MINIREVIEW

Two stress sensor proteins for the expression of sigmaE regulon: DegS and RseB

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In *E. coli*, sigmaE-dependent transcription is controlled by regulated-proteolysis of RseA. RseA, which holds sigmaE as an anti-sigma factor, is sequentially digested by DegS, RseP and cytoplasmic proteases to liberate sigmaE in response to dysfunction in outer-membrane biogenesis. Additionally, the sequential proteolysis is regulated by RseB binding to RseA (Fig. 1A). Direct interaction between RseA and RseB inhibits RseA-cleavage by DegS. Both proteolytic activation of DegS and binding disruption of RseB are thus required to initiate sigmaE-stress response. For the induction of sigmaE-stress response, DegS and RseB recognize the states of OMP and LPS for outer-membrane biogenesis. DegS is activated by binding of unfolded OMPs and RseB binding to RseA is antagonized by LPS accumulated in periplasm. In this regard, DegS and RseB are proposed to be stress sensor proteins for sigmaE signal transduction. Interestingly, biogenesis of OMP and LPS appears to cross-talk with each other, indicating that dysfunction of either OMP or LPS can initiate RseA proteolysis. This review aims to briefly introduce two stress sensor proteins, DegS and RseB, which regulate sigmaE-dependent transcription.

Keywords: sigmaE, RseA, RseB, DegS, OMP, LPS

Introduction

Sigma factor interacts with a multi-subunit RNA polymerase (a2ββ'ω) and initiates transcription by directly recognizing a promoter region only when it binds to RNA polymerase. In addition to a house-keeping sigma factor that controls the transcription of genes required for bacterial homeostasis during normal growth conditions, most bacteria harbor alternative sigma factors. In response to environmental and morphological changes, an alternative sigma factor is activated and controls the expression of a specialized regulon for adaptation to the altered environment. That is, activation of alternative sigma factor is dependent on signals generated by the change in cellular conditions and the activated sigma factor induces gene transcription by recognizing a particular promoter sequence distinct from those of other sigma factors. Normally, the activity of sigma factors is suppressed by antagonist of sigma factor, anti-sigma factor, in the absence of the proper signals (Hughes and Mathee, 1998; Gruber and Gross, 2003).

In *E. coli*, sigmaE controls transcription of the regulon required for outer-membrane integrity in response to enve-
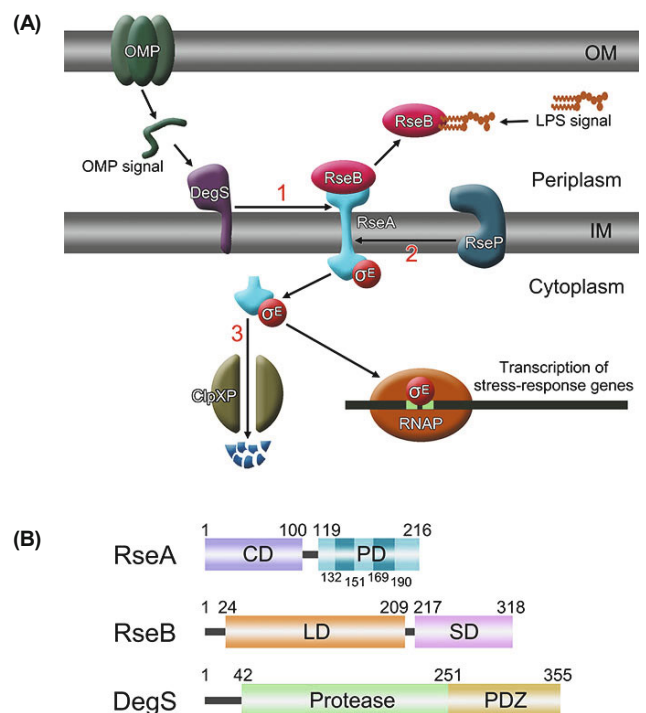

Fig. 1. Schematic drawing of sigmaE signaling pathway. (A) The model of sigmaE signaling pathway. As stress sensor proteins, DegS protease is activated by the binding of OMP C-terminus and RseB is relieved from RseA by LPS accumulated in the periplasm. RseA is sequentially digested by DegS, RseP and ClpXP, thereby releasing sigmaE in the cytoplasm. Finally, sigmaE with RNA polymerase can induce gene transcription required for outer-membrane biosynthesis. (B) Domain structures of RseA, RseB and DegS. RseA is composed of a cytoplasmic domain (CD) and a periplasmic domain (PD) connected by a single trans-membrane segment. The periplasmic domain contains two RseB binding motifs, RseA[132-151] and RseA[169-190]. RseB localized into periplasm consists of a large domain (LD) and a small domain (SD). DegS anchored to an inner-membrane contains a serine protease domain and a PDZ domain.

