Acta Biochimica Polonica

Vol. 52 No. 1/2005

35–43

QUARTERLY

Review

The Obg subfamily of bacterial GTP-binding proteins: essential proteins of largely unknown functions that are evolutionarily conserved from bacteria to humans✪

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Received: 07 July, 2004; accepted: 07 September, 2004

Key words: small GTP-binding proteins, ribosomes, chromosomal functions, DNA repair, gene expression

Members of the Obg subfamily of small GTP-binding proteins (called Obg, CgtA, ObgE or YhbZ in different bacterial species) have been found in various prokaryotic and eukaryotic organisms, ranging from bacteria to humans. Although serious changes in phenotypes are observed in mutant bacteria devoid of Obg or its homologues, specific roles of these GTP-binding proteins remain largely unknown. Recent genetic and biochemical studies, as well as determination of the structures of Obg proteins from *Bacillus subtilis* and *Thermus thermophilus*, shed new light on the possible functions of the members of the Obg subfamily and may constitute a starting point for the elucidation of their exact biological role.

GTP-binding proteins have been found in all living organisms examined thus far, and play crucial roles in the regulation of fundamental cellular processes. In eukaryotic cells, small monomeric GTP-binding proteins (i.e. GTP-binding proteins revealing relatively low

✪This work was supported by the Ministry of Science and Information Society Technology (grant No. 6 P04B 022 20)

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Abbreviations: CgtA, *Caulobacter* GTP-binding protein or common GTP-binding protein; Era, *Escherichia coli* Ras-like protein; Obg, Spo0B-associated GTP-binding protein.

molecular mass and occurring as monomers in their active form) are involved in a number of essential processes, for example: signal transduction, protein synthesis and translocation, and cell cycle regulation (for reviews see, for example, Sprang, 1997; Caldon & March, 2003). Perhaps surprisingly, relatively little information is currently available about the roles of GTP-binding proteins in prokaryotes.

The best known prokaryotic small GTP-binding protein is Era (named for '*Escherichia coli* Ras-like protein'). This protein is essential for bacterial growth, and mutants in the *era* gene reveal pleiotropic phenotypes, including alterations in the regulation of carbon metabolism, the stringent response, and cell division (Lerner & Inouye, 1991; Britton *et al.*, 1997; 1998). Era bears an RNA-binding motif (Chen *et al.*, 1999) and binds to the 30S ribosomal subunit (Sayed *et al.*, 1999).

Apart from Era, a group of other small GTP-binding proteins (revealing GTPase activities) was discovered in prokaryotic cells. Interestingly, members of this group have homologues in diverse organisms ranging from bacteria to humans (Okamoto & Ochi, 1998; Czyż *et al.*, 2001; Sikora-Borgula *et al.*, 2002; Ishikawa *et al.*, 2003). Recently, Leipe *et al.* (2002) presented an excellent work in which all available sequences and structures of the most abundant group of GTPases (so called P-loop GTPases) were analyzed, and their classification was proposed. According to this classification (shown in a graphic form in Fig. 1), a subfamily of proteins named Obg,

