo0210	gGTTTataattctcaataaaaGGTAAAc
8	LMRG.02643	223,505	LMRG.02643	+	10403S	1	Imo0221	cGAAATaaaatacaagaggtGGGCTTt
8	LMRG.02644	224,300	LMRG.02644	+	10403S	1	Imo0222	
9	LMRG.02674	245,054	<i>clpC</i>	+	10403S	1	Imo0232	aGTTTaatatttcctttacCGGATAg
9	LMRG.02675	244,003	<i>mcsB</i>	+	10403S	1	Imo0231	
9	LMRG.02676	243,488	<i>mcsA</i>	+	10403S	1	Imo0230	
10	LMRG.02646	276,274	<i>inlC2</i>	+	10403S	1	Imo0263	tGTTAatttggtctaaaaaGGGTATc
11	LMRG.02851	278,128	<i>inlD</i>	+	10403S	1	N/A	tGTCaataatcattacGGGTCTa
12	LMRG.02611	281,675	<i>dapE</i>	+	10403S	1	Imo0265	aGTTTgcctttatagagacGGGAAaAa
13	LMRG.02602	290,712	LMRG.02602	-	10403S	1	Imo0274	gGTTAcatggcctaaaaaGGGTATt
14	LMRG.02579	313,427	<i>htrA</i>	+	10403S	1	Imo0292	tGTTTtcatatttcataaaGGGAATa
15	LMRG.00013	346,711	LMRG.00013	+	10403S	1	Imo0321	gGTTTgcgaagggaataagaGGGAAAT

[†]TU number was arbitrarily assigned to each TU.

[‡]Genbank Assembly Accession ID of genomes for coordinates: 10403S (GCA.000168695.2), H7858 (GCA.000167155.1), EGD^e and other strains (GCA.000196035.1). When there is more than one strain, coordinates in the 10403S genome were listed.

[§]An initial list of 127 TUs was obtained from Liu *et al.* (2017), and for these TUs 10403S is the strain in which the Liu *et al.*'s study was conducted (which does not imply that this is the strain where this TU was first identified as σ^B -dependent); for all other TUs, the strain where a TU was initially identified as σ^B -dependent is listed. We did not attempt to determine the distribution of all σ^B -dependent TUs among *L. monocytogenes* strains as this represents a primary study that was defined as beyond the scope of this review.

[¶]References are coded as: 1 = [15]; 2 = [84]; 3 = [95]; 4 = [115]; 5 = [53]; 6 = [86]; 7 = [19]; 8 = [116]; 9 = [22].

[#]For TUs where there is more than one gene per TU, the promoter sequence is only listed for the first gene in the TU. The -10 and -35 promoter elements are in capital letters and underlined.

^{††}Mraheil *et al.* [84] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₂₋₁₇-GGG(A/T)A(A/T)' and allowing for one mismatch. The actual promoter sequence was not reported.

^{†††}Wurtzel *et al.* [115] reported identification of a σ^B promoter, however, the actual promoter sequence was not reported.

^{§§}Wemekamp-Kamphuis *et al.* [53] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₄-GGGTAA' and allowing for up to four mismatches. While only the -10 and -35 element sequences were reported in the original publication, we used the EGD^e genome sequence to identify the complete sequence of the promoter.

^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemekamp-Kamphuis *et al.* [53] 'GTTTGTN₁₄-GGGTAT' could not be found upstream of *gadC* in the EGD^e genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.

^{##}Millilo *et al.* [86] reported identification of a putative σ^B promoter up to 1 kb upstream of the gene, however, the promoter sequence was not reported.

^{††††}Ryan *et al.* [19] reported identification of a σ^B promoter upstream of the gene using the consensus sequence 'GTT-N₁₃₋₁₇-GGGAT' and allowing for several mismatches. The actual promoter sequence was not reported.

N/A: Not applicable; ncRNA: Noncoding RNA; sRNA: Small RNA; TU: Transcriptional unit.

Table 2. σ^B regulon members in <i>Listeria monocytogenes</i> . (cont.).									
TU no. [†]	Gene locus	Coordinates for the gene [‡]		Gene	Strand	Strain [§]	Ref [¶]	Gene locus in EGDe	Putative σ^B promoter sequence [#]
16	LMRG.00028	366,591	366,959	LMRG.00028	+	10403S	1	Imo0336	aGTTATtaccactgactgaaaaaGGGAATa
16	LMRG.00029	366,956	368,404	LMRG.00029	+	10403S	1	N/A	
16	LMRG.00030	369,383	369,754	LMRG.00030	+	10403S	1	N/A	
16	LMRG.00031	369,798	369,986	LMRG.00031	+	10403S	1	N/A	
16	LMRG.02931	368,875	369,162	LMRG.02931	+	10403S	1	N/A	
16	LMRG.02932	368,414	368,785	LMRG.02932	+	10403S	1	N/A	
17	LMRG.00050	386,130	386,990	LMRG.00050	+	10403S	1	Imo0359	gGATActgcttcgggttaaTGGTTCc
17	LMRG.00051	387,047	387,817	LMRG.00051	+	10403S	1	Imo0360	
18	LMRG.00098	426,428	427,435	LMRG.00098	+	10403S	1	Imo0405	cTTTTatattgtataaaaGGGTATa
18	LMRG.00099	427,451	427,831	LMRG.00099	+	10403S	1	Imo0406	
18	LMRG.00100	427,900	428,292	LMRG.00100	+	10403S	1	Imo0407	
18	LMRG.00101	428,305	428,727	LMRG.00101	+	10403S	1	Imo0408	
19	LMRG.00126	453,867	456,269	<i>inA</i>	+	10403S	1	Imo0433	tGTGTatttttgaaacataaGGGTAGa
19	LMRG.00127	456,354	458,246	<i>inB</i>	+	10403S	1	Imo0434	
20	LMRG.00131	460,567	461,835	LMRG.00131	-	10403S	1	Imo0439	tGTTTcacgcactgcttttcGGGAAAc
21	LMRG.00137	469,361	470,848	LMRG.00137	+	10403S	1	N/A	aGTAATttaaggcaaatgtGGTATAa
22	LMRG.02884	495,166	495,525	LMRG.02884	+	10403S	1	N/A	tGATTttttatgtctaaataGGGTATa
23	LMRG.00196	529,619	530,050	<i>uspA</i>	+	10403S	1	Imo0515	gGCTaaaaatcatttttataGGGTATg
24	LMRG.00205	538,707	540,368	LMRG.00205	-	10403S	1	Imo0524	tGATTgttctatgtcaaacGGGTAAa
25	LMRG.00208	542,971	544,446	LMRG.00208	+	10403S	1	Imo0527	tGTTTattataacccttttagTGGAAAa
25	LMRG.02879	544,439	545,935	LMRG.02879	+	10403S	1	N/A	
25	LMRG.00211	545,946	547,196	LMRG.00211	+	10403S	1	Imo0529	
25	LMRG.00212	547,212	549,263	LMRG.00212	+	10403S	1	Imo0530	
25	LMRG.00213	549,276	550,130	LMRG.00213	+	10403S	1	N/A	

[†]TU number was arbitrarily assigned to each TU.
[‡]Genbank Assembly Accession ID of genomes for coordinates: 10403S (GCA_000168695.2), H7858 (GCA_000167155.1), EGDe and other strains (GCA_000196035.1). When there is more than one strain, coordinates in the 10403S genome were listed.
[§]An initial list of 127 TUs was obtained from Liu *et al.* (2017), and for these TUs 10403S is the strain in which the Liu *et al.*'s study was conducted (which does not imply that this is the strain where this TU was first identified as σ^B -dependent); for all other TUs, the strain where a TU was initially identified as σ^B -dependent is listed. We did not attempt to determine the distribution of all σ^B -dependent TUs among *L. monocytogenes* strains as this represents a primary study that was defined as beyond the scope of this review.
[¶]References are coded as: 1 = [15]; 2 = [84]; 3 = [95]; 4 = [115]; 5 = [53]; 6 = [86]; 7 = [19]; 8 = [116]; 9 = [22].
[#]For TUs where there is more than one gene per TU, the promoter sequence is only listed for the first gene in the TU. The -10 and -35 promoter elements are in capital letters and underlined.
^{††}Mirahel *et al.* [84] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₂₋₁₇-GGG(A/T)A(A/T)' and allowing for one mismatch. The actual promoter sequence was not reported.
^{†††}Wurtzel *et al.* [115] reported identification of a σ^B promoter, however, the actual promoter sequence was not reported.
^{§§}Wemkamp-Kamphuis *et al.* [53] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT(A-N)₁₄-GGGTAA' and allowing for up to four mismatches. While only the -10 and -35 element sequences were reported in the original publication, we used the EGDe genome sequence to identify the complete sequence of the promoter.
^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemkamp-Kamphuis *et al.* [53] 'GTTTGT(N)₁₄-GGGTAT' could not be found upstream of *gadC* in the EGDe genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.
^{##}Millilo *et al.* [86] reported identification of a putative σ^B promoter up to 1 Kb upstream of the gene, however, the promoter sequence was not reported.
^{††††}Ryan *et al.* [19] reported identification of a σ^B promoter upstream of the gene using the consensus sequence 'GT(N)₃₋₁₇-GGGWAT' and allowing for several mismatches. The actual promoter sequence was not reported.
N/A: Not applicable; ncRNA: Noncoding RNA; sRNA: Small RNA; TU: Transcriptional unit.

Table 2. σ^B regulon members in *Listeria monocytogenes*. (cont.).

TU no. [†]	Gene locus	Coordinates for the gene [‡]	Gene	Strand	Strain [§]	Ref [¶]	Gene locus in EGD ^e	Putative σ^B promoter sequence [#]
26	LMRG.00221	557,807	<i>lacD</i>	-	10403S	1	Imo0539	tGTTTaaaaaaattattcagTGGTATa
27	LMRG.00236	572,432	<i>LMRG.00236</i>	+	10403S	1	Imo0554	gGTTTaaattttctaaaaaaGTTGTAIt
27	LMRG.00237	573,703	<i>dtgT</i>	+	10403S	1	Imo0555	
28	LMRG.00261	596,881	<i>LMRG.00261</i>	+	10403S	1	Imo0579	cGATTgttcgatgtgattgGGGTAAa
28	LMRG.00262	597,142	<i>LMRG.00262</i>	+	10403S	1	Imo0580	
29	LMRG.00271	610,787	<i>LMRG.00271</i>	+	10403S	1	Imo0589	aGTTTgcaaaagagcattataGGGGAAa
29	LMRG.00272	611,200	<i>LMRG.00272</i>	+	10403S	1	Imo0590	
29	LMRG.00273	612,966	<i>LMRG.00273</i>	+	10403S	1	Imo0591	
29	LMRG.00274	613,867	<i>LMRG.00274</i>	+	10403S	1	Imo0592	
30	LMRG.00275	614,637	<i>LMRG.00275</i>	+	10403S	1	Imo0593	tGTTTaaagagtttgaaacgGGGAAAt
31	LMRG.00278	618,323	<i>LMRG.00278</i>	+	10403S	1	Imo0596	gGTTTaaattcgttttttaGGCTAIt
32	LMRG.00285	624,079	<i>LMRG.00285</i>	+	10403S	1	Imo0602	cGCAItcttttggttaaaagGGGTAAa
33	LMRG.00288.as	625,465	<i>asRNA</i>	+	10403S	1	N/A	tGTTTataagtcagtagtagcGGGAAa
34	LMRG.00293	631,530	<i>LMRG.00293</i>	-	10403S	1	Imo0610	tGTTTaaacattactataaaagAGGAAt
35	LMRG.00311	650,750	<i>LMRG.00311</i>	+	10403S	1	Imo0628	cTTTtgaataaagtaaaatcGGGTATa
35	LMRG.00312	651,087	<i>LMRG.00312</i>	+	10403S	1	Imo0629	
36	LMRG.00335	672,255	<i>LMRG.00335</i>	+	10403S	1	Imo0648	aGTTTtttgatgcataataaGGGAAAg
37	LMRG.00334	671,873	<i>LMRG.00334</i>	-	10403S	1	Imo0647	tGATTtgatttaagatttAGGTAAAt
38	LMRG.00341	678,939	<i>LMRG.00341</i>	+	10403S	1	Imo0654	gGATTacattctattattgGGGAAa
38	LMRG.00342	679,216	<i>LMRG.00342</i>	+	10403S	1	Imo0655	
39	LMRG.00356	688,618	<i>LMRG.00356</i>	+	10403S	1	N/A	cGTTTtagctaaactggaGGGAAaGa
39	LMRG.00357	688,746	<i>LMRG.00357</i>	+	10403S	1	Imo0669	
39	LMRG.00358	689,645	<i>LMRG.00358</i>	+	10403S	1	Imo0670	
40	LMRG.00359.as	689,839	<i>asRNA</i>	-	10403S	1	N/A	cGTTTcgttttttaaaactGGGCTAa
41	rlt33	690,645	<i>ncRNA</i>	+	10403S	1	N/A	gGTTTggattgggtgagacGGTATt

[†]TU number was arbitrarily assigned to each TU.

