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Structure, function and regulation of the conserved serine proteases DegP and DegS of *Escherichia coli*

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Abstract

Two members of the widely conserved HtrA family of serine proteases, DegP and DegS, are key players in extracytoplasmic protein quality control. The underlying mechanisms of their main functions in stress sensing, regulation and protection during the unfolded protein response are discussed.

Keywords: DegP; DegS; HtrA; Protein quality control

1. Introduction

The highly dynamic process of protein quality control is tightly controlled on the genetic and biochemical levels to allow cells to survive under severe environmental conditions and to avoid waste products such as protein fragments to build up. Even under non-stress conditions, quality control factors play important roles, for example, in the normal folding pathways of individual proteins, in detection and treatment of aged proteins, assembly of protein complexes and insertion of membrane proteins. Therefore, this regulatory event is critical to cell fate. Protein quality control involves protein diagnosis, repair and turnover via molecular chaperones, folding catalysts and proteases.

2. The HtrA family of serine proteases

The HtrA family represents a unique class of oligomeric serine proteases. The defining feature of the family members is the combination of a catalytic domain with one or more C-terminal PDZ domains (Fig. 1). PDZ domains are protein modules that mediate specific protein-protein interactions and bind preferentially to the C-terminal 3–4 residues of the target protein. Recent bioinformatic analyses suggest that the HtrA family belongs to the core protease set of living cells [32]. Prokaryotic HtrAs have been attributed to tolerance against various folding stresses as well as to pathogenicity [8,34]. The four human homologues are believed to be involved in arthritis, cell growth, unfolded protein response, apoptosis,

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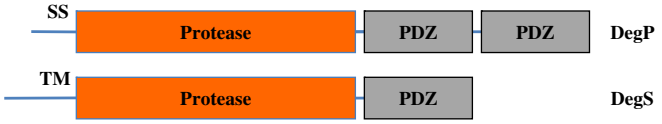

Fig. 1. **Schematic domain organization of Deep and DegS.** DegP is synthesized with a cleavable signal sequence (SS) and mature DegP is a soluble periplasmic protein composed of a protease domain resembling chymotrypsin followed by two PDZ domains. DegS is a monotopic integral cytoplasmic membrane protein with an N-terminal transmembrane segment (TM). It is composed of a protease domain homologous to DegP and one C-terminal PDZ domain.

cancer, ageing, placental development and function and in metabolism of amyloid precursor protein (for review see [4,7,8,13,31]).

3. History

DegP was the first HtrA protease discovered. It was described as a serine endoprotease in 1983 and named protease Do [44]. Subsequently, its gene was identified by two approaches. One was to isolate mutants that prevented cleavage of hybrid proteins between integral inner membrane proteins and alkaline phosphatase [43]. The other identified heat shock genes that were required for growth at elevated temperatures [29,43]; thus the name HtrA (high temperature requirement A). Likewise, but much later, the *degS* gene was identified by two laboratories at roughly the same time as a suppressor of a *tsp* mutant [3] and by sequencing of a gene that exhibited homology to *degP* [45]. The regulation of the *degP* promoter by the alternative sigma factor E was described in 1989 [12] and it was revealed in 1995 that *degP* is controlled by a second signaling pathway Cpx [9]. To date, *degP* is the only gene that is known to be regulated by both the sigmaE and Cpx pathways. In 1991, the implication of DegP in bacterial virulence was first reported [23], while DegS was found to be involved in pathogenesis in 2003 [36].

4. Functions of DegS and DegP

Escherichia coli has developed compartment-specific systems to respond to the presence of misfolded proteins. In the cell envelope, two major pathways have been identified, sigmaE and Cpx (Fig. 2) (for review see [1,10,14,35,39]). As stress occurs in the cell envelope, but regulation of gene expression is carried out in the cytoplasm, these systems must sense misfolded cell envelope proteins, transmit signals across the cytoplasmic membrane and stimulate transcription of protein folding and degradation factors in the cytoplasm. It is generally accepted that misfolded proteins, protein fragments and mislocalized outer membrane proteins (omps) are activators of these stress response pathways. Such activation occurs under any kind of extracellular stress that causes

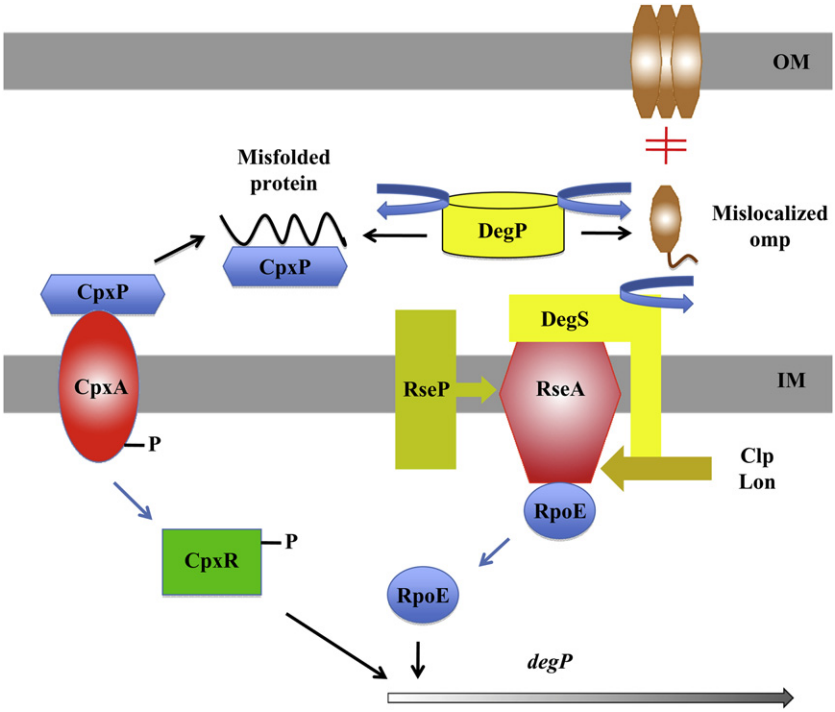

Fig. 2. **The Cpx and sigmaE unfolded protein response pathways of the cell envelope.** The signal transduction pathways Cpx and sigmaE regulate transcription of *degP*. Misfolded polypeptides are sensed by either CpxP or DegS. Free CpxP inactivates the sensor kinase CpxA. Upon binding of misfolded proteins to CpxP, this complex is degraded by DegP. Subsequently, CpxA activates CpxR via phosphorylation and phosphorylated CpxR acts on the *degP* promoter. In the sigmaE pathway, the anti-sigma factor RseA is degraded by DegS and other proteases before RpoE is released from the membrane to function as a sigma factor that induces *degP* expression. On the protein level, DegS is activated by binding of C-termini of mislocalized omps, while DegP activity is upregulated by C-termini of omps as well as misfolded periplasmic proteins. In both cases, activators bind to the PDZ domains inducing allosteric activation. OM is the outer membrane, IM is the cytoplasmic membrane.