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lope stress. In normal conditions, sigmaE binding to RNA polymerase is inhibited by tight interaction between sigmaE and the cytoplasmic domain of the inner-membrane protein, RseA. In other words, RseA holds sigmaE to prevent sigmaE-dependent transcription as an anti-sigma factor. Thus deletion of rseA gene can lead to full induction of sigmaE activity in normal conditions (De Las Penas *et al.*, 1997; Missiakas *et al.*, 1997; Campbell *et al.*, 2003). Under the stress environment, stress signals are transferred to the cytoplasm across the inner-membrane by regulated proteolysis of RseA, leading to sigmaE release into cytoplasm (Ades *et al.*, 1999).

The linkage between sigmaE activation signals and RseA degradation is mediated by the stress sensor proteins, DegS and RseB. Initially, OMPs (Outer-membrane porins) were identified as signals that trigger RseA destruction (Mecsas *et al.*, 1993). The C-terminal motif of unfolded- or unassembled OMP binds to DegS PDZ domain, converting inactive DegS to its active conformation (Walsh *et al.*, 2003; Wilken *et al.*, 2004; Sohn *et al.*, 2007). In addition to OMP, LPS (Lipopoly-saccharide) also functions as a signal for sigmaE release. Recent studies reveal that LPS accumulated in periplasm can dissociate RseB from RseA, thereby facilitating sigmaE liberation (Chaba *et al.*, 2011; Lima *et al.*, 2013). Robust signal transduction in response to periplasmic stress seems to require both OMP and LPS, rather than either signal independently inducing sigmaE release (Lima *et al.*, 2013).

Overall signaling pathway for sigmaE release

RseA is an inner membrane protein composed of a single transmembrane segment, N-terminal cytoplasmic domain (RseA^{cyto}) and C-terminal periplasmic domain (RseA^{peri}) (Fig. 1B). In the absence of a stress signal, RseA tightly interacts with two proteins, sigmaE and RseB. RseA^{cyto} binds sigmaE, thereby blocking association of sigmaE with RNA polymerase. RseA^{peri} binds RseB, which suppresses RseA proteolysis (De Las Penas *et al.*, 1997; Missiakas *et al.*, 1997; Campbell *et al.*, 2003; Kim *et al.*, 2010). In the presence of proper signals, RseA is sequentially cleaved by DegS and RseP proteases (Alba *et al.*, 2002; Kanehara *et al.*, 2002) (Fig. 1). DegS protease recognizes the C-terminal YxF motif of unfolded- or unassembled-OMP accumulated in response to envelope stress signals and is then activated (Mecsas *et al.*, 1993; Walsh *et al.*, 2003). In addition to DegS activation, RseA cleavage by DegS requires RseB dissociation from

RseA (Grigorova *et al.*, 2004; Cezairliyan and Sauer, 2007; Chaba *et al.*, 2011; Lima *et al.*, 2013). After RseA cleavage by DegS, RseP cleaves the trans-membrane region of RseA to release RseA^{cyto}/sigmaE complex into cytoplasm (Akiyama *et al.*, 2004; Li *et al.*, 2009). The complex is then further processed by multiple ATP-dependent proteases that specifically destruct RseA^{cyto}, resulting in the generation of free sigmaE (Flynn *et al.*, 2004; Chaba *et al.*, 2007). Free sigmaE can thus activate the regulon required for synthesis, assembly and homeostasis of OMP and LPS (Rhodius *et al.*, 2006).