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^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemekamp-Kamphuis et al. [53] 'GTTTGTN₁₄-GGGTAT' could not be found upstream of *gadC* in the EGD^e genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.

^{##}Millilo et al. [86] reported identification of a putative σ^B promoter up to 1 Kb upstream of the gene, however, the promoter sequence was not reported.

^{††††}Ryan et al. [19] reported identification of a σ^B promoter upstream of the gene using the consensus sequence 'GTT-N₁₃₋₁₇-GGGWAAT' and allowing for several mismatches. The actual promoter sequence was not reported.

N/A: Not applicable; ncRNA: Noncoding RNA; sRNA: Small RNA; TU: Transcriptional unit.

Table 2. σ^B regulon members in <i>Listeria monocytogenes</i> . (cont.).									
TU no. [†]	Gene locus	Coordinates for the gene [‡]		Gene	Strand	Strain [§]	Ref [¶]	Gene locus in EGDe	Putative σ^B promoter sequence [#]
42	LMRG.00362	692,165	693,085	<i>mogR</i>	-	10403S	1	N/A	<u>gTTT</u> TacacccaatcatcagGGTAAT
42	LMRG.00361	691,937	692,146	<i>LMRG.00361</i>	-	10403S	1	N/A	
43	LMRG.00411	733,935	735,665	<i>LMRG.00411</i>	+	10403S	1	Imo0722	<u>gAA</u> TactctttaaaacaGGGTAAa
44	LMRG.00472	789,623	790,090	<i>mpoA</i>	-	10403S	1	Imo0784	<u>gTTT</u> TctgactaatctttaGGGTAAt
44	LMRG.02869	789,138	789,623	<i>mpoB</i>	-	10403S	1	Imo0783	
44	LMRG.00470	788,152	788,964	<i>mpoC</i>	-	10403S	1	Imo0782	
44	LMRG.00469	787,255	788,133	<i>mpoD</i>	-	10403S	1	Imo0781	<u>gTTT</u> TccagtcacctcttctGGGAATa
45	LMRG.00482	804,255	804,896	<i>LMRG.00482</i>	-	10403S	1	Imo0794	
46	LMRG.00484	806,007	806,537	<i>LMRG.00484</i>	-	10403S	1	Imo0796	<u>gTTT</u> aattcttaagattaGCTAGa
47	LMRG.02263	852,984	853,454	<i>LMRG.02263</i>	-	10403S	1	N/A	<u>aGTC</u> TctcttttggttaaGGGCAAA
48	LMRG.02293	890,187	891,185	<i>LMRG.02293</i>	+	10403S	1	Imo0869	<u>aTTT</u> TagcaactcaaaaagGGGTATt
48	LMRG.02294	891,201	891,512	<i>LMRG.02294</i>	+	10403S	1	Imo0870	
49	LMRG.02304	900,048	901,436	<i>LMRG.02304</i>	+	10403S	1	Imo0880	<u>gTTT</u> TtaacaagaagttgGGGAACt
50	LMRG.02317	910,921	911,265	<i>rsbV</i>	+	10403S	1	Imo0893	<u>gTTT</u> TaattttattagtaGGGTAAa
50	LMRG.02318	911,249	911,722	<i>rsbW</i>	+	10403S	1	Imo0894	
50	LMRG.02319	911,700	912,479	<i>sigB</i>	+	10403S	1	Imo0895	
50	LMRG.02320	912,480	913,079	<i>rsbX</i>	+	10403S	1	Imo0896	
51	LMRG.02011	928,896	929,399	<i>LMRG.02011</i>	+	10403S	1	Imo0911	<u>gTTT</u> TtaacttgccctcaggcGGGTATt
52	LMRG.02013	930,540	932,015	<i>gabD</i>	+	10403S	1	Imo0913	<u>gATT</u> aaattttctgattgTGGAAAAa
53	LMRG.02028	948,041	948,709	<i>LMRG.02028</i>	+	10403S	1	Imo0929	<u>gATT</u> TaagtatgcaagattaGGGAAaAa
54	LMRG.02036	955,305	955,466	<i>LMRG.02036</i>	-	10403S	1	Imo0937	<u>gTTT</u> TaaagactgctcacGGGAATa
55	LMRG.02041	960,856	961,326	<i>fri</i>	+	10403S	1	N/A	<u>gTTT</u> TaagaattttatcagTGGTAAa
56	LMRG.02052	969,071	969,298	<i>LMRG.02052</i>	+	10403S	1	Imo0953	<u>gTTT</u> TtactctacttttaGGGAATa
57	LMRG.02055	970,896	972,029	<i>nagA</i>	+	10403S	1	Imo0956	<u>gTTT</u> TtttacttttttcGGGTAAa
57	LMRG.02056	972,045	972,749	<i>nagB</i>	+	10403S	1	Imo0957	
57	LMRG.02057	972,765	973,487	<i>yvaA</i>	+	10403S	1	Imo0958	

[†]TU number was arbitrarily assigned to each TU.
[‡]Genbank Assembly Accession ID of genomes for coordinates: 10403S (GCA.000168695.2), H7858 (GCA.000167155.1), EGDe and other strains (GCA.000196035.1). When there is more than one strain, coordinates in the 10403S genome were listed.
[§]An initial list of 127 TUs was obtained from Liu *et al.* (2017), and for these TUs 10403S is the strain in which the Liu *et al.*'s study was conducted (which does not imply that this is the strain where this TU was first identified as σ^B -dependent); for all other TUs, the strain where a TU was initially identified as σ^B -dependent is listed. We did not attempt to determine the distribution of all σ^B -dependent TUs among *L. monocytogenes* strains as this represents a primary study that was defined as beyond the scope of this review.
[¶]References are coded as: 1 = [15]; 2 = [84]; 3 = [95]; 4 = [115]; 5 = [53]; 6 = [86]; 7 = [19]; 8 = [116]; 9 = [22].
[#]For TUs where there is more than one gene per TU, the promoter sequence is only listed for the first gene in the TU. The -10 and -35 promoter elements are in capital letters and underlined.
^{††}Mraheil *et al.* [84] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₂₋₁₇-GGG(A/T)A(A/T)' and allowing for one mismatch. The actual promoter sequence was not reported.
^{†††}Wurtzel *et al.* [115] reported identification of a σ^B promoter, however, the actual promoter sequence was not reported.
^{§§}Wemekamp-Kamphuis *et al.* [53] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTTAA-N₁₄-GGGTAA' and allowing for up to four mismatches. While only the -10 and -35 element sequences were reported in the original publication, we used the EGDe genome sequence to identify the complete sequence of the promoter.
^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemekamp-Kamphuis *et al.* [53] 'GTTTGT-N₁₄-GGGTAT' could not be found upstream of *gadC* in the EGDe genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.
^{##}Millilo *et al.* [86] reported identification of a putative σ^B promoter up to 1 Kb upstream of the gene, however, the promoter sequence was not reported.
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N/A: Not applicable; ncRNA: Noncoding RNA; sRNA: Small RNA; TU: Transcriptional unit.

Table 2. σ^B regulon members in *Listeria monocytogenes*. (cont.).

TU no. [†]	Gene locus	Coordinates for the gene [‡]	Gene	Strand	Strain [§]	Ref [¶]	Gene locus in EGDe	Putative σ^B promoter sequence [#]
58	LMRG.02094	1,006,561	LMRG.02094	-	10403S	1	Imo0994	<u>tGTTTagcgtctaacaacCGGAAA</u> g
59	LMRG.02095	1,006,959	LMRG.02095	-	10403S	1	Imo0995	<u>gGATAagcgttacagaatctaGGGTAA</u> a
60	LMRG.02114	1,025,623	LMRG.02114	+	10403S	1	Imo1014	<u>tGCTTttttaaaagtgatatGGCCG</u> a
60	LMRG.02115	1,026,809	LMRG.02115	+	10403S	1	Imo1015	
60	LMRG.02116	1,027,671	LMRG.02116	+	10403S	1	Imo1016	
61	LMRG.00529	1,075,768	LMRG.00529	+	10403S	1	Imo1067	<u>cGGCTcagctatgctataatAGGTAA</u> g
62	LMRG.00530	1,077,778	LMRG.00530	+	10403S	1	Imo1068	<u>tGCATtattttatgtaaaaaGGGAAT</u> a
63	LMRG.00583	1,132,104	LMRG.00583	-	10403S	1	Imo1140	<u>aACATaattgaacattttcGGGTAT</u> a
64	LMRG.00594	1,140,296	LMRG.00594	+	10403S	1	Imo1151	<u>aGTAAaatactatttttgagaAGGAGG</u> t
64	LMRG.00595	1,140,576	LMRG.00595	+	10403S	1	Imo1152	
64	LMRG.00596	1,141,398	LMRG.00596	+	10403S	1	Imo1153	
64	LMRG.00597	1,143,100	LMRG.00597	+	10403S	1	N/A	
64	LMRG.00598	1,143,776	LMRG.00598	+	10403S	1	N/A	
64	LMRG.00599	1,144,333	LMRG.00599	+	10403S	1	Imo1156	
64	LMRG.00600	1,146,150	LMRG.00600	+	10403S	1	Imo1154	
64	LMRG.00601	1,146,510	LMRG.00601	+	10403S	1	N/A	
64	LMRG.00602	1,146,972	LMRG.00602	+	10403S	1	Imo1159	
64	LMRG.00603	1,147,251	LMRG.00603	+	10403S	1	N/A	
64	LMRG.00604	1,147,907	LMRG.00604	+	10403S	1	N/A	
64	LMRG.00605	1,148,743	LMRG.00605	+	10403S	1	N/A	
64	LMRG.00606	1,149,200	LMRG.00606	+	10403S	1	N/A	
64	LMRG.00607	1,149,505	LMRG.00607	+	10403S	1	Imo1164	
64	LMRG.00608	1,150,507	LMRG.00608	+	10403S	1	N/A	
64	LMRG.00609	1,151,932	LMRG.00609	+	10403S	1	N/A	
64	LMRG.00610	1,153,078	LMRG.00610	+	10403S	1	N/A	
64	LMRG.00611	1,153,848	LMRG.00611	+	10403S	1	Imo1168	

[†]TU number was arbitrarily assigned to each TU.

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Table 2. σ^B regulon members in *Listeria monocytogenes*. (cont.).