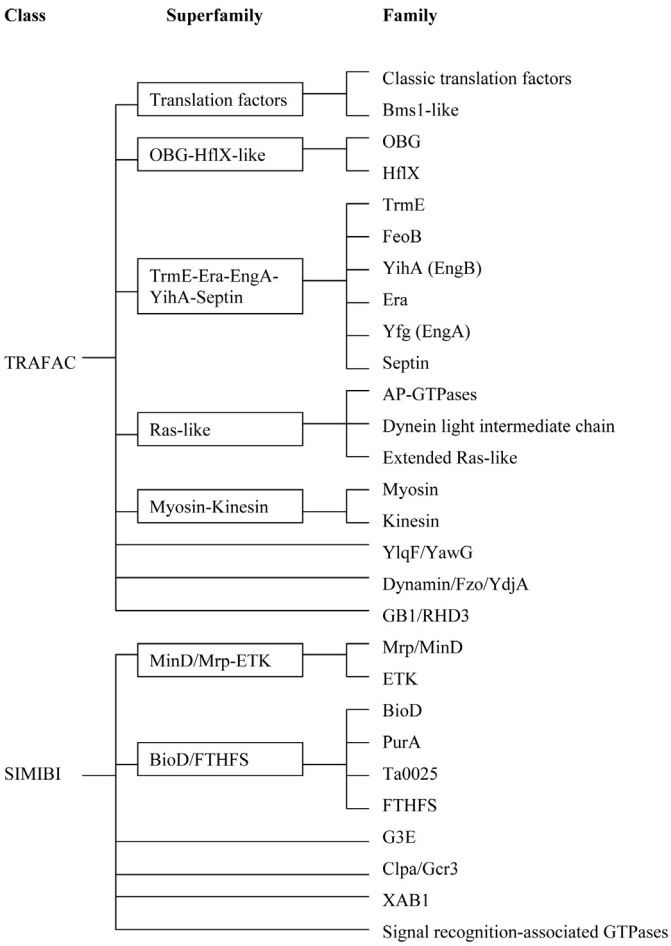

Figure 1. GTPases and related ATPases which bear the P-loop structure, classified according to the proposal of Leipe *et al.* (2002).

The schematic classification is shown at the levels of classes, superfamilies and families.

after its best investigated member – the Obg protein of *Bacillus subtilis*, has been distinguished. The Obg subfamily, together with four other subfamilies (DRG, YyaF/YchF, Ygr210, and NOG1) forms the OBG family, which includes both bacterial and eukaryotic GTP-binding proteins. Together with the HflX family, OBG forms the OBG-HflX superfamily (Leipe *et al.*, 2002).

Examples of bacterial members of the Obg subfamily are Obg proteins from *B. subtilis*, *Streptomyces griseus* and *S. coelicolor*, CgtA proteins from *Caulobacter crescentus*, *Escherichia coli* (*E. coli* CgtA is also called ObgE) and *Vibrio harveyi*, and YhbZ from *Haemophilus influenzae* (Trach & Hoch, 1989; Maddock *et al.*, 1997; Okamoto & Ochi, 1998; Czyż *et al.*, 2001; Kobayashi *et al.*, 2001; Dutkiewicz *et al.*, 2002). Below, some of these proteins are described in more detail in the light of results of recent studies that provided basic information about their structure and possible functions.

THE Obg PROTEIN OF *BACILLUS SUBTILIS*

The *obg* gene was discovered in *B. subtilis* by Trach and Hoch (1989). Its name is for 'Spo0B-associated GTP-binding protein' since the *obg* gene product was found to be involved in the control of sporulation. Namely, genetic studies led to proposals that Obg may regulate initiation of sporulation (Trach & Hoch, 1989; Vidwans *et al.*, 1995). Results of other experiments suggested that Obg may be involved in the control of DNA replication (Kok *et al.*, 1994), but the proposed hypothesis was highly speculative. Subsequent studies demonstrated that the *obg* gene function is necessary for stress-dependent activation of transcription factor σ^B (Scott & Haldenwang, 1999).

It was proposed that Obg can function by sensing intracellular GTP level (Kok *et al.*, 1994) and may be required to stimulate the activity of the phosphorelay system (Vidwans *et al.*, 1995). More recent evidence points to a role of Obg in ribosome function. In *B. subtilis* cells, the Obg protein exists as a large cytoplasmic complex, coelutes with ribosomal subunits and specifically interacts with the ribosomal protein L13 (Scott *et al.*, 2000).

As can be deduced from the description presented above, Obg, one of six essential GTP-binding proteins discovered in *B. subtilis* (Morimoto *et al.*, 2002), is involved in many crucial physiological processes, but its exact cellular function is unknown. Recent studies on the structure of this protein shed new light on a possible role for this protein. Buglino *et al.* (2002) have determined the 2.6 Å resolution X-ray structure for Obg. This structure reveals common features of the G domain. Such a domain typically contains six β strands and five α helices (see Wittinghofer, 2002). In fact, the whole Obg protein consists of three domains. The N-terminal domain (residues 1–158) contains a sequence highly conserved among other members of the OBG family, but it does not reveal structural similarity to any other known protein. The second domain (residues 161–342) is a conserved GTP-binding domain similar to that found in small Ras-like GTPases. The C-terminal domain (residues 342–428) of Obg is structurally similar to a domain found in bacterial stress response proteins, among others the SpoT protein, and is called TGS.

The global structure of Obg from *Thermus thermophilus* (Fig. 2), described recently by Kukimoto-Niino *et al.* (2004), is similar to that of *B. subtilis*. However, detailed analysis of the structural data led to a suggestion about a possible domain rearrangement of Obg, and a potential role of its C-terminal domain in the regulation of nucleotide binding (Kukimoto-Niino *et al.*, 2004).