For the sequential proteolysis of RseA, accumulation of OMP and LPS in periplasm appears to be converted to a signal required for the next step of proteolysis by exposing residues as a signal. In the first step of RseA cleavage, DegS cleaves between residue V148 and S149 of RseA, when it is activated by the YxF motif exposed in the C-terminus of unassembled OMP (Walsh *et al.*, 2003). In the second step, RseP cleaves the trans-membrane region of RseA$^{1-148}$ generated by DegS activation (Alba *et al.*, 2002; Kanehara *et al.*, 2002). The cleavage between residue A108 and C109 of RseA by RseP liberates N-terminal fragment of RseA from plasma membrane localization (Akiyama *et al.*, 2004). In the last step, SspB adaptor protein recognizes RseA$^{1-108}$ released by RseP activation and delivers RseA$^{1-108}$/sigmaE complex to ClpXP, which destroys the RseA fragment and then releases sigmaE (Flynn *et al.*, 2004). Thus, substrates or ligands newly generated by sequential proteolysis might be regulators of sigmaE signaling transduction.

However, the mechanism of sequential digestion is not fully understood. For example, the manner of regulated cleavage by RseP is still obscure and controversial. Kanehara *et al.* (2003) suggested that glutamine rich regions in RseA (residues 162–169 and 190–200) suppress RseP-mediated proteolysis, as the removal of the motifs by DegS (the removal of RseA$^{149-216}$) can induce RseP cleavage. In other studies, residue V148 in RseA exposed by DegS cleavage was required as an RseP activation signal in an *in vitro* biochemical assay (Li *et al.*, 2009), whereas the residue was not essential for RseA cleavage and sigmaE-dependent transcription in an *in vivo* assay (Hizukuri and Akiyama, 2012).

DegS, the sensor protein of OMP signals

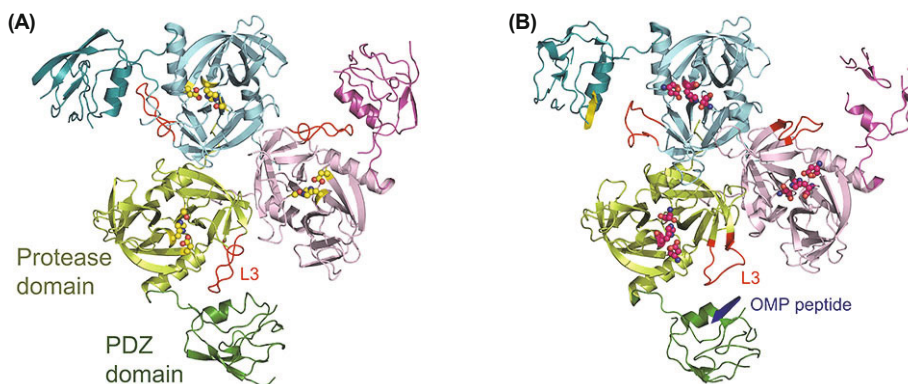DegS is a periplasmic protease anchored to an inner-membrane. It contains a protease domain and a PDZ domain

Fig. 2. The structure of DegS trimer. The structures of apo-DegS (A) and DegS in complex with OMP peptides (B) are drawn as ribbon diagram in the same orientation. Atomic coordinate files were obtained from PDB (PDB id: 1SOT and 1SOZ). Each subunit of DegS trimer is colored differently (green, cyan, and magenta). A protease domain and a PDZ domain in each subunit are distinguished as bright and dark color. Two OMP peptides in (B) are colored yellow and blue. L3 is colored red in (A) and (B). Binding of OMP peptide in PDZ domain disrupts auto-inhibitory interaction formed between L3 loop and the PDZ domain and subsequently induces the activation of DegS protease.

(Bass *et al.*, 1996; Waller and Sauer, 1996) (Fig. 1B). In the crystal structure, DegS trimer forms a funnel-like shape with fully accessible active sites (Wilken *et al.*, 2004). PDZ domain tightly attaches to the protease domain at fixed orientation without blocking the active site of the protease domain. The structure is maintained by the tight interaction between PDZ domain and protease domain (Fig. 2A). A protease domain in apo-DegS has inactive geometry in an oxyanion hole and a catalytic triad, like HtrA family proteins (Wilken *et al.*, 2004; Sohn *et al.*, 2007).