TU no. [†]	Gene locus	Coordinates for the gene [‡]		Gene	Strand	Strain [§]	Ref [¶]	Gene locus in EGDe	Putative σ^B promoter sequence [#]
65	LMRG.00672	1,208,314	1,211,514	LMRG.00672	+	10403S	1	Imo1226	aGTTTaaactatctcagaaaaGGGAATa
66	LMRG.00687	1,226,174	1,227,436	LMRG.00687	+	10403S	1	Imo1241	cGATTgagatcacaacagGGGTATg
67	LMRG.00710	1,244,576	1,245,715	LMRG.00710	-	10403S	1	Imo1261	cGTTTaaacttttagcttttGGGAATa
68	LMRG.00745	1,325,948	1,326,181	hfq	+	10403S	1	Imo1295	tGTTTggtaagaagaataaaGGGTATt
69	LMRG.00790	1,326,481	1,327,572	LMRG.00790	+	10403S	1	Imo1340	tGTTTtagctcttctgaaaaGGGTAAa
70	sbrA	1,358,285	1,358,354	ncRNA	+	10403S	1	N/A	tGTTTtaacttaggttttagcGGGTATt
70	LMRG.00826	1,358,624	1,359,718	LMRG.00826	+	10403S	1	Imo1375	
71	LMRG.00873	1,410,734	1,411,720	LMRG.00873	+	10403S	1	Imo1421	gGAATatttagggaagtatttaGGGTAAt
71	LMRG.00874	1,411,717	1,413,231	LMRG.00874	+	10403S	1	Imo1422	
72	LMRG.00880	1,417,969	1,419,162	opuCA	-	10403S	1	Imo1428	aGTTTaaatctatactagtttaGGGAAAt
72	LMRG.00879	1,417,309	1,417,965	opuCB	-	10403S	1	Imo1427	
72	LMRG.00878	1,416,381	1,417,307	opuCC	-	10403S	1	Imo1426	
72	LMRG.00877	1,415,695	1,416,366	opuCD	-	10403S	1	Imo1425	
73	LMRG.00885	1,423,129	1,424,220	LMRG.00885	-	10403S	1	Imo1433	cGTTTgaaagtgaatcagacGGGAAAAa
73	LMRG.00884	1,422,426	1,423,076	LMRG.00884	-	10403S	1	Imo1432	
74	LMRG.00891	1,431,900	1,432,508	LMRG.00891	-	10403S	1	N/A	gGTTTaaacttttagtttcaGGGAAAAa
75	LMRG.00906	1,445,400	1,446,524	rpoD	-	10403S	1	Imo1454	cGTTTtaaacgcgctaataigaTGGTATt
76	LMRG.01444	1,520,453	1,520,797	LMRG.01444	-	10403S	1	Imo1526	cGTTTtTaataagacagacaaacGGGTACa
77	LMRG.01431	1,533,837	1,534,655	LMRG.01431	-	10403S	1	Imo1539	gGTTTAaactctcgcaattgGGGTAAa
77	LMRG.01432	1,532,269	1,533,762	LMRG.01432	-	10403S	1	Imo1538	
78	LMRG.01365	1,604,884	1,605,339	LMRG.01365	-	10403S	1	Imo1602	aGTTTtagaggggaatactcaGGGTATa
78	LMRG.01366	1,604,338	1,604,862	LMRG.01366	-	10403S	1	Imo1601	
79	LMRG.01360	1,609,075	1,611,429	LMRG.01360	-	10403S	1	Imo1606	tGTTTaaagccctctattatcaAGGTATt
79	LMRG.01361	1,607,437	1,608,780	LMRG.01361	-	10403S	1	Imo1605	

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[‡]Genbank Assembly Accession ID of genomes for coordinates: 10403S (GCA_000168695.2), H7858 (GCA_000167155.1), EGDe and other strains (GCA_000196035.1). When there is more than one strain, coordinates in the 10403S genome were listed.

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Table 2. σ^B regulon members in *Listeria monocytogenes*. (cont.).

TU no. [†]	Gene locus	Coordinates for the gene [‡]	Gene	Strand	Strain [§]	Ref [¶]	Gene locus in EGDe	Putative σ^B promoter sequence [#]
80	LMRG.01301	1,675,776	<i>lapB</i>	-	10403S	1	Imo1666	aGTTTgtcatagataaaatagGGGAATa
81	LMRG.02772	1,721,784	LMRG.02772	-	10403S	1	Imo1698	aGTTTatttttaataaaatGGGTATa
82	LMRG.02778	1,725,929	LMRG.02778	-	10403S	1	Imo1704	aGCTTtaataactacgaagcGGGTATt
82	LMRG.02777	1,724,485	LMRG.02777	-	10403S	1	Imo1703	
82	LMRG.02776	1,724,069	LMRG.02776	-	10403S	1	Imo1702	
82	LMRG.02775	1,723,687	LMRG.02775	-	10403S	1	Imo1701	
83	LMRG.02556	1,733,561	LMRG.02556	+	10403S	1	Imo1713	tGTTTaaataatgcttataagGTGAAaAa
84	LMRG.02813	1,819,521	LMRG.02813	+	10403S	1	Imo1789	tGTACctaactcggtggaacGGGTATc
84	LMRG.02814	1,820,129	LMRG.02814	+	10403S	1	Imo1790	
85	LMRG.00977	1,862,459	LMRG.00977	+	10403S	1	Imo1830	cGTTTtttttcttaatttaGGGTAGa
86	LMRG.00985	1,871,682	LMRG.00985	-	10403S	1	Imo1838	aGCACtttttccactgtttGGCTCTa
86	LMRG.00984	1,870,414	LMRG.00984	-	10403S	1	Imo1837	
86	LMRG.00983	1,869,326	LMRG.00983	-	10403S	1	Imo1836	
86	LMRG.00982	1,866,121	LMRG.00982	-	10403S	1	Imo1835	
86	LMRG.00981	1,865,334	LMRG.00981	-	10403S	1	Imo1834	
86	LMRG.00980	1,864,423	LMRG.00980	-	10403S	1	Imo1833	
86	LMRG.00979	1,863,725	LMRG.00979	-	10403S	1	Imo1832	
86	LMRG.00978	1,863,099	LMRG.00978	-	10403S	1	Imo1831	
87	LMRG.01030	1,912,109	<i>chiA</i>	-	10403S	1	Imo1883	aGTTTatttttctactgttGGGTATt
88	LMRG.01080	1,964,027	LMRG.01080	-	10403S	1	Imo1933	gGTTTctctgttttagaataGGGAATa
88	LMRG.01079	1,963,201	LMRG.01079	-	10403S	1	Imo1932	
88	LMRG.01078	1,962,465	LMRG.01078	-	10403S	1	Imo1931	
88	LMRG.01077	1,961,489	LMRG.01077	-	10403S	1	Imo1930	
88	LMRG.01076	1,961,027	LMRG.01076	-	10403S	1	Imo1929	

[†]TU number was arbitrarily assigned to each TU.

[‡]Genbank Assembly Accession ID of genomes for coordinates: 10403S (GCA.000168695.2), H7858 (GCA.000167155.1), EGDe and other strains (GCA.000196035.1). When there is more than one strain, coordinates in the 10403S genome were listed.

[§]An initial list of 127 TUs was obtained from Liu *et al.* (2017), and for these TUs 10403S is the strain in which the Liu *et al.*'s study was conducted (which does not imply that this is the strain where this TU was first identified as σ^B -dependent); for all other TUs, the strain where a TU was initially identified as σ^B -dependent is listed. We did not attempt to determine the distribution of all σ^B -dependent TUs among *L. monocytogenes* strains as this represents a primary study that was defined as beyond the scope of this review.

[¶]References are coded as: 1 = [15]; 2 = [84]; 3 = [95]; 4 = [115]; 5 = [53]; 6 = [86]; 7 = [19]; 8 = [116]; 9 = [22].

[#]For TUs where there is more than one gene per TU, the promoter sequence is only listed for the first gene in the TU. The -10 and -35 promoter elements are in capital letters and underlined.

^{††}Mraheil *et al.* [84] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₂₋₁₇-GGG(A/T)A(A/T)' and allowing for one mismatch. The actual promoter sequence was not reported.

^{†††}Wurtzel *et al.* [115] reported identification of a σ^B promoter, however, the actual promoter sequence was not reported.

^{§§}Wemekamp-Kamphuis *et al.* [53] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₄-GGGTAA' and allowing for up to four mismatches. While only the -10 and -35 element sequences were reported in the original publication, we used the EGDe genome sequence to identify the complete sequence of the promoter.

^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemekamp-Kamphuis *et al.* [53] 'GTTGTN₁₄-GGGTAT' could not be found upstream of *gadC* in the EGDe genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.

^{##}Millilo *et al.* [86] reported identification of a putative σ^B promoter up to 1 Kb upstream of the gene, however, the promoter sequence was not reported.

^{††††}Ryan *et al.* [19] reported identification of a σ^B promoter upstream of the gene using the consensus sequence 'GTT-N₁₃₋₁₇-GGGWA' and allowing for several mismatches. The actual promoter sequence was not reported.

N/A: Not applicable; ncRNA: Noncoding RNA; sRNA: Small RNA; TU: Transcriptional unit.

Table 2. σ^B regulon members in *Listeria monocytogenes*. (cont.).

TU no. [†]	Gene locus	Coordinates for the gene [‡]		Gene	Strand	Strain [§]	Ref [¶]	Gene locus in EGDe	Putative σ^B promoter sequence [#]
89	LMRG.01140	2,022,210	2,022,929	LMRG.01140	+	10403S	1	Imo1992	gTTTaaatctttttttacGGATAAa
90	LMRG.01199.as	2,088,657	2,088,808	asRNA	-	10403S	1	N/A	aGATTacaaggttaaaattgTGGAAATa
91	LMRG.01217	2,102,959	2,103,936	bsh	-	10403S	1	Imo2067	tGTTTactccaactccgaGGGTACt
92	LMRG.01236	2,118,805	2,120,493	LMRG.01236	-	10403S	1	Imo2085	tGTTTcttttgcgtttttatGGGTATt
93	LMRG.01243	2,128,550	2,130,073	LMRG.01243	+	10403S	1	Imo2092	tGTTAccttttgcatacatgGGGAAAt
94	LMRG.01284	2,171,179	2,173,002	LMRG.01284	-	10403S	1	Imo2130	gGTTAattatcttataatGGGTATg
95	LMRG.02808	2,175,183	2,175,893	LMRG.02808	+	10403S	1	Imo2132	aGTTTatgcgttatattgcGGGAAAc
96	sbrE	2,183,996	2,184,506	ncRNA	+	10403S	1	N/A	cGTTTactatttttagaacGGTTATa
97	LMRG.01676	2,198,898	2,199,239	LMRG.01676	+	10403S	1	Imo2156	gGATTtctgttagtaacaaacGGGATAa
98	LMRG.01675	2,199,294	2,201,195	sepA	-	10403S	1	Imo2157	gGTTTgaaataattttttgAGGTATa
99	LMRG.01674	2,201,324	2,201,509	csbD	-	10403S	1	Imo2158	tGTTTtagcttctctatttgTGGAAAAa
100	LMRG.01658	2,215,733	2,216,806	LMRG.01658	-	10403S	1	Imo2174	tGAATagttgtgagcatactgGGGTATt
100	LMRG.01659	2,214,260	2,215,627	LMRG.01659	-	10403S	1	N/A	
101	LMRG.01641	2,238,749	2,239,144	spxA	-	10403S	1	Imo2191	aGTTTaaacaagttatagtagGGGTATc
101	LMRG.01642	2,237,864	2,238,517	LMRG.01642	-	10403S	1	Imo2190	
102	LMRG.01627	2,253,000	2,253,689	gpmA	-	10403S	1	Imo2205	gGTTTgacacttctactgaaaGGGAAAa
103	LMRG.01619	2,261,743	2,262,246	hmoB	+	10403S	1	Imo2213	tGTTTcaattatgaaaaacgTGGAAAa
104	LMRG.01602	2,279,640	2,280,065	arsC	+	10403S	1	Imo2230	tGTTTtagtaattttaaataaaGGGTAGa
104	LMRG.01601	2,280,130	2,280,999	LMRG.01601	+	10403S	1	Imo2231	
104	LMRG.01600	2,281,255	2,282,559	LMRG.01600	+	10403S	1	Imo2232	
105	LMRG.01561	2,319,172	2,319,528	LMRG.01561	-	10403S	1	Imo2269	gGTTTtaattagctcaaacgGGGTAAa
106	LMRG.01484	2,381,316	2,382,047	LMRG.01484	-	10403S	1	Imo2358	tGCTTtagaaaaaatagtgGGGTAAAt
106	LMRG.01485	2,380,769	2,381,299	LMRG.01485	-	10403S	1	N/A	
107	LMRG.02731	2,416,208	2,416,681	LMRG.02731	+	10403S	1	Imo2386	gGTTTtaataagctcattgTGGTAAa
108	LMRG.02732	2,416,792	2,418,018	LMRG.02732	+	10403S	1	Imo2387	aGTTTcacgctatgtttaaGGGAAAa

[†]TU number was arbitrarily assigned to each TU.