The discovery of the TGS domain in the Obg protein was intriguing. SpoT is a protein bearing two opposite enzymatic activities: that of guanosine-5′-diphosphate-3′-diphosphate (ppGpp) synthetase and of ppGpp-ase

(see Mechold *et al.*, 2002 and references therein). ppGpp is a specific nucleotide, synthesized extensively in amino acid-starved cells, which plays a role as a starvation alarmone and a global regulator of gene expression due to its direct interaction with RNA polymerase (for a review see Cashel *et al.*, 1996). More detailed structural studies revealed that Obg contains a bound nucleotide. This nucleotide was identified as ppGpp by Buglino *et al.* (2002). These authors speculated that the Obg protein may have evolved to recognize ppGpp in response to changes in the cellular environment.

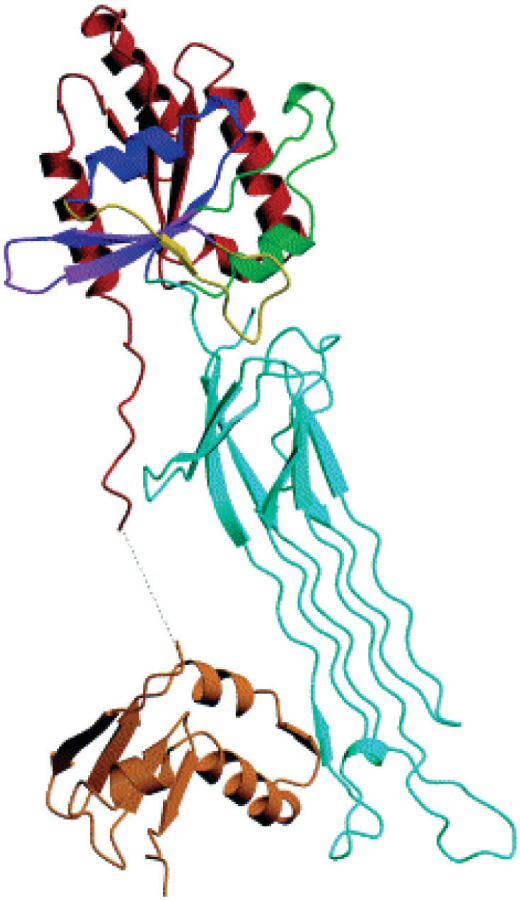

Figure 2. A model for *Thermus thermophilus* Obg protein.

Particular colors represent: cyan, the N-terminal domain; orange, the C-terminal domain; yellow, the switch-I region of the G domain; green, the switch-II region of the G domain; purple and red, other parts of the G domain. The atomic coordinates of the Obg protein from *T. thermophilus* are available from the Protein Data Bank, with the accession code 1UDX. This figure is reprinted from: Kukimoto-Niino M, *et al.*, (2004) *J Mol Biol.*; **337**: 761–770, with permission from Elsevier.

It is of special interest that the biochemical properties of the Obg protein of *B. subtilis* and its homologue from human cells have been found to be very similar (Buglino *et al.*, 2002). These results were found intriguing because it was generally believed that ppGpp is not involved in eukaryotic stress response (see Wittinghofer, 2002). However, recent studies demonstrated that ppGpp is produced in eukaryotic cells, namely in a unicellular photosynthetic organism, *Chlamydomonas reinhardtii* (Kasai *et al.*, 2002), and also possibly in *Arabidopsis* (van der Biezen *et al.*, 2000). In *C. reinhardtii*, ppGpp localizes to chloroplasts (Kasai *et al.*, 2002). These results imply that, contrary to previous assumptions, ppGpp may be involved in the intracellular signaling in plants. Thus, a lack of ppGpp function in animal and human cells seems not to be so obvious how as it was assumed a few years ago.

THE CgtA PROTEIN OF *CAULOBACTER CRESCENTUS*

A homologue of the *B. subtilis* Obg protein was found in *C. crescentus*, a bacterium that has a special developmental program, in which two types of cells are produced. This protein was named CgtA, for '*Caulobacter* GTP-binding protein' (Maddock *et al.*, 1997). CgtA is essential for cell viability and is present at low levels throughout the cell cycle (Maddock *et al.*, 1997). Furthermore, it was shown that the CgtA protein displays unique guanine nucleotide binding and exchange parameters (Lin *et al.*, 1999; Lin & Maddock, 2001; Lin *et al.*, 2001). Whereas the well-studied eukaryotic Ras-like proteins bind guanine nucleotides with high affinity, CgtA binds them with only moderate affinity. In addition, CgtA exchanges GDP and GTP rapidly. These

biochemical features are consistent with a model in which the intracellular guanine nucleotide pools govern the guanine nucleotide occupancy of CgtA.