Accumulation of OMP in the periplasm increases RseA cleavage by DegS (Ades *et al.*, 1999). Walsh *et al.* (2003) demonstrated that the PDZ domain in DegS directly recognizes the YxF motif in the OMP C-terminus and the binding of OMP peptide converts inactive DegS to proteolytic active state, thereby leading to initiation of a proteolytic cascade. Deletion of DegS PDZ domain also results in an increase of sigmaE activity, indicating that the PDZ domain is involved in negative regulation of DegS proteolytic activity. Indeed, crystal structure of DegS in complex with a peptide containing the YxF motif shows the conformational change of the active site induced by OMP peptide binding to apo-DegS, indicating that OMP binding antagonizes the inhibitory function of the PDZ domain (Wilken *et al.*, 2004). In the crystal structure, the inhibitory interaction between the PDZ domain and L3 (residues 176-189) in the protease domain is disrupted by the binding of OMP peptide in the PDZ domain, Subsequently, the catalytic triad (residues H96, D126, and S201) and the oxyanion hole are rearranged to active form (Fig. 2). Sohn *et al.* (2007) suggested that DegS is an allosteric enzyme in which equilibrium state is shifted to proteolytic active conformation from inactive state by YxF peptides binding to a PDZ domain (Sohn *et al.*, 2007). In contrast to the scaffold model in which the penultimate residue (x in YxF motif) in OMP bridges proteolytic activation (Hasselblatt *et al.*, 2007), the allosteric model of DegS suggests that peptide binding itself induces small conformational changes of the active site, relieving inhibitory contacts between PDZ domain and protease domain. In their experiments, the disruption of inhibitory interactions by point mutations or deletion of a PDZ domain increased RseA cleavage, similarly to DegS with OMP peptide binding (Sohn *et al.*, 2007, 2009; Sohn and Sauer, 2009). Consistently, the steric-clash model suggests that residue N182 of L3 loop in the protease domain interacts with residue M319 in the PDZ domain for auto-inhibitory function of apo-DegS and the interaction is disrupted by presence of OMP peptide binding, resulting in DegS activation

(de Regt *et al.*, 2015). As a trimeric allosteric enzyme, DegS shows the properties of positive cooperativity. Kinetics curves of both ligand binding (OMP peptide) and substrate binding (RseA^{Peri}) to DegS are sigmoidal. In addition to intrinsic allosteric property of DegS, upstream sequences of YxF in OMP peptides influence the extent of DegS activation, implying that different sensitivity of individual OMPs to environmental stress might result in the differential induction of the sigmaE-stress response (Sohn and Sauer, 2009).

RseB, the sensor protein of LPS signals

RseB is a periplasmic protein that binds to inner membrane-anchored-RseA with 1:1 binding stoichiometry (Cezairliyan and Sauer, 2007; Kim *et al.*, 2007, 2010). The crystal structure of RseB reveals that it contains an N-terminal large domain (residues 25–209) and a C-terminal small domain (residues 217–315) connected by a flexible loop (Fig. 3). The large domain shares high structural similarity with proteins involved in outer-membrane localization of lipoprotein, such as LppX (Sulzenbacher *et al.*, 2006; Kim *et al.*, 2007; Wollmann and Zeth, 2007). RseB forms two types of homo-oligomers, a dimer form that is able to bind RseA and a larger oligomeric form that is inactive in RseA-RseB interaction. Thus RseB binding to RseA might be regulated by the change in RseB homo-oligomeric state (Cezairliyan and Sauer, 2007; Lima *et al.*, 2013). RseA has two RseB binding regions, residues 132–151 and 169–190. The two motifs are located in a groove formed by a large domain and a small domain of RseB (Cezairliyan and Sauer, 2007; Kim *et al.*, 2007, 2010; Ahuja *et al.*, 2009). In the crystal structure of RseA^{peri}/RseB complex, residues 169-190 in RseA (RseA$^{169-190}$) exhibit a helical conformation and appear to be a major binding site for RseB binding, because RseA$^{169-190}$ was sufficient to tightly interact with RseB in pull-down experiments and fluorescent anisotropy assays (Fig. 3B). Additionally, residues 132-151 in RseA bind to large domains of RseB dimer, indicating that RseB dimerization might contribute to the stability of the RseA conformation (Fig. 3B).

