

# Bacterial Cold Shock Proteins - the Molecular Chaperones for Multiple Stress Tolerance



Rajasheker G<sup>1</sup>, Anil Kumar S<sup>2</sup>, Hima Kumari P<sup>1</sup> and Kavi Kishor PB<sup>1\*</sup>

<sup>1</sup>Department of Genetics, Osmania University, India

<sup>2</sup>Department of Biotechnology, Vignan's Foundation for Science, Technology and Research, India

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\*Corresponding author: Kavi Kishor PB, Department of Genetics, Osmania University, Hyderabad 500 007, India

## Abstract

Bacteria overcome the cold environmental conditions by inducing cold shock proteins (Csps) in response to rapid downshift temperature. Due to cold shock, membrane fluidity decreases, resulting in stabilization of nucleic acid secondary structures and impairment of overall metabolic activities. Csps are highly conserved structural proteins that bind to RNA binding motifs RNP-1 and RNP-2. Cold Shock Domain (CSD) is the characteristic feature of Csps, and conserved across bacteria, animals, and plants. However, in humans, CSD are represented as Y-box proteins. Csp homologs have been identified in plants which play a major role in cold, salt, and drought stress tolerance. Overexpression of Csps in plants resulted in high accumulation of proline, antioxidative activity with improved yield. The present mini-review focuses on the activity of Csps with special emphasis on their homologs which has not been covered earlier.

**Keywords:** Chaperones; Cold shock domain; Cold shock proteins; homologs; stress

**Abbreviations:** Csps: Cold Shock Proteins; CSD: Cold Shock Domain; CIPs: Cold-Induced Proteins; *E. coli* - *Escherichia coli*; PNP: Polynucleotide phosphorylase; RNP-1: RNA binding motif1; RNP-2: RNA binding motif2

## Introduction

Bacteria encounter different changing environments but resist the environmental changes by developing an array of mechanisms which protect them from adverse conditions. During cold conditions, fluidity of cell membranes decreases, and this results in lowering of active transport and protein secretion [1]. Further, all the molecular mechanisms gets impaired due to stabilization of secondary structures of DNA, RNA, and proteins [2]. RNA binding proteins (RNA chaperones) are ubiquitous and found in all living organisms and help to resolve the misfolded RNA structures under abiotic stress conditions. During rapid drop in temperatures, cold-induced proteins (Cips) are produced to protect the cells. With an increase in the cold conditions, the production of Cips also increases [3]. Different types of Cips like cold shock protein (Csp) family, RNA helicase *csdA*, exoribonucleases, PNPase and RNaseR, initiation factors 2a and 2b, NusA, and RecA [4-7] have been identified in *Escherichia coli* (*E. coli*). The Csps are one of the major Cips produced under cold conditions mainly in bacteria [4,8].

The Csps are the small, acidic, nucleic acid-binding proteins ranging from 65 to 75 amino acids that are highly induced during low temperature conditions and serves as RNA chaperones to prevent the misfolding of mRNA [9]. Based on sequence similarity (46-91%), a total of 9 Csps (CspA, B, C, D, E, F, G, H, and I) have

been identified in *E. coli* and 3Csps (CspB, CspC, CspD) in *Bacillus*, 5 Csps (cspA to cspE) in *Lactococcus lactis* and 3 Csps (CspL, P, and C) in *Lactococcus plantarum* respectively [4,8,10,11]. Later, Csps and its homologs were identified in several bacteria, animals and plants [12]. Of the 9 *E. coli* Csps, 4 are induced by cold (CspA, CspB, CspG and CspI), 1 by starvation (CspD), 2 (CspC and CspE) show constitutive expression at 37 °C, and 2 are uncharacterized proteins (CspF and CspH) [13-19]. *Acinetobacter oleivorans* CspE is also induced by cold shock [20]. Earlier, Horn et al. [19] reviewed the structure and functions of Csps and Keto-Timonen [21] reviewed the role of Csp family with a focus on *Yersinia*. The present mini-review describes the activity of Csps with emphasis on Csp homologs which has not been covered earlier. Also, a note is added on how these Csps protected the bacterial systems against the cold temperatures.

