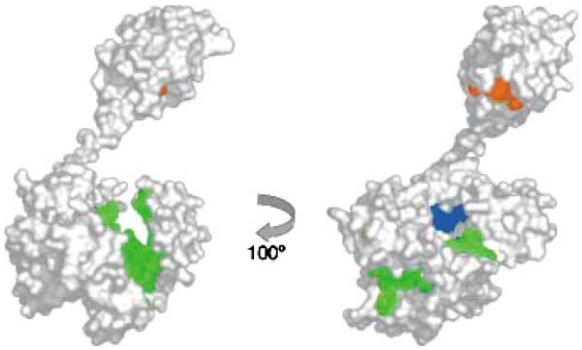

Views of the Putative Polypeptide Binding Channel in SurA

Surface rendering of SurA, highlighting the channel and putative polypeptide binding surface (green) and the proline binding pockets of the inactive (blue) and active (orange) PPIase domains (kindly provided by E. Bitto and D. McKay). The left SurA molecular is shown in the same orientation as the first figure.

tide binding channel finds further support in crystal-packing interactions. In the crystallographic unit, a short helical peptide segment that sits piggyback on SurA binds to the flap-like structure of the adjacent SurA molecule. However, there are at least two caveats with this interaction identifying the substrate binding pocket. First, it spans only a fraction of the actual capacity of the crevice. More importantly, the bound peptide has α-helical conformation whereas the known SurA substrates, the outer membrane porins, are β stranded. Is the channel indeed the polypeptide binding site relevant to the chaperone function in SurA, and if so, which parts of it actually form the binding surface? Is the observed binding specificity of SurA [7] determined by primary polypeptide sequence, secondary structure, or possibly both?

The crystal structure of SurA is the foundation stone to understanding SurA functions at a molecular level. The urgent questions of how SurA recognizes, binds, and releases its outer membrane protein substrates and how it facilitates their maturation without the driving force of ATP hydrolysis can now be directly addressed. New, exciting insights are likely to emerge within the near future. Moreover, the structure paves the way to face the next big challenge—studying the protein dynamics involved in substrate binding and release.

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Obg, a G Domain with a Beautiful Extension

The structure of Obg, a protein involved in a complicated genetic network that regulates stress response and sporulation in *Bacillus subtilis*, reveals a completely new type of guanine nucleotide binding protein and provides some hints about its function.

Guanine nucleotide binding proteins (GNBPs) regulate many different types of processes in both prokaryotes and eukaryotes. They come in a large variety of different sequences and shapes. The most important and widely studied groups are the family of protein biosynthesis factors acting on the ribosome, the heterotrimeric G proteins, the Ras superfamily of small 20–25 kDa proteins, and the factors involved in signal recognition (SR proteins and the corresponding receptors) and cotranslational transport of proteins into the endoplasmic reticulum (ER). The remaining GNBPs form a large group of different proteins [1]. The common property shared by these is that they contain a more or less conserved structural module, the G domain, which is usually involved in the switching of the protein between a GDP-bound and a GTP-bound conformation [2–4]. With the exception of translation factors, the signal recognition particle and its receptor, most of the guanine nucleotide binding proteins mentioned above are found only in eukaryotes. Recently, in large part fuelled by the large sequencing projects going on worldwide, it has become clear that there are a number of guanine nucleotide binding proteins that are conserved from bacteria to man and that the functions of most of these are unknown [1].

One of these is the protein Obg, which was first discovered in the *Bacillus subtilis* spo0 operon as a protein involved in a complicated genetic network that regulates stress response and sporulation. Hence the name, Obg,

which derives from spo*0B*-associated *G*TP binding protein. The exact function of this protein is not known, and many proposals have been put forward for its biological function. To approach the functional role from a structural perspective, the group of Chris Lima, in the course of a structural genomics project, has now solved the structure of the *Bacillus subtilis* Obg, which appears in this issue of *Structure* [5].

Unlike the G domain-only proteins of the Ras superfamily, Obg is a large protein that consists of three domains, an N-terminal glycine-rich domain, a Ras-like G domain, and a C-terminal TGS domain. The latter is a small domain found in a number of proteins that have the common property of being involved in bacterial stress response. Unlike Ras or Gα proteins, Obg, like a number of other GNBPs, shows micromolar affinity for GDP/GTP, which results in fast exchange of the nucleotide and thus does not require a guanine nucleotide exchange protein (GEF), which, in Ras and Gα, regulates activation. It has a very slow GTPase, with a rate on the same order as that of the Ras proteins ($\sim$0.02 min^{-1}), suggesting that there may be a GTPase-activating protein (GAP) or another mechanism that increases the rate of the reaction [6]. However, like guanine nucleotide binding proteins such as hGBP, dynamin, and septins, it does not have a glutamine residue in the switch II region, which has been shown to be crucial for the GTPase reaction of Ras and Gα proteins, suggesting a rather different mechanism of GTP hydrolysis.

The structure of Obg shows the well-known features of the G domain, which typically contains six β strands and five α helices. Obg has one additional β strand in the switch I region and one additional α helix in the switch II region. The putative switch regions are involved in the interaction with the rest of the structure, such that one could envision nucleotide-dependent changes in the interface between the G domain and the rest of the molecule. While the structure was solved in the presence of various nucleotides, no significant structural changes were observed, although this could be due to constraints of the crystal packing.

The most remarkable feature of the structure is the N-terminal part of the Obg, which is unique and is thus called the Obg fold. It is an elongated barrel, the lower part of which consists of an eight-membered β sheet sitting on top of, and interfacing with, the G domain. The glycine-rich part of the Obg fold consists of a six-helix bundle, where the helices share structural features with a type II polyproline helix. The six helices pack together in parallel and antiparallel pairs. There is an extensive main chain hydrogen bonding pattern between the helices. Probably for steric reasons, most of the invariant glycines are in the interior of the fold, which lacks a normal hydrophobic core and is instead stabilized by side chain interaction on the outside of the fold.

Some hints about the function of Obg come from some lucky accidents. Although the protein was purified without the addition of nucleotides, one of the monomers in the dimeric asymmetric unit contained, in addition to the 5′ phosphates sitting in the P loop, additional density bound to ribose, which was modeled as ppG-3′pp, a nucleotide that is part of a stress response and accumulates to millimolar concentrations in the cell. Incidentally, the TGS domain, which was absent in the present structure, is found in a number of proteins known to interact with ppGpp. While this seemed to suggest a contribution of the TGS domain, the biochemical experiments did not reveal such a contribution. Although it is not completely clear whether the presence of ppGpp is functionally relevant, biochemical experiments showed that ppGpp is having some effect on the rate of GTP hydrolysis. However no direct binding of the nucleotide was observed, and the effects on the GTPase were somewhat inconsistent. In any case the fact that ppGpp, and not any other guanine nucleotide, was found in the protein and was retained during the purification procedure warrants further experiments to test the importance of this observation for the role of Obg in stress response. Nothing at all is known about the role of mammalian Obg proteins. Since ppGpp is not involved in eukaryotic stress response, we still have to look ahead for some more biology on this seemingly important GTP binding proteins.

Obg is a completely new type of guanine nucleotide binding protein. It is just another example of how a conserved module, the G domain, has been used for many different switching reactions. As with other guanine nucleotide binding proteins, the structures of the nucleotide-free and the ppGpp-bound forms are only the beginning. More structures are needed to fully understand the switching mechanism and what biological processes it drives, but the present structure is a marvelous beginning.

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