number of molecules) are initially parallel to the substrates (part *a* in the figure). Transparent electrodes are used to apply an electric field normal to the substrates. The field induces a dipole preferentially along the long axis of the aligned molecules, and drives them towards an upright orientation. This can be described as the effect of an anisotropy in the material's dielectric permittivity. Similarly, an anisotropy in refractive index translates the changing alignment into an optical modulation when observed between polarizers.

The molecules can fall into either of the arrangements in part *b* in the figure, and if no precautions are taken the display will contain domains with each of these profiles. The optical transmission of obliquely passing light is different in each case, and so the display has a patchy appearance. Moreover, the domains are separated by a transition line that is clearly visible between polarizers and deteriorates the image.

Parts *c* and *d* of the figure show that the occurrence of two possible orientations can be avoided by giving the director at each substrate a bias tilt. So an alignment method for liquid crystals should not only provide a preferential direction for the molecules in the plane of the substrate, it should also define a suitable surface bias tilt, typically between 2° and 10°.

The old technique[3] of rubbed polymer films has been brought to high enough sophistication to meet these requirements[4]. The selection and processing of these polymers is partly a science and partly a craft, or even an art. But it generates dust, which conflicts with the extremely clean manufacturing conditions needed, and there is a risk of electrostatic damage to the thin film transistors in the displays commonly used for television and computer monitors.

In 1992, researchers at Hoffman–La Roche in Basel and NIOPIK in Moscow achieved in-plane control of liquid-crystal orientation, though without bias tilt, using linearly polarized ultraviolet light[5]. The light breaks bonds that happen to be oriented parallel to its polarization direction, and then new bonds form perpendicular to this direction.

A lot of work has been done since 1992 to qualify this photoalignment technique for application in the liquid-crystal display industry, but a satisfactory value for the bias tilt has not been reported. Attempts to break the symmetry of the liquid-crystal layer on top of the polymer film by using obliquely incident light were without success, because the liquid crystal orients itself parallel to the molecules of the substrate, that is, perpendicular to the polarization direction of the ultraviolet light.

The paper of Schadt and colleagues[1] reports on a material that, instead, aligns the liquid crystal more or less parallel to the polarization direction of the light. This is crucial for making photoalignment a viable alternative to the conventional rubbing technique. There are still practical issues to be addressed, however, such as the processing of the materials, their stability and their transparency, and the contamination of the liquid crystal by the orientation layer or its solvent.

The photoalignment technique can not only simplify display manufacture. It can also be used to make novel, better displays by forming patterns of orientation within each display element[1,6] to reduce the dependence of visibility on the direction of view — an obvious shortcoming of liquid-crystal television and computer screens.

Several approaches to this problem are now being industrialized. They include adding birefringent compensators, alternative liquid-crystal configurations in which twist angle varies in response to electric fields, combinations of collimating and diffusing foils that enclose the liquid-crystal cell, and the division of picture elements into differently oriented subpixels or subpixels in series with small capacitors. It is an open question which approach will become the mainstream technology for future high-quality liquid-crystal displays. The results of Schadt and colleagues certainly increase the chances of the subpixel method.

One might pursue this topic to replace existing techniques, to improve existing products or to make entirely new components or devices. For example, the new technique could be used to make stacks of birefringent layers with, in principle, independent control over the orientation of each layer. Among other things, this could be used as a 'copy-proof' way of making images that are visible in polarized light only[7]. The paper of Schadt, Seiberle and Schuster adds an intriguing item to the list of exciting things that can be done at the interface of optics, polymer chemistry and liquid-crystal device technology. □