## Structure and characterization of Csps

High structural conservation was noticed among Csps, but with variable thermostability. The melting temperature of Csps of *Thermus aquaticus* was as high as 76 °C with more rigid structure which infers higher structural flexibility is needed to accommodate nucleic acids upon cold shock [22]. The half-life of Csps also increases upon cold shock from 12 seconds to 20 minutes [23]. It has also been pointed out that the CspA mRNA adopts

to different stable secondary functional structures by thermosensing the environmental temperature [24,25]. Csps show highly conserved CSD domain proteins, with approximate molecular weights 7.4 KD, which specifically bind to single stranded nucleic acids (ssDNA and ssRNA), but unlikely to bind to double stranded DNA [26]. Csps also known as RNA binding proteins, interact with nucleic acids through moderately conserved conical forms of RNA binding motifs RNP-1 (K/R-G-F/Y-G/A-F-V/I-X-F/Y) and RNP-2 (L/I-F/Y-V/I-G/K-N/G-L) [19]. Nuclear Magnetic Resonance (NMR) studies revealed five  $\beta$  strands that are arranged into an antiparallel  $\beta$ -pleated sheet forms. One is a closed  $\beta$  barrel, two are  $\beta$  sheet surfaces, and the barrel is stabilized by the hydrophobic interactions between two  $\beta$ -pleated sheets  $\beta$ 1 and  $\beta$ 2. Similarly,  $\beta$ 2 and  $\beta$ 3 are interconnected by very short loops L1 and L2 respectively as well as L3 and L4 are connected by  $\beta$ 3 and  $\beta$ 4,  $\beta$ 4 and  $\beta$ 5 respectively, and L3 loop contains small  $\alpha$  helicals in TmCsp (Thermotoga maritima) [27].

It has been shown that CspA co-operatively binds to RNA and ssDNA and upon CspA binding, the RNA substrate becomes more sensitive to nuclease digestion. This suggests that CspA functions as an RNA chaperone to prevent secondary structure formation in mRNAs at low temperatures, thus enhancing the translation efficiency [28]. CspC and CspE are originally identified as the multicopy suppressors of the chromosomal partition defect of an *E. coli* muk B mutant [29]. Csp E has been shown to interact with nascent RNA in a complex with RNA polymerase [30]. Nakaminami et al. [31] determined the importance of C-terminal region of a plant Cold Shock Domain Protein (CSDP). They showed that deletion of all C-terminal zinc fingers in wheat WCSP1 abolished the growth stimulatory activity in *E. coli* during cold stress indicating that the CCHC-type zinc fingers in CSDPs are highly vital for growth.

### Cold shock proteins and abiotic stress tolerance

CspA regulates its own synthesis by binding to RNA hair pin (cold box) and suppresses gene expression [32]. CspA is significantly induced in harsh condition of cold, acidic, oxidative stresses in *Brucella melitensis*, the most dangerous pathogen [33]. This suggests that CspA protects bacteria from multiple abiotic stresses. CspA isolated from *Caulobacter crescentus* is the most prominent for cold adaption in comparison with CspB, and CspA deletion mutant showed major effect on growth at a lower temperature [34]. *Bacillus* CspB protein is a 67 amino acid, small, acidic protein, highly homologous with CspA, mostly binds to polypyrimidines in single stranded DNA strand, exponentially expressed during log phase and prevents cell damage during ice crystal formation [35]. CSPs are well conserved in bacteria, animals as well as in plants. In bacteria, Csps have one CSD, but in eukaryotes, Csps are flanked by N- and C-terminal domains. CSD homologs were also reported in eukaryotes, for example CSD shows high homology with human Y-box protein YB-1 and others [36,37].

*E. coli* display cold sensitivity during quadruple-deletion (CspA, CspB, CspE, and CspG), suggesting that CspA and its homologs

protect the *E. coli* against cold stress conditions. Overexpression of all Csps except CspD (associated with starvation) resulted in the suppression of cold sensitivity in bacteria. Bacterial systems overexpressed with Csps have not been tried for tolerance to drought and multiple stresses given simultaneously. Also, overexpression of CspD resulted in lethality. The S1 domain of polynucleotide phosphorylase (PNPase) is a structural homolog of CspA and also suppresses the cold sensitivity of the mutant [38]. Thus, except CspD, other Csps appear to be vital for cold stress tolerance in bacteria. Plants also have Csp homologs, and play a pivotal role in growth, development and stress adaptations too [12]. However, studies dealing with overexpression of plant Csps are meager.