[‡]Genbank Assembly Accession ID of genomes for coordinates: 10403S (GCA_000168695.2), H7858 (GCA_000167155.1), EGDe and other strains (GCA_000196035.1). When there is more than one strain, coordinates in the 10403S genome were listed.

[§]An initial list of 127 TUs was obtained from Liu *et al.* (2017), and for these TUs 10403S is the strain in which the Liu *et al.*'s study was conducted (which does not imply that this is the strain where this TU was first identified as σ^B -dependent); for all other TUs, the strain where a TU was initially identified as σ^B -dependent is listed. We did not attempt to determine the distribution of all σ^B -dependent TUs among *L. monocytogenes* strains as this represents a primary study that was defined as beyond the scope of this review.

[¶]References are coded as: 1 = [15]; 2 = [84]; 3 = [95]; 4 = [115]; 5 = [53]; 6 = [86]; 7 = [19]; 8 = [116]; 9 = [22].

[#]For TUs where there is more than one gene per TU, the promoter sequence is only listed for the first gene in the TU. The -10 and -35 promoter elements are in capital letters and underlined.

^{††}Mraheil *et al.* [84] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₂₋₁₇-GGG[A/T]A[A/T]' and allowing for one mismatch. The actual promoter sequence was not reported.

^{†††}Wurtzel *et al.* [115] reported identification of a σ^B promoter, however, the actual promoter sequence was not reported.

^{§§}Wemekamp-Kamphuis *et al.* [53] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTTAA-N₁₄-GGGTAA' and allowing for up to four mismatches. While only the -10 and -35 element sequences were reported in the original publication, we used the EGDe genome sequence to identify the complete sequence of the promoter.

^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemekamp-Kamphuis *et al.* [53] 'GTTTGT-N₁₄-GGGTAT' could not be found upstream of *gadC* in the EGDe genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.

^{##}Millilo *et al.* [86] reported identification of a putative σ^B promoter up to 1 kb upstream of the gene, however, the promoter sequence was not reported.

^{††††}Ryan *et al.* [19] reported identification of a σ^B promoter upstream of the gene using the consensus sequence 'GTF-N₃₋₁₇-GGGAT' and allowing for several mismatches. The actual promoter sequence was not reported.

N/A: Not applicable; ncRNA: Noncoding RNA; sRNA: Small RNA; TU: Transcriptional unit.

Table 2. σ^B regulon members in *Listeria monocytogenes*. (cont.).

TU no. [†]	Gene locus	Coordinates for the gene [‡]	Gene	Strand	Strain [§]	Ref. [¶]	Gene locus in EGDe	Putative σ^B promoter sequence [#]
109	LMRG.02736	2,421,703	LMRG.02736	+	10403S	1	Imo2391	gGTTTatttttttactaccGGGAAAa
110	LMRG.01850	2,426,928	ltrC	+	10403S	1	Imo2398	tGTTTtagaatcctgtataaCGTCTATc
111	LMRG.01814	2,456,888	gadD3	-	10403S	1	Imo2434	gGTTTgtctctgtgttttaagtGGTATt
112	LMRG.01794	2,480,430	LMRG.01794	-	10403S	1	Imo2454	tGTTTtaaaataaacgagagGGGTAAAt
113	rli70-2	2,487,988	ncRNA	-	10403S	1	N/A	tGTTTCatttttttagagaggTGGAAAa
113	LMRG.01788	2,486,836	cggR	-	10403S	1	Imo2460	
113	LMRG.01789	2,485,794	gap	-	10403S	1	Imo2459	
113	LMRG.01790	2,484,469	pgk	-	10403S	1	Imo2458	
113	LMRG.01791	2,483,668	tpi	-	10403S	1	Imo2457	
113	LMRG.01792	2,482,134	pgm	-	10403S	1	Imo2456	
113	LMRG.01793	2,480,706	eno	-	10403S	1	Imo2455	
114	LMRG.01784	2,493,072	LMRG.01784	-	10403S	1	N/A	tGTTTggcatatgtataaaagAGGTATa
114	LMRG.01785	2,490,831	LMRG.01785	-	10403S	1	Imo2463	
114	LMRG.01786	2,489,826	LMRG.01786	-	10403S	1	Imo2462	
115	LMRG.01763	2,514,100	LMRG.01763	-	10403S	1	Imo2485	cGTTTataataatgaaaggaGGGAAAa
115	LMRG.01764	2,513,738	LMRG.01764	-	10403S	1	Imo2484	
116	LMRG.01754	2,524,174	phoU	-	10403S	1	Imo2494	gGTTAactatcgaataaaagtGGGTATg
117	LMRG.01737	2,544,528	LMRG.01737	-	10403S	1	Imo2511	gGTTTgcggaagcggtatttagTGGAAATa
118	LMRG.02695	2,605,244	LMRG.02695	-	10403S	1	Imo2573	tGCATtattttaagaataatcGGGAAAa
118	LMRG.02696	2,604,717	LMRG.02696	-	10403S	1	Imo2572	
118	LMRG.02697	2,604,084	LMRG.02697	-	10403S	1	Imo2571	
118	LMRG.02698	2,603,446	LMRG.02698	-	10403S	1	Imo2570	
118	LMRG.02699	2,601,649	LMRG.02699	-	10403S	1	N/A	
119	LMRG.02146	2,651,609	LMRG.02146	+	10403S	1	Imo2602	tGTTTtggtttaatgcacaaGGGAAATa
119	LMRG.02147	2,652,389	LMRG.02147	+	10403S	1	Imo2603	

[†]TU number was arbitrarily assigned to each TU.

[‡]Genbank Assembly Accession ID of genomes for coordinates: 10403S (GCA_000168695.2), H7858 (GCA_000167155.1), EGDc and other strains (GCA_000196035.1). When there is more than one strain, coordinates in the 10403S genome were listed.

[§]An initial list of 127 TUs was obtained from Liu et al. (2017), and for these TUs 10403S is the strain in which the Liu et al.'s study was conducted (which does not imply that this is the strain where this TU was first identified as σ^B -dependent); for all other TUs, the strain where a TU was initially identified as σ^B -dependent is listed. We did not attempt to determine the distribution of all σ^B -dependent TUs among *L. monocytogenes* strains as this represents a primary study that was defined as beyond the scope of this review.

[¶]References are coded as: 1 = [15]; 2 = [84]; 3 = [95]; 4 = [115]; 5 = [53]; 6 = [86]; 7 = [19]; 8 = [116]; 9 = [22].

[#]For TUs where there is more than one gene per TU, the promoter sequence is only listed for the first gene in the TU. The -10 and -35 promoter elements are in capital letters and underlined.

^{††}Mraheil et al. [84] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₂₋₁₇-GGG(A/T)A(A/T)' and allowing for one mismatch. The actual promoter sequence was not reported.

^{†††}Wurtzel et al. [115] reported identification of a σ^B promoter, however, the actual promoter sequence was not reported.

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^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemekamp-Kamphuis et al. [53] 'GTTTGTN₁₄-GGGTAT' could not be found upstream of *gadC* in the EGDc genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.

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Table 2. σ^B regulon members in *Listeria monocytogenes*. (cont.).

TU no. [†]	Gene locus	Coordinates for the gene [‡]		Gene	Strand	Strain [§]	Ref [¶]	Gene locus in EGDe	Putative σ^B promoter sequence [#]
120	LMRG.02217	2,707,930	2,708,736	LMRG.02217	-	10403S	1	Imo2672	tGATTAaagagaaaattttgTGGTACT
120	LMRG.02216	2,707,516	2,707,884	LMRG.02216	-	10403S	1	Imo2671	
120	LMRG.02215	2,707,157	2,707,519	LMRG.02215	-	10403S	1	Imo2670	
121	LMRG.02218	2,708,852	2,709,322	uspA2	+	10403S	1	Imo2673	tGCTTctttttttttttatGGGTATt
121	LMRG.02219	2,709,368	2,709,823	rplB	+	10403S	1	Imo2674	
122	LMRG.02000	2,736,180	2,736,554	LMRG.02000	+	10403S	1	Imo2697	cGTTTgactttctagtaaaGGGAAAAt
122	LMRG.02001	2,735,580	2,736,176	LMRG.02001	+	10403S	1	Imo2696	
122	LMRG.02002	2,734,569	2,735,558	LMRG.02002	+	10403S	1	Imo2695	
123	LMRG.01972	2,761,515	2,761,958	LMRG.01972	-	10403S	1	Imo2724	aGTTTaaagtaaacgaattGGGTATt
124	LMRG.01963	2,767,847	2,769,805	LMRG.01963	+	10403S	1	Imo2733	tGTTTtgcatacctagacaGGCAATa
124	LMRG.01962	2,769,866	2,772,514	LMRG.01962	+	10403S	1	N/A	
124	LMRG.01961	2,772,516	2,774,198	LMRG.01961	+	10403S	1	Imo2735	
124	LMRG.01960	2,774,195	2,775,328	LMRG.01960	+	10403S	1	N/A	
125	LMRG.01948	2,785,937	2,786,356	LMRG.01948	-	10403S	1	Imo2748	tGTTTaaagccgggagcgagTGGAAAg
125	LMRG.01949	2,784,319	2,785,602	LMRG.01949	-	10403S	1	Imo2747	
125	LMRG.01950	2,784,048	2,784,299	LMRG.01950	-	10403S	1	Imo2746	
126	LMRG.01913	2,828,463	2,830,379	LMRG.01913	-	10403S	1	N/A	tGTTTcaactgaactttttGGGCTAg
127	LMRG.02094	1,006,561	1,006,929	LMRG.02094	-	10403S	1	Imo0994	aGGTtattttactaaatgGGGTAAa
128	rl95	2,106,222	2,106,324	ncRNA	+	EGDe	2	rl95	σ^B box match reported ^{††}
129	rl47	2,226,036	2,226,349	ncRNA	+	EGDe	2	rl47	σ^B box match reported ^{††}
130	anti0946	981,423	981,635	asRNA	-	EGDe	2	anti0946	σ^B box match reported ^{††}
131	anti2270	2,360,500	2,360,555	asRNA	-	EGDe	2	anti2270	σ^B box match reported ^{††}
132	Lysine	826,431	826,710	sRNA	-	EGDe	2	Lysine	σ^B box match reported ^{††}
133	Imo1580	1,622,583	1,623,047	yxjE	+	EGDe	3	Imo1580	tGGTtcttttagaaaagaGGGTAAa
134	Imo1694	1,757,771	1,758,673	yfhF	+	EGDe	3	Imo1694	gGTTTtaactactactaaaaGGGAATa

[†]TU number was arbitrarily assigned to each TU.

[‡]GenBank Assembly Accession ID of genomes for coordinates: 10403S (GCA_000168695.2), H7858 (GCA_000167155.1), EGDc and other strains (GCA_000196035.1). When there is more than one strain, coordinates in the 10403S genome were listed.

[§]An initial list of 127 TUs was obtained from Liu *et al.* (2017), and for these TUs 10403S is the strain in which the Liu *et al.*'s study was conducted (which does not imply that this is the strain where this TU was first identified as σ^B -dependent); for all other TUs, the strain where a TU was initially identified as σ^B -dependent is listed. We did not attempt to determine the distribution of all σ^B -dependent TUs among *L. monocytogenes* strains as this represents a primary study that was defined as beyond the scope of this review.