The biochemical data described above suggest a model in which in the absence of a guanine nucleotide dissociation inhibitor, the guanine nucleotide bound state of CgtA would be controlled by the relative ratio of cellular concentrations of GTP and GDP. Similarly to the Obg protein of *B. subtilis*, CgtA of *C. crescentus* cofractionates with ribosomes (Lin *et al.*, 2004). Therefore, one could also speculate that CgtA might either be involved in ribosome assembly or in monitoring the assembly-state of the ribosomes. However, perhaps unexpectedly, recent studies on conditional *C. crescentus cgtA* mutants revealed that the lethal phenotype of *cgtA* dysfunction is not due to impaired ribosome function (Datta *et al.*, 2004). Moreover, the same studies revealed that CgtA is necessary for DNA replication and progression through the cell cycle (Datta *et al.*, 2004). Definitely, further studies are necessary to understand the precise role of CgtA in *C. crescentus* cells.

THE CgtA (ObgE) PROTEINS OF BACTERIA THAT DO NOT SPORULATE AND DO NOT HAVE A SPECIAL DEVELOPMENTAL PROGRAM

The first *obg* gene was discovered in *B. subtilis*, and was considered to be involved in the regulation of sporulation (Trach & Koch, 1989). Extensive biochemical studies were performed with the CgtA protein from *C. crescentus*, a bacterium that have a special developmental program, in which two types of cells are produced (see preceding paragraph). However, homologues of Obg/CgtA proteins are present in all bacteria investigated thus far (Czyż *et al.*, 2001 and references therein). Therefore, it is perhaps surprising that relatively little information is available about the member of the Obg subfamily from *E. coli*. Arigoni *et al.* (1998) demonstrated that the gene coding for this protein, formerly catalogued as *yhbZ*, is essential for *E. coli* growth, but no specific function of this gene was determined at that time. Currently, even the nomenclature of this gene is controversial. It was proposed to call this gene *obgE*, for '*obg* of *E. coli*' (Kobayashi *et al.*, 2001). However, the name *obg* was established for 'Spo0B-associated GTP-binding protein' of *B. subtilis*, whereas *E. coli* does not sporulate and there is no homologue or analogue of the Spo0B protein in this bacterium. Therefore, the name *obgE* was considered as confusing by Dutkiewicz *et al.* (2002) who proposed the name *cgtA*, which is identical to that of the *C. crescentus* gene coding for a member of the Obg subfamily. However, different etymology was proposed, namely 'common GTP-binding protein' (Dutkiewicz *et al.*, 2002), which would better symbolize the features of this gene than the names *yhbZ* or *obgE*.

Kobayashi *et al.* (2001) constructed a temperature-sensitive *cgtA* (*obgE*) allele, which was expressed from a plasmid in *E. coli* cells devoid of a functional chromosomal copy of this gene. Studies on such a strain indicated that partitioning of daughter chromosomes after a replication round is impaired in the absence of CgtA (ObgE) function. Similar conclusions were presented on the basis of studies on another Gram-negative, non-sporulating and non-differentiating bacterium, *Vibrio harveyi* (Słomińska *et al.*, 2002). Moreover, a weak DNA binding activity of the CgtA (ObgE) protein was found *in vitro* (Kobayashi *et al.*, 2001). Experiments with the use of bacteria overproducing *E. coli* CgtA (ObgE) suggested that this protein may have a role in synchronization of DNA replication, although the kinetics of DNA, RNA and protein syntheses were not significantly affected under these conditions (Dutkiewicz *et al.*, 2002).

Contrary to the suggestions of Kobayashi *et al.* (2001), it has recently been demonstrated

that *E. coli* CgtA (ObgE) protein is involved in DNA replication regulation. Namely, although replication of ColE1-like plasmids was not affected in the *cgtA* mutant, dysfunction of this gene caused a strong inhibition of λ plasmid DNA replication (Ulanowska *et al.*, 2003). Bacteriophage λ development was also severely impaired in the *cgtA* mutant. Replication of other plasmid replicons (derivatives of F, R1, R6K and RK2) was moderately influenced by the *cgtA* mutation (Ulanowska *et al.*, 2003).