### Pleiotropic effects of Csps and its homologs

CSPs help in bacterial growth under low temperature conditions [39]. Bacterial Csps act as chaperones to destabilise mRNA secondary structures and enhance the translation process [21,40,41]. Csps allow mRNAs to efficiently translate at low temperatures and also regulate transcription and transcription antitermination there by maintain mRNA stability [42]. CspA, the most induced Csp accounts for 13% of the total cellular protein at low temperatures [13]. CspA also regulates its own synthesis at 37 °C and cold by premature termination of unusual long 5'-UTR, a binding site of regulatory proteins [43]. CspA (cold-shock DEAD-box protein A) RNA helicase destabilize the secondary RNA structures during cold temperature involve in the biogenesis of the 50S ribosomal subunits [44]. Wang et al. [17] found that CspA and CspB genes are vital for microbial growth under cold stress. Jiang et al. [28], Graumann and Marahiel [37] pointed out both CspA and CspB increase the protein translation in cold conditions through the elimination of stabilized RNA secondary structures. Castiglioni et al. [45] expressed CspA and CspB genes in maize which conferred abiotic stress tolerance with improved grain yield. Likewise, improved drought stress tolerance in wheat was noticed with the overexpression of synthetic bacterial cold shock protein gene *Se CspA* [46]. It is observed that *E. coli* CspE functions as anti-terminator in transcription and efficiently increases expression of the gene [47]. But, CspD suppress growth at stationary phase, inhibits the *oriC* replication, through prepriming complex formation [48].

Hunger et al. [49] found out that CSPs work in concert with a DEAD box helicase to rescue misfolded mRNA and help in transcription [50]. Bae et al. [51] showed that CspA, CspC, and CspE genes act as antiterminators and regulate the expression of cold-inducible genes. Plants have CSD proteins which differ from that of CSPs that are known to occur in prokaryotes [52]. Several of the bacterial CSPs and plant CSDs were found induced under cold stress conditions [53,54]. Interestingly, though *E. coli* CSPs are responsive to cold stress and function as RNA chaperones [37], they share a domain with AtCSP3, which plays a pivotal role in low temperature tolerance as noticed by Kim et al. [55]. Park et al. [56] showed that CSDPs affect seed germination and growth of Arabidopsis plants under abiotic stress. It has been

suggested by Sasaki & Imai [52] that CSDPs regulate embryo development, flowering time and fruit development indicating their diverse roles in plants unlike that of bacteria. Melencion et al. [57] demonstrated an RNA chaperone function of a universal stress protein in Arabidopsis which displayed enhanced cold stress tolerance in plants. *E. coli* CspA and CspB genes increased cold tolerance when overexpressed in Arabidopsis thaliana [46].

This suggests that the synthetic genes had identical functions to Arabidopsis AtCSP3 in imparting cold stress tolerance [46]. Conversely, SeCspA and SeCspB did not improve cold stress in transgenic wheat but showed that synthetic CspA gene improves drought stress under the field conditions [46]. Sasaki et al. [58] showed that Arabidopsis AtCSDP2 negatively regulates freezing tolerance. Further, they demonstrated that overexpression of AtCSP2 resulted in reduced salt stress tolerance in Arabidopsis, indicating that it is a negative regulator of salt stress. It may be noted here that *E. coli* CSPs share a domain with Arabidopsis AtCSP3. Overexpression of AtCSP3, which shares a *E. coli* CSP domain resulted in improved salt and drought stress tolerance by upregulating the expression of stress related proteins [59]. Yu et al. [46] showed that overexpression of CspA and CspB genes caused the upregulation of TaCDPK3 transcription factor in wheat. It is known that CDPKs play vital roles in stress signal transduction and regulate the downstream genes that can be activated in turn by ABA [60].

### Conclusions

Food production needs to be addressed with an ever increase in population and decrease in natural resources. Development of plants which can withstand adverse conditions is certainly the need of the hour. Csps act as molecular chaperones and protect bacteria from cold shock conditions. Csps are the promising genes which involve a cross talk between cold, salt, and drought stresses and are efficient in developing plant resilience. Csps are abundantly found in bacteria and are constitutively expressed during stress conditions. Transgenic plants overexpressing bacterial Csps have been found to be tolerant to cold, salt, and drought stresses. Thus, Csps are efficient chaperons, but need to be exploited further for developing transgenic plants that are resilient to the changing environment.

### Author contributions

RG conceived and written the manuscript. SAK, PHK and PBK have gone through the MS critically and refined it.

### Conflict of interest

Authors declare no conflict of interest.

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