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[#]For TUs where there is more than one gene per TU, the promoter sequence is only listed for the first gene in the TU. The -10 and -35 promoter elements are in capital letters and underlined.

^{††}Mirahel *et al.* [84] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₂₋₁₇-GGG[A/T]A[A/T]' and allowing for one mismatch. The actual promoter sequence was not reported.

^{†††}Wurtzel *et al.* [115] reported identification of a σ^B promoter, however, the actual promoter sequence was not reported.

^{§§}Wemekamp-Kamphuis *et al.* [53] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTTAA-N₁₄-GGGTAA' and allowing for up to four mismatches. While only the -10 and -35 element sequences were reported in the original publication, we used the EGDc genome sequence to identify the complete sequence of the promoter.

^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemekamp-Kamphuis *et al.* [53] 'GTTTGT-N₁₄-GGGTAT' could not be found upstream of *gadC* in the EGDc genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.

[#]Millilo *et al.* [86] reported identification of a putative σ^B promoter up to 1 kb upstream of the gene, however, the promoter sequence was not reported.

^{†††}Ryan *et al.* [19] reported identification of a σ^B promoter upstream of the gene using the consensus sequence 'GTTN₃₋₁₇-GGGWAT' and allowing for several mismatches. The actual promoter sequence was not reported.

N/A: Not applicable; ncRNA: Noncoding RNA; sRNA: Small RNA; TU: Transcriptional unit.

Table 2. σ^B regulon members in *Listeria monocytogenes*. (cont.).

TU no. [†]	Gene locus	Coordinates for the gene [‡]	Gene	Strand	Strain [§]	Ref [¶]	Gene locus in EGD ^e	Putative σ^B promoter sequence [#]
135	lmo2175	2,257,754	<i>dhbA</i>	-	EGDe	3	lmo2175	gGATTataataaaatagaaGGGAATg
136	rli118	199,775	<i>sRNA</i>	+	EGDe	4	rli118	σ^B box match reported ^{††}
137	rli119	215,458	<i>sRNA</i>	-	EGDe	4	rli119	σ^B box match reported ^{††}
138	rli127	1,473,701	<i>sRNA</i>	-	EGDe	4	rli127	σ^B box match reported ^{††}
139	rli128	1,575,917	<i>sRNA</i>	-	EGDe	4	rli128	σ^B box match reported ^{††}
140	anti0671	707,612	<i>asRNA</i>	+	EGDe	4	anti0671	σ^B box match reported ^{††}
141	anti1255	1,279,721	<i>asRNA</i>	-	EGDe	4	anti1255	σ^B box match reported ^{††}
142	anti0605	643,891	<i>asRNA</i>	-	EGDe	4	anti0605	σ^B box match reported ^{††}
143	anti0647-1	689,541	<i>asRNA</i>	-	EGDe	4	anti0647-1	σ^B box match reported ^{††}
144	anti0675-677	712,208	<i>asRNA</i>	+	EGDe	4	anti0675-677	σ^B box match reported ^{††}
145	anti2270	2,360,435	<i>asRNA</i>	+	EGDe	4	anti2270	σ^B box match reported ^{††}
146	lmo2362	2,431,688	<i>gadC</i>	+	EGDe	5	lmo2362	tGAATagttacggaagaaatGGGAACA ^{¶¶}
146	lmo2363	2,433,224	<i>gadB</i>	+	EGDe	5	lmo2363	
147	lmo2468	2,543,014	<i>clpP</i>	+	EGDe	5	lmo2468	cGTTTgacctagtttgaccattcGTGTATg ^{§§}
148	lmo1571	1,610,206	<i>pfk</i>	-	EGDe	5	lmo1571	gGTTTgttgagcttgctGTTTAA ^{§§}
149	lmo2477	2,552,312	<i>galE</i>	-	EGDe	5	lmo2477	aATAGtaagaagaaactcgaaatGGGTCTg ^{§§}
150	lmo1339	1,366,457	<i>lmo1339</i>	+	EGDe	5	lmo1339	aGTTTaaatttaattgattataaGGAGAAc ^{§§}
151	F-lmo.0374		<i>lsilA</i>		F2365	6	N/A	σ^B box match reported ^{¶¶}
152	lmo0036	40,705	<i>arcB</i>	+	LO28	7	lmo0036	σ^B box match reported ^{†††}
152	lmo0037	41,803	<i>arcD</i>	+	LO28	7	lmo0037	
153	lmo1367	1,390,209	<i>argR</i>	+	LO28	7	lmo1367	σ^B box match reported ^{†††}

[†]TU number was arbitrarily assigned to each TU.

[‡]Genbank Assembly Accession ID of genomes for coordinates: 104035 (GCA.000168695.2), H7858 (GCA.000167155.1), EGD^e and other strains (GCA.000196035.1). When there is more than one strain, coordinates in the 104035 genome were listed.

[§]An initial list of 127 TUs was obtained from Liu et al. (2017), and for these TUs 104035 is the strain in which the Liu et al.'s study was conducted (which does not imply that this is the strain where this TU was first identified as σ^B -dependent); for all other TUs, the strain where a TU was initially identified as σ^B -dependent is listed. We did not attempt to determine the distribution of all σ^B -dependent TUs among *L. monocytogenes* strains as this represents a primary study that was defined as beyond the scope of this review.

[¶]References are coded as: 1 = [15]; 2 = [84]; 3 = [95]; 4 = [115]; 5 = [53]; 6 = [86]; 7 = [19]; 8 = [116]; 9 = [22].

[#]For TUs where there is more than one gene per TU, the promoter sequence is only listed for the first gene in the TU. The -10 and -35 promoter elements are in capital letters and underlined.

^{††}Mraheil et al. [84] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₂₋₁₇-GGG(A/T)A(A/T)' and allowing for one mismatch. The actual promoter sequence was not reported.

^{†††}Wurtzel et al. [115] reported identification of a σ^B promoter, however, the actual promoter sequence was not reported.

^{§§}Wemekamp-Kamphuis et al. [53] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTTAA-N₁₄-GGGTAA' and allowing for up to four mismatches. While only the -10 and -35 element sequences were reported in the original publication, we used the EGD^e genome sequence to identify the complete sequence of the promoter.

^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemekamp-Kamphuis et al. [53] 'GTTTGTN₁₄-GGGTAT' could not be found upstream of *gadC* in the EGD^e genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.

[#]Millilo et al. [86] reported identification of a putative σ^B promoter up to 1 kb upstream of the gene, however, the promoter sequence was not reported.

^{†††}Ryan et al. [19] reported identification of a σ^B promoter upstream of the gene using the consensus sequence 'GTT-N₁₃₋₁₇-GGGWAAT' and allowing for several mismatches. The actual promoter sequence was not reported.

N/A: Not applicable; nRNA: Noncoding RNA; sRNA: Small RNA; TU: Transcriptional unit.

Table 2. σ^B regulon members in *Listeria monocytogenes*. (cont.).

TU no. [†]	Gene locus	Coordinates for the gene [‡]		Gene	Strand	Strain [§]	Ref. [¶]	Gene locus in EGDc	Putative σ^B promoter sequence [#]
154	lmo0373	399,645	400,979	lmo0373	+	FSL J1-208	8	lmo0373	tGTTTttaataaatgtatgCTATAtt
155	lmo2668	2,740,888	2,742,970	lmo2668	-	FSL J1-194	8	lmo2668	aGATTttaataaaacgaacAGGAGGg
155	lmo2667	2,740,390	2,740,868	lmo2667	-	FSL J1-194	8	lmo2667	
155	lmo2666	2,740,052	2,740,347	lmo2666	-	FSL J1-194	8	lmo2666	
155	lmo2665	2,738,719	2,740,005	lmo2665	-	FSL J1-194	8	lmo2665	
156	lmo0398	419,531	420,002	lmo0398	+	10403S	8	lmo0398	gGTTTcattagaatgtaattGTAAgc
156	lmo0399	419,987	419,992	lmo0399	+	10403S	8	lmo0399	
156	lmo0400	420,318	420,323	lmo0400	+	10403S	8	lmo0400	
156	lmo0401	421,452	424,096	lmo0401	+	10403S	8	lmo0401	
156	lmo0402	424,116	426,064	lmo0402	+	10403S	8	lmo0402	
157	peg.418	412,643	413,485	LMRG.00233	+	H7858, 10403S	9	lmo0551	aGGCTattttaaggagggtgaGGGAAGa
158	peg.539	530,186	530,794	LMRG.00359	+	H7858, 10403S	9	lmo0671	cGTTTtagcgtaaaactggaGGGAAGa
159	peg.591	576,055	577,860	LMRG.00412	+	H7858, 10403S	9	lmo0723	tGAATactcttttaaaaaacaGGTAAa
159	peg.592	577,873	578,601	LMRG.00413	+	H7858, 10403S	9	lmo0724	
160	peg.1164	1,121,859	1,123,154	LMRG.00750	+	H7858, 10403S	9	lmo1300	tGTTTgatgtttggcaaatagAGGCATa
161	peg.1957	1,951,051	1,951,701	LMRG.01245	-	H7858, 10403S	9	lmo2094	aGGATcactttgcgcgataaTGGCAAag
161	peg.1958	1,951,703	1,952,635	LMRG.01246	-	H7858, 10403S	9	lmo2095	

[†]TU number was arbitrarily assigned to each TU.
[‡]Genbank Assembly Accession ID of genomes for coordinates: 10403S (GCA_000168695.2), H7858 (GCA_000167155.1), EGDc and other strains (GCA_000196035.1). When there is more than one strain, coordinates in the 10403S genome were listed.
[§]An initial list of 127 TUs was obtained from Liu *et al.* (2017), and for these TUs 10403S is the strain in which the Liu *et al.*'s study was conducted (which does not imply that this is the strain where this TU was first identified as σ^B -dependent); for all other TUs, the strain where a TU was initially identified as σ^B -dependent is listed. We did not attempt to determine the distribution of all σ^B -dependent TUs among *L. monocytogenes* strains as this represents a primary study that was defined as beyond the scope of this review.
[¶]References are coded as: 1 = [15]; 2 = [84]; 3 = [95]; 4 = [115]; 5 = [53]; 6 = [86]; 7 = [19]; 8 = [116]; 9 = [22].
[#]For TUs where there is more than one gene per TU, the promoter sequence is only listed for the first gene in the TU. The -10 and -35 promoter elements are in capital letters and underlined.
^{††}Mraheil *et al.* [84] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₂₋₁₇-GGG[A/T]A[A/T]' and allowing for one mismatch. The actual promoter sequence was not reported.
^{†††}Wurtzel *et al.* [115] reported identification of a σ^B promoter, however, the actual promoter sequence was not reported.
^{§§}Wemekamp-Kamphuis *et al.* [53] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTTAN₁₄-GGGTAA' and allowing for up to four mismatches. While only the -10 and -35 element sequences were reported in the original publication, we used the EGDc genome sequence to identify the complete sequence of the promoter.
^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemekamp-Kamphuis *et al.* [53] 'GTTGT-N₁₄-GGGTAT' could not be found upstream of *gadC* in the EGDc genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.
^{##}Millilo *et al.* [86] reported identification of a putative σ^B promoter up to 1 Kb upstream of the gene, however, the promoter sequence was not reported.
^{††††}Ryan *et al.* [19] reported identification of a σ^B promoter upstream of the gene using the consensus sequence 'GTN₁₋₃-GGGWAAT' and allowing for several mismatches. The actual promoter sequence was not reported.
N/A: Not applicable; ncRNA: Noncoding RNA; sRNA: Small RNA; TU: Transcriptional unit.

Table 2. σ^B regulon members in *Listeria monocytogenes*. (cont.).