It is worth mentioning that two other essential GTP-binding proteins of *B. subtilis*, Bex and YqeH, appear to participate in the regulation of chromosome replication (Morimoto *et al.*, 2002). It seems that DNA synthesis *per se* is not affected by CgtA in *E. coli*, and that this protein may control replication initiation indirectly, by regulation of the function(s) or production of one or more replication factors. In fact, it was found that level of the host-encoded replication protein DnaA is significantly decreased in the *cgtA* mutant (Ulanowska *et al.*, 2003). This indicates that CgtA is involved in the regulation of gene expression, which had not been noticed previously.

CgtA-mediated gene expression seems also to play a crucial role in the mechanism of enhancement of survival of cells after UV irradiation. Expression of the *cgtA* gene was found to be enhanced after UV-irradiation of cells (Zielke *et al.*, 2003). Moderate overexpression of *cgtA* resulted in increased UV-resistance of *E. coli* wild-type and *dnaQ* strains but not of *uvrA, uvrB, umuC* and *recA* mutants (Zielke *et al.*, 2003), suggesting that the RecA-dependent excinuclease and error-prone DNA repair systems may be stimulated by CgtA. It was also demonstrated that the basal level of the RecA protein was lower in a temperature-sensitive *cgtA* mutant of *E. coli* than in the $cgtA^+$ strain, and unlike in wild-type bacteria, no significant increase in the *recA* gene expression was observed after UV irradiation of this *cgtA* mutant (Zielke *et al.*, 2003). Therefore, it appears that the *cgtA* gene product is involved in DNA repair processes, most probably by stimulation of *recA* gene expression and resultant activation of RecA-dependent DNA repair pathways. Interestingly, the impairment of DNA repair efficiency in *cgtA* mutants was used in a new microbiological test to detect mutagenic pollution of the environment (Czyż *et al.*, 2000; 2002; 2003; Węgrzyn & Czyż, 2003). Overexpression of the *cgtA* (*obgE*) gene suppressed the phenotype normally associated with defects in the *rrmJ* (*ftsJ*) gene, coding for an rRNA methyltransferase, by an unknown mechanism (Tan *et al.*, 2002).

Very recent studies by Foti *et al.* (2005) provided another support for the proposal that CgtA is involved in DNA replication regulation. They have isolated an *E. coli* mutant in the *cgtA* gene (called again *obgE* by them) which was very sensitive to various DNA replication inhibitors. Genetic analysis suggested that chromosome brakes and regressed replication forks may accumulate in this mutant. Overproduction of CgtA caused spreading of the SeqA protein within the cell (SeqA is normally localized to replication forks, and can be observed as specific foci). Therefore, Foti *et al.* (2005) proposed that CgtA is involved in promotion of bacterial cell survival when replication forks are arrested. Moreover, report by Foti *et al.* (2005) opens many more questions and provide further suggestions about involvement of CgtA in the regulation of chromosomal DNA replication at various stages, including the initiation step.

Similarly to the Obg protein from *B. subtilis* and CgtA from *C. crescentus*, the CgtA protein from *E. coli* cofractionates with the large ribosomal subunit (Wout *et al.*, 2004). In the light of the discovery that ppGpp may be bound to CgtA, it was intriguing that CgtA may directly interact with SpoT (a ppGpp synthetase and hydrolase), as revealed by coprecipitation experiments and by two-hybrid assays (Wout *et al.*, 2004). Undoubtedly, studies on the putative interplay between GTP-binding proteins

and those involved in ppGpp metabolism may lead to very interesting discoveries which might tell us more about the physiological functions of CgtA and related proteins.

PERSPECTIVES

The evolutionary conservation of the members of the Obg subfamily of GTP-binding proteins, from bacteria to humans, is comparable to that found in a group of heat shock proteins (Leipe *et al.*, 2002). This implies crucial functions of Obg-like proteins in cells of most, if not all, organisms. Recent studies have revealed that these proteins are involved in many basic cellular processes, including chromosomal functions, reactions of the protein synthesis machinery, control of gene expression, and regulation of stress responses and developmental processes. Determination of the Obg protein structure of *B. subtilis*, construction of mutants in the homologous genes of other bacteria, and purification and basic biochemical characterization of Obg and CgtA (from *C. crescentus*) allowed us to learn about basic functions of these very important proteins (Caldon & March, 2003). Nevertheless, it is still unknown what is the primary role of the members of the Obg subfamily, and how so many different cellular processes can be regulated by these relatively small proteins.

We are grateful to Janine Maddock for many fruitful discussions, and to members of our team who have participated in projects on Obg-like proteins.

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