An *in vitro* experiment revealed that RseA-RseB interaction inhibits RseA-cleavage by DegS, indicating that RseB can negatively regulate RseA degradation and thereby suppress sigmaE-dependent transcription (Cezairliyan and Sauer, 2007). Consistent with the biochemical data, structure of RseA^{peri}/RseB complex show that DegS cleavage site in RseA (V148-S149) is not accessible under RseB binding (Kim *et al.*, 2010). But *in vivo* data showed that RseA degradation
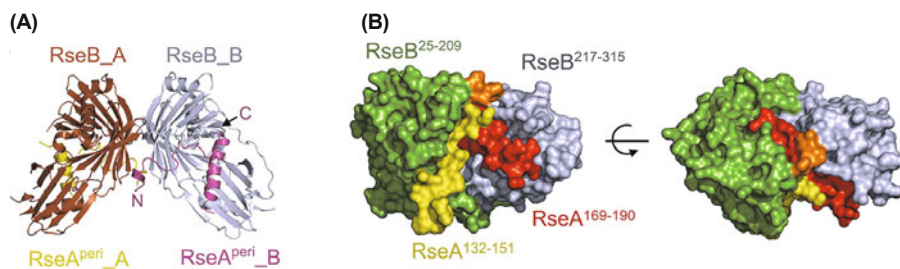

(A)

RseB_A   RseB_B

RseA^{peri}_A   RseA^{peri}_B

(B)

RseB$^{25-209}$ RseB$^{217-315}$

RseA$^{169-190}$

RseA$^{132-151}$

Fig. 3. The structure of RseB in complex with RseA^{peri} (PDB id: 3M4W). (A) Ribbon diagram of RseA^{peri}/RseB hetero-tetramer. Four subunits are colored differently. (B) Surface model of RseA^{peri}/RseB dimer is drawn in two different orientations. RseB$^{25-210}$ (large domain), RseB$^{210-216}$ (linker sequence), RseB$^{215-315}$ (small domain), RseA$^{132-151}$ (minor binding motif) and RseA$^{169-190}$ (major binding motif) are colored green, slate, brown, yellow and red, respectively. RseA^{peri} is located in the groove formed by a large domain and a small domain of RseB.

and sigmaE activity increased maximally 2-fold in the absence of RseB, suggesting that RseB may not be a critical regulator for sigmaE-stress response (Grigorova *et al.*, 2004).

  Recently, Chaba *et al.* (2011) showed that DegS activation by DegSΔPDZ or point mutations that unleash DegS activity increased sigmaE induction more than 10-fold in the absence of RseB, indicating that both RseB removal and DegS activation are required for sigmaE-stress response, contrary to previous observations. Additionally, they also observed that the motif between 10 and 20 residues upstream from the OMP C-terminus was required for sigmaE induction. But the OMP signal of C-terminal 20 residues did not induce RseA cleavage by DegS in the presence RseB *in vitro*, suggesting that the upstream motif in OMPs might antagonize RseB indirectly rather than by direct binding (Chaba *et al.*, 2011). Interestingly, Lima *et al.* (2013) observed that LPS or LPS fragment containing lipid-A can dissociate RseB from RseA and induce the formation of inactive RseB tetramer in an *in vitro* experiment, thereby facilitating RseA cleavage by DegS in the presence of RseB. Moreover, RseA-RseB dissociation by LPS was inhibited by the presence of LptA, which shuttles LPS to outer-membrane in periplasm. This suggests that the periplasmic accumulation of LPS by a defect in LPS biogenesis can dissociate RseB from RseA. Indeed, sigmaE activity is elevated by mutations of genes involved in LPS transport or by alteration of LPS structure *in vivo* (Tam and Missiakas, 2005; Klein *et al.*, 2009; Lima *et al.*, 2013). Taken together, these data suggest that RseB is both a stress-sensor protein that responds to defects in LPS transport and a negative regulator of sigmaE activation.

Cooperation of DegS and RseB for sigmaE signal transduction

As explained above, DegS is activated by recognition of OMP signals and RseB is antagonized by binding of lipid-A in LPS (Lima *et al.*, 2013). Although both DegS activation and RseB inhibition are required for initiation of RseA proteolysis and subsequent sigmaE activation, sigmaE activity is increased by either accumulation of OMP or LPS mutations *in vivo* (Walsh *et al.*, 2003; Chaba *et al.*, 2011; Lima *et al.*, 2013), indicating that there is crosstalk between OMP and LPS biogenesis that can induce sigmaE activation. That is, defects in biogenesis of one signal can create problems in biogenesis of the other signal.

Acknowledgements

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