TU no. [†]	Gene locus	Coordinates for the gene [‡]	Gene	Strand	Strain [§]	Ref. [¶]	Gene locus in EGD [§]	Putative σ^B promoter sequence [#]
162	peg.2644	2,629,813	LMRG.01861	-	H7858, 10403S	9	Imo2837	tGTTCCgcttcgattcGGGTATt
162	peg.2643	2,628,742	LMRG.01862	-	H7858, 10403S	9	Imo2836	
162	peg.2642	2,627,935	LMRG.01863	-	H7858, 10403S	9	Imo2835	
162	peg.2641	2,626,847	LMRG.01864	-	H7858, 10403S	9	Imo2834	
163	peg.679	666,801	LMRG.02246	+	H7858, 10403S	9	Imo0821	tGTGTtagcggcgaaaaaacGGGTATt
164	peg.95	86,548	LMRG.02326	+	H7858, 10403S	9	Imo0075	aGAATgaaataactatatacGGGAACa
164	peg.96	87,318	LMRG.02327	+	H7858, 10403S	9	Imo0076	
165	peg.125	118,980	LMRG.02354	+	H7858, 10403S	9	Imo0105	gGTTTataaatcaaaatcgGGGTGAa
166	peg.2467	2,440,597	LMOH7858.2920	+	H7858	9	N/A	aGTTTtagatgtttgtgttaaGGGAAa
167	peg.525	520,891	LMOH7858.0721.1	+	H7858	9	N/A	cGATTttttcatggataaaaGGGTATa
167	peg.526	521,748	LMOH7858.0723	+	H7858	9	N/A	
168	peg.1531	1,497,392	LMOH7858.1776	-	H7858	9	N/A	gGTTTagttaacggtatttaattGGGTAAt
169	peg.2775	2,774,201	LMOH7858.0394	+	H7858	9	N/A	tGTTTctgtgtgataagaaaatGGGAACa
170	peg.333	330,370	LMOH7858.0523	+	H7858	9	Imo0460	tGTTTctatcgacaaagaaGGGATAT
170	peg.334	332,575	LMOH7858.0524	+	H7858	9	N/A	
171	peg.335	334,497	LMOH7858.0524.1	+	H7858	9	Imo0461	cCTATgaagaagaaaagagtaGTGATTa
171	peg.336	334,891	LMOH7858.0524.2	+	H7858	9	Imo0462	
171	peg.337	335,404	LMOH7858.0527	+	H7858	9	Imo0463	
171	peg.338	335,908	LMOH7858.0528	+	H7858	9	Imo0464	

[†]TU number was arbitrarily assigned to each TU.

[‡]Genbank Assembly Accession ID of genomes for coordinates: 10403S (GCA.000168695.2), H7858 (GCA.000167155.1), EGD[§] and other strains (GCA.000196035.1). When there is more than one strain, coordinates in the 10403S genome were listed.

[§]An initial list of 127 TUs was obtained from Liu et al. (2017), and for these TUs 10403S is the strain in which the Liu et al.'s study was conducted (which does not imply that this is the strain where this TU was first identified as σ^B -dependent); for all other TUs, the strain where a TU was initially identified as σ^B -dependent is listed. We did not attempt to determine the distribution of all σ^B -dependent TUs among *L. monocytogenes* strains as this represents a primary study that was defined as beyond the scope of this review.

[¶]References are coded as: 1 = [15]; 2 = [84]; 3 = [95]; 4 = [115]; 5 = [53]; 6 = [86]; 7 = [19]; 8 = [116]; 9 = [22].

[#]For TUs where there is more than one gene per TU, the promoter sequence is only listed for the first gene in the TU. The -10 and -35 promoter elements are in capital letters and underlined.

^{††}Mraheil et al. [84] reported identification of a σ^B promoter up to 50 nt upstream of the gene using the consensus sequence 'GTTT-N₁₂₋₁₇-GGG(A/T)A(A/T)' and allowing for one mismatch. The actual promoter sequence was not reported.

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^{¶¶}The σ^B -dependent promoter for *gadC* reported by Wemekamp-Kamphuis et al. [53] 'GTTTGN₁₄-GGGTAT' could not be found upstream of *gadC* in the EGD[§] genomic sequence; in fact that promoter sequence matches to the one upstream of *gadD* (TU111). We examined the sequence upstream of *gadC* and identified a putative σ^B promoter 460 nt upstream of *gadC*, which is the one listed here.

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N/A: Not applicable; ncRNA: Noncoding RNA; sRNA: Small RNA; TU: Transcriptional unit.

Table 3. σ^B regulon members grouped by function.

Function	σ^B regulon members (n)	Comments [†]
1. Stress response	73	Includes 23 and 5 genes also classified into the general categories 'virulence' and 'metabolism'
1.1. Osmotic	18	Two genes also classified into 1.6, one gene also classified into 1.4
1.2. Oxidative	14	One gene also classified into 1.3
1.3. Acid	12	One gene also classified into 1.2
1.4. Antibiotic resistance	6	One gene also classified into 1.1
1.5. Bile response	3	
1.6. Alkaline stress	2	Two genes also classified into 1.1
1.7. Other stresses [‡]	22	
2. Virulence	51	Includes 23 and 4 genes also classified into the general categories 'stress response' and 'metabolism'
3. Metabolism	101	Includes five and four genes also classified into the general categories 'stress response' and 'virulence'
3.1. Carbon metabolism	73	One gene also classified into 3.6
3.2. Nucleotide metabolism	9	
3.3. Ion transport	8	
3.4. Vitamin metabolism	5	
3.5. Protein metabolism	4	One gene also classified in 3.6
3.6. Other metabolisms [§]	4	One gene also classified into 3.1, one gene also classified in 3.5
4. Other functions [¶]	9	
5. Unknown	102	
Total	304	

[†]In the 'Comments' column, overlaps between the general function categories are listed. Under one general category, overlaps between the subgroups of functions in this category are also shown.

[‡]Other stress responses include response to cold stress and general stress.

[§]Other metabolisms include cell wall metabolism and lipid metabolism.

[¶]Other functions include competence, and regulators of unknown functions.

Function search strategy & reference categories

Genes of interest were searched individually for studies on their functions in *L. monocytogenes* and other bacteria. Evidence for functions was classified into four categories: Functions with experimental evidence in *L. monocytogenes*; Functions with experimental evidence in *Bacillus*, other firmicutes or any bacteria; Functions suggested by GO terms and conserved amino acid motif; and Unknown function. Functions not based on references in category 1 need to be further explored with complementary experiments. Searches for studies on gene functions were performed through Google scholar and Pubmed, while the databases Subtiwiki, QuickGO, and Uniprot were searched for functions in *Bacillus*, GO terms and homology in protein products. Gene names, as well as *locus* name in 10403S (LMRG) and EGDe (lmo) were used as keywords in searching. A snowballing approach [23] was also used to find references on gene functions.

Functional groups

While specific functions of σ^B -dependent genes were found during the function search, broader functional groups could provide insights in the connections and cooperation of these genes and allow easier classification. Generally, gene functions were divided into five general categories based on known roles of σ^B , including stress response, virulence, metabolism, other functions and unknown function. While more than 100 genes with unknown functions were found, most of the genes with identified putative functions were classified into the 'stress response,' 'virulence' and 'metabolism' categories. Some genes were classified into more than one general category (Table 3).

Results & discussion

Functions associated with the σ^B regulon members

Stress response (including osmotic, oxidative, acid, antibiotic, bile, alkaline & other stresses)

Since the first report of σ^B in *L. monocytogenes* in 1998 [10], modulation of stress response has been recognized as a key role of σ^B in this organism, consistent with the role of σ^B in other firmicutes, including *Bacillus* and *Staphylococcus*

spp. [7]. Transcriptional, translational and phenotypic data support contribution of σ^B to this bacterium's ability to survive and grow under different stresses outside a host, such as osmotic stress, as well as specific stresses inside a host, such as bile stress [12,24–27]. In this review, we identified 73 σ^B regulon members that are involved in different aspects of stress response and survival, including osmotic, oxidative, acid, alkaline and bile stress, or are involved in antibiotic resistance. Identification of these 73 σ^B regulon members in response to different stress conditions confirms the role of σ^B as the general stress response regulator in *L. monocytogenes*, allowing this pathogen to cope with host defense mechanisms and to survive under stress conditions.

The σ^B regulon includes 18 members involved or putatively involved in osmotic stress response

Soon after its initial discovery, σ^B has been reported to contribute to the osmotic stress resistance of *L. monocytogenes*, as supported by a variety of phenotypic [11,20,28] as well as gene expression studies [29,30]. The 18 σ^B regulon members identified with known or putative roles in osmotic stress resistance include eight genes that represent three well-studied σ^B -dependent osmotic stress resistance systems, including OpuC (*opuCABCD*), Gbu (*gbuABC*) and BetL (*betL*). All three of these systems facilitate accumulation of compatible solutes under high osmolarity conditions. Specifically, OpuC is required for carnitine accumulation while Gbu and BetL are two betaine transporters. These systems transport carnitine and glycine betaine into the cytoplasm from outside of the cell membrane to combat high salt stress [29,31]. An additional eight genes that are part of the σ^B regulon encode proteins with putative roles in osmotic stress resistance. For three of these genes (LMRG_00884, LMRG_00583 and LMRG_01600) transposon insertions affected the growth of *L. monocytogenes* LO28 under high salt conditions [32]; however, mechanisms and specific functions of these genes have not yet been reported. LMRG_01658 as well as three genes (LMRG_00208, LMRG_00211–00212) in a five-gene TU are σ^B regulon members that have been reported as induced by salt stress; Ribeiro *et al.* hypothesized that under salt stress, expression of these genes allowed for enhanced synthesis of exopolysaccharides in response to osmolarity changes [33]. While transcriptomic data indicate a contribution to osmotic stress response by these genes, further physiologic studies are needed to clearly define their functions.

We identified three genes (LMRG_00672, *hfq* and *dtgT*) that are also involved in other functions in addition to osmotic stress response. Phenotypic characterization of LMRG_00672 transposon insertion mutants has revealed that this gene supports growth of *L. monocytogenes* in sodium chloride, and it is involved in resistance to streptomycin as well as attachment and virulence [34]. Furthermore, two σ^B regulon members (*hfq*, *dtgT*) have been reported to play important roles in *L. monocytogenes*' osmotic stress resistance as well as other stress responses. Hfq is a regulator binding to small RNAs (sRNAs) during intracellular growth [35]. Hfq mutants show attenuated virulence and impaired resistance to osmotic stress and ethanol stress [36]. The di- and tripeptide transporter *dtgT* is involved in salt stress protection as well as in virulence, as shown in a mouse infection model [37]. Overall, the apparent involvement of at least 18 σ^B regulon members in osmotic stress further supports a key role of σ^B in *L. monocytogenes*' resistance and response to osmotic stress, a stress that this pathogen is likely to encounter in a variety of environments, including but not limited to certain foods (e.g., food preserved with salt, such as many cheeses and smoked seafood) as well as the environment encountered in the small intestine [38].