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PROTEIN TARGETING

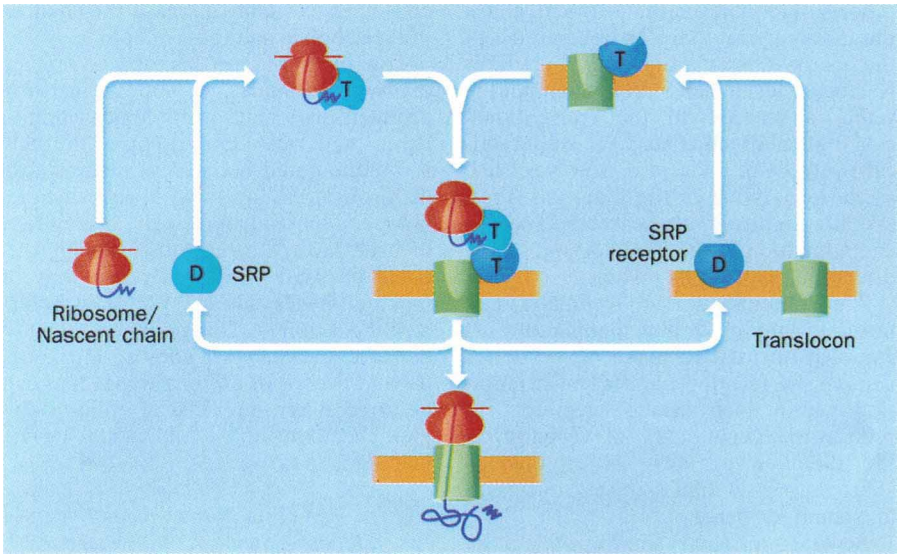
The ribosome talks back

Ted Powers and Peter Walter

THE synthesis of most mammalian membrane and secretory proteins begins on free, cytosolic ribosomes that are targeted co-translationally to the membrane of the endoplasmic reticulum (ER). The mechanism by which these nascent proteins are selected requires three distinct, directly interacting GTPases which serve as adapters between the translation apparatus in the cytosol and the protein translocation apparatus, the translocon, in the ER membrane[1]. The function and regulation of these GTPases has become the object of intensive study, and now, as described on page 248 of this issue[2], Bacher *et al.* have made the intriguing observation that the GTP-binding activity of one of these GTPases is modulated by the ribosome itself.

To place this work in context, proteins are synthesized by a common pool of ribosomes, but only those proteins that carry a hydrophobic signal peptide are imported into the ER. These include all transmembrane proteins, most secreted proteins and most proteins destined to be stored in the lumen of intracellular organelles such as the Golgi apparatus, lysosomes and endosomes. As the protein is synthesized, the signal-recognition particle (SRP) binds to both the hydrophobic signal peptide and to the ribosome, directing them to the SRP receptor on the cytosolic surface of the ER membrane. After the complex has docked, the protein is translocated across the ER membrane through the translocon, and may remain in the ER lumen or be distributed to other destinations in the cell.

The component in question here is the 54K subunit (SRP54) of the signal-recognition particle, which is the cytosolic ribonucleoprotein that first identifies those ribosomes that synthesize nascent chains bearing ER-directed signal sequences[1]. SRP is composed of an RNA and six polypeptides, of which SRP54 can be viewed as the most central player. It contains an amino-terminal GTPase domain and a carboxy-terminal domain which binds directly to signal sequences and SRP RNA. Homologues of SRP54, as well as the small motif in SRP RNA to which it binds, can be traced all the way to eubacteria and archaebacteria, where they are



Model for regulation of GTP binding to the signal-recognition particle (SRP) and its receptor during co-translational targeting of pre-proteins to the membrane of the endoplasmic reticulum (ER). The branch on the left depicts binding of SRP to a ribosome-nascent polypeptide that contains a signal sequence. As shown by Bacher *et al.*[2], the ribosome acts as a GTP loading factor for SRP54 and locks it into its GTP-bound form (indicated as 'T'), thus 'turning on' SRP for docking to its receptor at the ER membrane. The branch on the right is speculative and proposes that a component of the translocon similarly turns on the SRP receptor by stabilizing the GTP-bound form of the α-subunit of the SRP receptor; the role of the β-subunit of the SRP receptor in targeting is unclear, although a functional GTP-binding domain is required for translocation (S. Ogg and P. Walter, unpublished data). Binding of GTP to SRP54 and the α-subunit of the SRP receptor is required for their tight association and leads to formation of the ribosome–membrane junction. Subsequent hydrolysis of GTP to GDP (indicated as 'D') by SRP and its receptor results in their dissociation and allows for another round of targeting.

likely to perform similar functions in protein targeting.

After binding to ribosomes and signal sequences, SRP interacts with its receptor, an ER membrane protein composed of two subunits, SRα and SRβ, both of which also contain GTPase domains. In the presence of GTP, the SRP receptor causes SRP to be released from the ribosome-nascent chain, and the latter becomes tightly associated with components of the translocon, composed principally of the heterotrimeric Sec61p complex[3]. These targeting events only require GTP binding, not its hydrolysis, as non-hydrolysable analogues can substitute and promote a round of targeting. GTP hydrolysis is required for a subsequent step that releases SRP from the receptor so that it can return to the cytosol[4]. But how, mechanistically, do the three individual GTPases — SRP54, SRα and SRβ — collaborate to drive a targeting cycle?

The first insight into this question came by studying the interaction between purified SRP and its SRP receptor *in vitro*[5]. Monitoring GTP and GDP binding to individual proteins by ultraviolet crosslinking, it was found that SRP receptor both promoted GTP binding to SRP54 and then activated its GTPase. Interestingly, SRP receptor did not affect the affinity of SRP54 for GDP, in contrast to other, well-characterized guanine nucleotide exchange factors. This suggested that SRP receptor acts as a novel 'GTP-loading factor', increasing the affinity of SRP54 for GTP directly. Furthermore, nucleotide binding to SRP54 was blocked in the presence of synthetic signal peptides. By extrapolation, these results pointed to a model whereby SRP is stabilized in a nucleotide-free state by signal sequences within a targeting complex; subsequent interaction with the receptor at the membrane facilitates release of the signal sequence in exchange for binding of GTP to SRP.

Enter Bacher *et al.*[2], who have now used similar assays to include bona fide ribosome-nascent chain complexes. Their most important observation is that the affinity of SRP54 for GTP is increased by about an order of magnitude in the presence of a ribosome that carries a nascent chain with a signal sequence. Thus before encountering the SRP receptor, the ribosome already acts as a GTP-loading factor for SRP54, thereby moving the step in which GTP enters the targeting cycle up by one notch. The GTP-loading activity of the ribosome apparently overrides the inhibitory effect caused by signal peptides alone.

These results are appealing because they offer a simple mechanism for how targeting is regulated. In the presence of a signal sequence, SRP binds tightly to the ribosome and becomes 'turned on', by GTP binding, for docking to its receptor. The SRP receptor would then stabilize SRP54 in its GTP-bound state and induce dissociation of SRP from the ribosome. In turn, this would lead to release of the signal sequence by SRP54 and docking of the ribosome-nascent chain at the translocon. Finally, GTP hydrolysis would allow dissociation of SRP from the membrane.

Bacher *et al.* also observe that the GTP-loading activity of the ribosome affects even free SRP54 (that is, in the absence of SRP RNA and the other SRP proteins), indicating that SRP54 interacts directly with some ribosomal component or components. It will be interesting to ask in future experiments whether this activity is caused by the same ribosomal component(s) involved in interactions with other well-characterized GTPases that bind to the ribosome, such as elongation factors.

Intriguingly, the GTPase domains of the SRα subunit of the SRP receptor and of SRP54 are phylogenetically related, being more similar to each other than to any other member of the superfamily of GTPases. As for SRP54, SRα must also be in its GTP-bound form to engage SRP[6], and their prokaryotic homologues engage in a similarly symmetrical interaction. Bacterial SRP54 and SRα function as reciprocal GTPase-activating proteins for each other, each needing to be bound to GTP to show this activity[7]. It is therefore likely that SRα will similarly be turned on by interacting with another component that promotes its GTP binding. A likely candidate would be the translocon itself.

According to this view, the GTPase cycles of SRP and the SRP receptor would be coupled directly to their roles as molecular matchmakers, recruiting cytosolic and membrane-bound components, respectively, to catalyse formation of the ribosome–membrane junction (see figure). Each would be turned on and ready to interact after having found its appropriate cargo. Although this model incorporates the requirement for two GTPase switches, the need for a third, in SRβ, remains a mystery — indicating that, even with these new insights and speculations, we are still far from a full picture of events. □

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