The σ^B regulon includes 14 members involved or putatively involved in oxidative stress response

While *L. monocytogenes* can survive under oxidative stress conditions encountered inside macrophages, the role of σ^B in regulation of oxidative stress response remains controversial. Previous phenotypic studies have reported results ranging from hypersensitivity to hyper-resistance for *sigB* null mutants, suggesting a complex σ^B -regulated network responding to different oxidative conditions (recently reviewed in [39]). In our systematic review, 14 σ^B regulon members are classified into the subgroup of oxidative stress response. Oxidative stress caused by products such as reactive oxygen species is a critical part of host defense mechanisms, so it is not surprising that 6 of 14 genes are also grouped into virulence. The four-gene TU *qoxABCD* encodes QoxAB, an aa₃-type oxidase, which is required for aerobic growth of *Bacillus* [40]. In *L. monocytogenes*, QoxAB has been found to contribute to aerobic respiration and intracellular replication, as well as the initial stage of murine infection in experiments using a $\Delta qoxAB$ mutant [41]. The σ^B regulon member SpxA, encoded by LMRG_01641, is required for pathogenesis and oxidative stress response in *L. monocytogenes* as an *spxA* mutant showed impaired ability of vacuolar escape and increased sensitivity to both peroxide and disulfide stress [42]. In addition, the superoxide dismutase (Sod), encoded by the σ^B regulon member LMRG_00891, protects organisms against superoxides and reactive oxygen species. Deletion of *sod* results in impaired survival within macrophages and mice, indicating its contribution to virulence [43]. In addition, two σ^B regulon members, *uspA* and *yqhD*, may be involved in oxidative stress response as well as other

functions. The universal stress protein A (UspA), encoded by LMRG_00196, contributes to extracellular survival of *L. monocytogenes* under acid stress and oxidative stress [44]. In *E. coli*, *yqhD* encodes a NADPH-dependent aldehyde reductase, which is part of a glutathione-independent mechanism in response to oxidative stress [45]. In addition, *yqhD* has been reported to contribute to isobutanol production in *E. coli* [46]. The role of *yqhD* in *L. monocytogenes* has not been fully confirmed.

Other σ^B regulon members in the oxidative stress response group include five genes and one noncoding RNA (ncRNA). The σ^B -dependent TU LMRG_02643-02644 contains *hlsO* and *coaX*. The heat-shock proteins HslO is redox regulated and protects both thermally and oxidatively damaged proteins from irreversible aggregation [47]. In *Bacillus*, *coaX* encodes a type III pantothenate kinase that is responsible for the conversion of pantothenate into Coenzyme A [48]. LMRG_00885, encoding a glutathione reductase, has also been reported to play roles in oxidative stress resistance in *E. coli* [49]. Transcriptional studies have revealed upregulation of putative oxidoreductase-encoding genes including LMRG_00357 [24] and LMRG_02813, when *L. monocytogenes* is exposed to oxidative stresses such as chlorine dioxide [50]. The ncRNA *sbrE* contributes to the expression of TU LMRG_00319-00320 and has been reported to be upregulated when *L. monocytogenes* is exposed to oxidative stress [51]. Further studies are needed to define the roles of these six σ^B regulon members in *L. monocytogenes*' defense against oxidative stress. Taken as a whole, the regulation of these genes and ncRNA suggests important contributions of σ^B to *L. monocytogenes*' response to endogenous oxidative stress in an aerobic environment, and exogenous oxidative stress caused by host immune system as it has been shown in *Staphylococci* [52].

The σ^B regulon includes 12 members involved or putatively involved in acid stress response

σ^B directly regulates the transcription of 12 genes contributing to acid resistance. The glutamate decarboxylase (GAD) system is one of the principal systems for *L. monocytogenes* to withstand acid stress. Among genes encoding components of the GAD system, *gadB*, *gadC* and *gadD* belong to σ^B regulon [53,54]. The GAD system consists of a glutamate decarboxylase enzyme and a glutamate- γ -aminobutyrate (GABA) antiporter. This system produces accumulated GABA and collaborates to reduce acidification inside the cell. In addition, *gadD* is involved in GABA metabolism via the GABA shunt pathway. Deletion of *gadD* increased survival of *L. monocytogenes* under acid treatment by increasing accumulation of GABA [55]. Another crucial mechanism activated by σ^B under acid stress involves putative arginine deiminase genes, which have been shown to play a role in the acid tolerance of other bacterial genera. A σ^B -dependent putative regulator ArgR, regulates transcription of the *arcA*, *arcB*, *arcD* locus where an additional putative σ^B -dependent promoter was identified upstream [19]. In addition to these two systems, *uspA* is crucial for *L. monocytogenes*' resistance to acid stress, and as discussed above, this gene is also involved in oxidative stress [44]. Other σ^B regulon members identified to contribute to acid resistance of *L. monocytogenes* include LMRG_00484 and LMRG_02736. Importance of these genes in acid resistance has been confirmed in gene knockout experiments, but their function remains unknown [56]. LMRG_02736 and LMRG_01387 have putative roles in acid stress as suggested by their homology to *B. subtilis* general stress proteins and induction under acid stress [57]. Overall, these 12 genes reveal important σ^B -dependent systems responsible for *L. monocytogenes*' adaption to acid stress.

The σ^B regulon includes six members involved or putatively involved in antibiotic resistance

While previous studies report a low prevalence of resistant strains [58,59], it is likely that *L. monocytogenes* is exposed to antibiotics in different environmental niches. There are six σ^B regulon members involved in antibiotic resistance mechanisms, with five of them also having additional functions. The TU *mpoABCD* is involved in carbon metabolism and resistance to class IIa bacteriocins in *L. monocytogenes* [60]. This TU encodes a mannose PTS permease similar with that encoded by the *mpt* operon. Mutants of *mpo* showed an intermediate resistance to class IIa bacteriocins. In 2011, characterization of *mpo* mutant also showed that this PTS system plays an important role in PrfA inhibition [61]. The stress response gene LMRG_00672 is a drug exporter of the RND superfamily, responsible for the streptomycin resistance exhibited by *L. monocytogenes* strain 10403S [34]. The overlap of antibiotic resistance and other functions is further supported by the upregulation of stress and virulence genes under subinhibitory concentrations of antibiotics [62]. The fosfomycin resistance protein (FosX) encoding gene is also part of σ^B regulon, and it helps *L. monocytogenes* to respond to antibiotic stress by catalyzing the hydration of fosfomycin [63]. These six σ^B regulon members contributing to antibiotic resistance in *L. monocytogenes* point to a future direction of work on the role of σ^B in the regulation of antibiotic resistance in *L. monocytogenes*.

The σ^B regulon includes three members involved or putatively involved in bile stress response

In host animals, *L. monocytogenes* is typically exposed to a bile stress environment with more than 0.3% (wt/vol) bile salts [64]. Three important genes in bile resistance are directly regulated by σ^B : *bsh*, *bileA* and *bileB*. *bsh* encodes a bile-salt hydrolase, and the TU of *bileAB* (*opuB*) encodes a bile-exclusion system [65]. *Bsh* is the only bile-salt hydrolase in *L. monocytogenes*, and deletion of *bsh* results in decreased resistance to bile and reduced virulence and liver colonization in mice [66]. *Bile*, a transporter similar to the OpuC protein, was believed to be a weak regulator of osmotic stress response, but phenotypic experiments have supported its specific role in bile stress response and intestinal colonization of *L. monocytogenes* [65]. These three genes have also been reported to be directly regulated by PrfA and, therefore, are considered virulence-related [67]. Regulation of bile stress response by σ^B and PrfA is an important example of the regulatory networks that govern the transition between environmental stresses in *L. monocytogenes*' passage through the digestive tract.

The σ^B regulon includes 24 members involved or putatively involved in other stress responses

A σ^B -dependent positive feedback loop regulates transcription of the *sigB* and *rsb* genes in the σ^B operon [7]. As the σ^B operon has a σ^B -dependent promoter, this four-gene TU of *rsbV-rsbW-sigB-rsbX* is included in the σ^B regulon. This operon is also crucial for the post-transcriptional regulation of σ^B activity. Briefly, the activation of σ^B is allowed when the anti-sigma factor RsbW binds to anti-anti-sigma factor RsbV, and σ^B is released from the anti-sigma factor to initiate the transcription [68]. Other stress response genes in σ^B regulon include two involved in alkaline stress, one involved in cold stress and 21 with roles in general stress response. LMRG_00583 and LMRG_01600 are involved in alkaline stress and osmotic stress [32]. σ^B has been reported to be required for *L. monocytogenes* to grow at low temperature with nutrition restriction, a gene essential for this bacterium to grow at cold, *ltrC*, is σ^B -dependent [69–71]. Among the σ^B -dependent general stress response genes, five genes are also virulence-related, including *htrA*, *fri* and the TU of *clpC-mcsAB*. *HtrA* is a serine protease required for optimal growth of *L. monocytogenes* under stress conditions including salt, heat and oxidants [72]. *Fri* promotes tolerance to stresses such as iron limitation and oxidative stress, as well as contributes to intracellular growth in *L. monocytogenes* [73]. The *clpC* operon is involved in response to stresses including iron limitation, heat and osmotic stress, as well as in virulence [74]. The other 12 genes were identified as putatively involved with general stress response as homology to stress response genes in other species was found. Further studies in *L. monocytogenes* are needed to define the roles of these putative stress response genes.

Virulence

Overall, 51 σ^B regulon members were classified in the 'virulence' group. The 51 σ^B regulon members in the 'virulence' group included: 23 genes also classified into the group 'stress response', four genes also classified into the group 'metabolism' and 24 genes classified into the 'virulence' group only. Genes classified into both 'virulence' and 'stress response' groups are typically required for survival and multiplication under host-related conditions such as bile and acidic pH in the gastric environment or oxidative stress in the host-cell phagosome.

Among the 24 σ^B -regulated, virulence-specific genes, we identified the key transcription activator of *L. monocytogenes*' virulence gene expression, positive regulatory factor A (PrfA). PrfA can be transcribed from multiple promoters, regulated by σ^B , σ^A and PrfA itself [67]. The tightly regulated expression of PrfA is required for optimal growth inside and outside the host, as virulence gene expression is costly under limited resources [75]. Meanwhile, several virulence-specific genes are under coregulation of PrfA and σ^B , including internalin-encoding genes *inlA* and *inlB*, which are required for adhesion and invasion of *L. monocytogenes* into host cells [76]. Other σ^B -dependent internalin genes include *inlC2*, *inlD* and LMRG_00293, as well as H7858 specific σ^B regulon members LMOh7858_2920, LMOh7858_0394 and LMOh7858_0527. In addition, *srtA*, which is involved in proteolysis and processing of internalin proteins [77], is required for infection. Two virulence genes *chiA* and LMRG_02354 encode proteins in chitin catabolic process. Chitinase expressed by bacterial pathogens have proven to be crucial for infecting animals and humans, and in *L. monocytogenes*, the mutants lacking *chiA* were defective for growth in the livers and spleens of mice [78,79]. Other important virulence genes include *mogR*, which regulates flagellar motility genes as a transcriptional repressor [80]; *lapB*, which is required for entry into eukaryotic cells [81]; *mecA*, which regulates virulence genes needed for escape from phagosomes [82]; and LMRG_02556, which is involved in cell morphogenesis and intracellular replication [83]. Three σ^B -dependent ncRNAs also contributing to pathogenesis were identified: *Lysine*, strain-specific *lsiA* and *rili33* [84–86].

It is worth noting that specific metabolism activities (e.g., glycolysis, glycerol metabolism) are involved in the pathogenesis of intracellular pathogens like *L. monocytogenes*. A well-studied example highlighting the overlap between metabolism and virulence is the interaction between the PTS system and PrfA [87,88], which shows a close link between the glucose-, mannose- and cellobiose-specific PTS permeases and the modulation of the PrfA activity in *L. monocytogenes* [87,88]. There are four σ^B regulon members involved in both virulence and carbon metabolism. LMRG_01789 encodes glyceraldehyde 3-phosphate dehydrogenase (Gap), one of the most important enzymes in glycolysis, while LMRG_01793 encodes enolase (Eno). In *L. monocytogenes*, Gap and Eno have been shown to also bind to human plasminogen, suggesting a role in virulence [89]. In addition, *lacD* and *pfk* have been identified as virulence-related in other Firmicutes; in *Streptococcus pyogenes*, *lacD* is responsible for lactose and galactose utilization as well as virulence gene regulation [90], and the glycolytic gene *pfk* is also a putative virulence-related gene in *Bacillus anthracis* [91]. Together, σ^B regulon members, including transcriptional regulators, expose important features of virulence regulation by σ^B in *L. monocytogenes*, such as the regulation of metabolism and stress response genes contributing to infection.

Metabolism (including carbon, nucleotide, ion, vitamin, protein & others)

Accumulating evidence suggests that σ^B is also involved in regulation of metabolism-related functions in *L. monocytogenes*. In particular, σ^B -regulated carbon metabolism (e.g., PTS and glycerol metabolisms) has been well established [56,87,92]. Changes in carbon metabolism do not only provide energy to the bacterium under conditions with limited nutrients but also allow indirect regulation of other genes (e.g., glycerol metabolism affects PrfA activity). Other metabolic activities are also important for *L. monocytogenes* homeostasis and pathogenesis; for example, modulation of ion uptake is crucial for intracellular growth as host immune systems could reduce the bioavailability of ions to invading microbial pathogens [93]. Overall, the involvement of more than 100 σ^B regulon members in metabolism confirms a key role of *L. monocytogenes* σ^B in regulation of metabolic functions, particularly in carbon metabolism, which involves 73 σ^B regulon members. Since the role of σ^B -regulated genes in the transition of carbon metabolism contributes to intracellular growth, together with metabolism of other macronutrients, micronutrients and cell wall, it seems feasible that σ^B assists the cell to maintain homeostasis during growth and adaptation to changing conditions.

The σ^B regulon includes 73 members involved or putatively involved in carbon metabolism

Previous studies clearly suggest a major role of σ^B in regulating carbon and energy metabolism presumably allowing *L. monocytogenes* to utilize the limited nutrients available in the changing environments [94,95]. With 73 σ^B regulon members, carbon metabolism is the largest functional subgroup. The full list of 73 σ^B regulon members is provided in Supplementary Table 2. Out of the 73 σ^B regulon members assigned to carbon metabolism, five are also involved in stress response, four are also involved in virulence and the remaining 64 are carbon metabolism-specific genes directly regulated by σ^B . Among the 64-carbon metabolism-specific genes, there are three regulators of carbon metabolism, CggR, LMRG_02213 and NagR. CggR is the central glycolytic gene regulator controlling the transcription of the *gapA* operon in *Bacillus* [96]. LMRG_02213 is involved in the phosphoenolpyruvate-dependent sugar phosphotransferase system. NagR acts as a transcriptional inhibitor in the absence of N-acetylglucosamine (GlcNAc) by repressing the expression of *nagA* and *nagB* and is also a gene product of the three-gene TU *nagABR* [97]. NagA and NagB are two deaminases responsible for GlcNAc degradation while NagA is also essential for cell wall components biosynthesis [98]. As a major component of chitin, GlcNAc can be utilized by *Listeria* species as the source of carbon and nitrogen in a temperature-dependent way in the absence of glucose [99]. The ability of utilizing GlcNAc may contribute to the saprophytic lifestyle of *L. monocytogenes* in soil [99]. Another TU, LMRG_00594-00611, contains 18 genes that are involved in 1,2-propanediol utilization via a *pduD*-dependent pathway [100]. 1,2-propanediol is an important intracellular carbon source during infection for bacterial pathogens like *Salmonella* [101] and has been reported to be degraded by *L. innocua* [100]. Another confirmed σ^B -dependent multigene TU involved in carbon metabolism is LMRG_01431-01432 encoding a glycerol kinase and a glycerol uptake facilitator involved in glycerol metabolism [87]. Several genes involved in pyruvate metabolism are directly regulated by σ^B , such as the pyruvate oxidase gene (LMRG_00411) and the acetolactate decarboxylase gene (LMRG_00142). Other σ^B regulon members with confirmed carbon metabolism functions in *L. monocytogenes* include LMRG_01627 (*gpmA*), which is involved in glycolysis, and LMRG_00977 [56]. Functions of these genes involved in carbon metabolism support that the transition of metabolism, including utilization of alternative carbon sources, is regulated by σ^B . While not directly related to virulence functions such as invasion, the transition of

carbon source utilization and energy metabolism is required for optimal intracellular growth [92]. Additionally, as 38 genes with putative roles in carbon metabolism do not have sufficient data in *L. monocytogenes* to support a clear function, σ^B regulation of carbon metabolism could extend beyond the intracellular life.

The σ^B regulon includes nine members involved or putatively involved in nucleotide metabolism

A nine-gene σ^B -dependent TU (LMRG_00978-00985) is involved in nucleotide metabolism. Genes in this TU encode a set of enzymes involved in a pyrimidine ribonucleotide *de novo* biosynthesis pathway. In *L. monocytogenes*, *pyrE* is required for intracellular proliferation of *L. monocytogenes*, suggesting that pyrimidine is not provided by the host cell, but must be synthesized by the bacterium machinery [83,102]. The reported studies support σ^B as one of the key regulators for nucleotide metabolism responsible for *L. monocytogenes* to survive and thrive in the intracellular environment.

The σ^B regulon includes eight members involved or putatively involved in ion transport

We identified eight σ^B -dependent genes that have a confirmed or putative function in ion transport, including iron (*hmoB* and *dhbA*), cation (LMRG_01601), magnesium (LMRG_00335), sulfate (LMRG_00205), arsenite (LMRG_00750) and phosphate ion (LMRG_00098 and *phoU*). In *L. monocytogenes*, HmoB is involved in degradation of hem, the most abundant source of iron in the human body [103]. In *Bacillus subtilis*, DhbA is directly regulated by the ferric uptake regulator and is involved in synthesis of the siderophore bacillibactin, which contributes to iron uptake, especially under iron-deficient conditions [104]. While *L. monocytogenes* has never been found to synthesize siderophores, it can acquire iron by transporting ferric siderophores produced by other microbes [105]. LMRG_01601 encodes a cation efflux family protein similar to *czcD*, a proton-driven transporter [95,106]. In *E. coli*, *phoU* mutation causes accumulation of inorganic polyphosphate [107]. The last four σ^B -dependent genes (LMRG_00098, LMRG_00205, LMRG_00335 and LMRG_00750) have putative roles in ion transport as suggested by their GO annotations. Overall, these eight members in σ^B regulon indicate that several transport systems for different inorganic ions in *L. monocytogenes* are controlled by σ^B . This ability of σ^B to regulate ion concentrations suggests a role in resilience under imbalanced ion challenges.

The σ^B regulon includes five members involved or putatively involved in vitamin metabolism

Five genes encoded in two σ^B -dependent TUs are involved in vitamin metabolism. A four-gene TU (LMRG_01077-01080) contributes to menaquinone (vitamin K2) biosynthesis [108], as well as folic acid biosynthesis [109] in *B. subtilis*. The gene LMRG_02696 is putatively involved in the riboflavin (vitamin B2) biosynthetic process suggested by its GO annotation. Although additional experiments in *L. monocytogenes* are required to confirm the function of these genes, their proposed function suggests that σ^B also regulates metabolisms of micronutrients like vitamins.

The σ^B regulon includes four members involved or putatively involved in protein metabolism

Four members of the σ^B regulon have protein metabolism-related functions. LMRG_02611 encodes DapE, an enzyme that contributes to lysine metabolism and cell wall metabolism in *E. coli* [110]. GO annotations suggest that three more σ^B -dependent genes are involved in protein metabolism: LMRG_00826 encoding a peptidase, *hpf* encoding ribosome hibernation promoting factor and LMRG_01786 encoding a dipeptidase. Future work is needed to better define a possible regulatory role of σ^B in protein metabolism.

The σ^B regulon includes four members involved or putatively involved in other metabolisms

Three σ^B regulon members are involved in cell wall metabolism, *murC*, *nagA* and *dapE*. Cell wall metabolism is crucial for bacterial cell growth, cell division and sensitivity to antibiotics, however, the role of σ^B -dependent regulation of these genes in specific cell wall metabolism processes is not understood. MurC and NagA are both involved in peptidoglycan biosynthesis of the bacterial cell wall. MurC is a L-alanine ligase in *Mycobacterium* [111], while NagA is essential for *L. monocytogenes* to maintain its envelope shape and to divide normally [98]. DapE is upregulated in stationary phase and within host cells, with a potential role in anchoring surface proteins [14]. Additionally, another σ^B -dependent gene involved in metabolism is LMRG_00273, which is suggested by GO annotation to be part of lipid metabolism.

Other functions & unknown functions

The nine σ^B regulon members involved in ‘other functions’ include LMRG_01950, which is homologous to the competence gene *tfoX* in *Vibrio cholera* [112]. While *L. monocytogenes* has never been reported as naturally competent, it possesses conserved mechanisms for regulation of its competence components [113], and these competence components have been proposed to contribute to other functions such as virulence [114]. Additionally, eight genes that encode proteins homologous to transcriptional regulators with unknown function are also included in this category. Furthermore, a total of 102 genes in the σ^B regulon have unknown function, therefore, future studies are required to identify the functions of this a third of the σ^B regulon.

Conclusion

In this review, previous transcriptomic and proteomic studies were summarized to generate an overall list of σ^B regulon members in a reproducible way. Based on data for 9 *L. monocytogenes* strains, we show that the σ^B pan regulon consists of 304 genes, including 102 genes with unknown function; the function of more than 30% of the σ^B regulon thus still remains to be elucidated. Grouping σ^B regulon members into functional groups, helped improve our understanding of the roles of this important alternative sigma factor in *L. monocytogenes*. While most of the functions conferred by σ^B regulon members confirm the well-known role of σ^B in virulence and stress response, new insight into novel roles for σ^B in metabolism and overall resilience of *L. monocytogenes* were also identified. Experimental work to define the functions of a number of specific σ^B -regulated genes is still needed though to provide a more thorough understanding of the regulatory networks governed by σ^B in *L. monocytogenes*.

Executive summary

The σ^B regulon in *L. monocytogenes*

- Alternative sigma factors are the key transcriptional regulators governing the response to changing environmental conditions.
- In *L. monocytogenes*, σ^B has the largest regulon, which includes genes encoding important stress response and virulence functions.

Review of literature on σ^B in *L. monocytogenes*

- We defined the σ^B regulon as genes that are in an operon where (i) at least a part of the operon showed evidence for higher transcript levels in the presence of σ^B as compared to an isogenic null mutant and (ii) where an upstream consensus σ^B dependent promoter was identified.
- Based on this literature review, we identified 43 relevant papers; analysis of these data revealed 171 σ^B dependent transcription units (TUs) that encompassed 304 genes.

Summary of the σ^B regulon in *L. monocytogenes* strains

- Most regulon studies in *L. monocytogenes* have been performed in the most common lab strains: 10403S, EGDe and EGD.
- Other strains used less frequently include LO28, H7858, and clinical isolates.
- We searched for and summarized σ^B regulon members in 9 different strains of *L. monocytogenes*: 10403S, EGDe, EGD, F2365, LO28, FSL J1-208, FSL J1-194, FSL J2-071, H7858

Function search strategy and reference categories

- We divided the gene functions into five general categories based on known roles of σ^B , including (i) stress response, (ii) virulence, (iii) metabolism, (iv) other functions and (v) unknown function.
- Some genes were classified into more than one general category.

Functions associated with the σ^B regulon members

- Stress response (including osmotic, oxidative, acid, antibiotic, bile, alkaline and other stresses).
 - We identified 73 σ^B regulon members that are involved in different aspects of stress response and survival, including osmotic, oxidative, acid, alkaline, and bile stress, or are involved in antibiotic resistance.
 - These genes confirm the role of σ^B as the general stress response regulator in *L. monocytogenes*.
- Virulence.
 - We classified 51 σ^B regulon members involved in virulence.
 - The ‘virulence’ group included genes also classified into ‘stress response’ and ‘metabolism’.
 - These genes confirm the role of σ^B as a regulator of virulence-related functions in *L. monocytogenes*.
- Metabolism (including carbon, nucleotide, ion, vitamin, protein, and others).
 - Over 100 σ^B regulon members are involved in metabolism, including 73 involved in carbon metabolism, suggesting a key role of *L. monocytogenes* σ^B in regulation of metabolic functions.
- Other functions and unknown functions.
 - Over 30% of the σ^B regulon corresponds to genes with unknown function.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fmb-2019-0072

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- **Original research paper describing the SigB regulon in different strains of *L. monocytogenes*.**