generate a magnetic flux amounting to half the standard flux quantum $hc/2e (= 2 \times 10^{-7}$ G cm^{-2}) of a superconductor, equivalent to a magnetic moment exceeding that of the electron by many orders of magnitude. Strangely, this device does not have a stable state with zero magnetic flux. The magnetic moment of such a superconducting loop should indeed act like a paramagnet, as it aligns parallel to the external field in a similar manner to a magnetic needle. So this device is an example of a system displaying the PME.

The effect in this case is a quantum coherence phenomenon specific to the superconducting state of high-temperature superconductors. No effect of this kind has been observed in any conventional superconductor. The observation of this frustration phenomenon was crucial in proving the unconventional symmetry of the superconducting state in high-temperature superconductors — the chief motivation for performing this experiment[6].

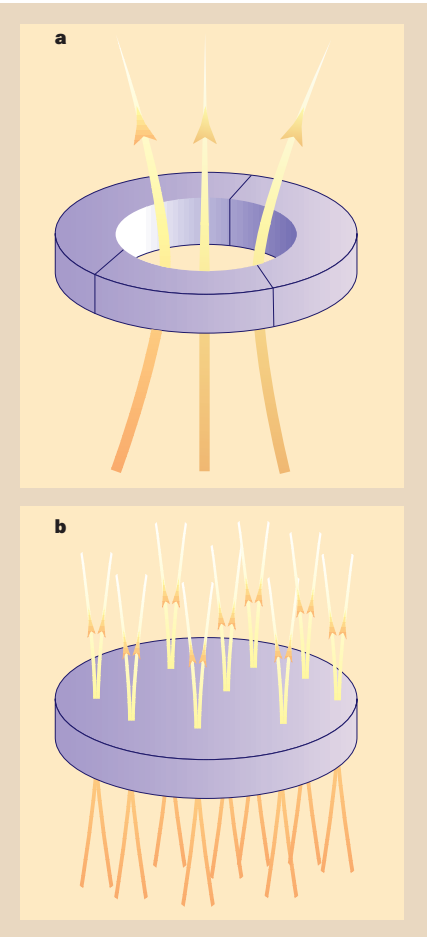

Figure 1 **Magnetism in mesoscopic superconductors.** a, **A loop made of three crystals of a high-temperature superconductor[5] frustrates the phase of the superconducting state. As a result a spontaneous current flows generating a magnetic flux.** b, **A mesoscopic superconducting aluminium disc[1] in an external magnetic field hosts various vortex patterns, including some metastable magnetic states. Both mechanisms can lead to paramagnetism.**

But during the past few years, several groups have also reported paramagnetic responses in millimetre-sized single crystals of conventional superconductors such as niobium. Again, to test ideas about how this could happen in mesoscopic grains, we need a highly controlled experiment on these small scales. Geim and co-workers[1] have now demonstrated paramagnetism in micrometre-scale discs of aluminium, a substance that is superconducting below 1.2 K.

The miniaturization means that very few magnetic vortices are present, and there is a discrete set of states consisting of different arrangements of vortices which may be characterized by 'quantum' numbers, similar to those describing electron states in atoms. Most of these states are metastable, but may become stable if a magnetic field of the right strength is applied externally.

Geim *et al.* triggered transitions between different vortex states in their aluminium disc by varying the magnetic field. That produces large changes in the magnetization of the superconductor and so in the number of magnetic vortices threaded through the superconducting disc. Here, the PME originates from one of the metastable states with a large number of vortices, which must decay upon application of a strong external disturbance.

This property of metastability distinguishes the PME in the current-carrying loop and the disc, as the former is clearly in a stable state, like a magnetic needle in a magnetic field. The PME of granular high-temperature superconductors corresponds to the stable rather than the metastable situation, and appears to be caused by large magnetic moments like those generated by the frustrated current loops[7]. Presumably the loops here consist of several connected grains. And the presence of spontaneous magnetic moments in zero external field has been directly observed[8] in granular $Bi_2Sr_2CaCu_2O_8$ samples which show the PME.

But the metastable vortex states seen in the superconducting discs might also contribute to the PME of the granular high-temperature superconductors. Indeed, the effect is increased in samples where the grain structure favours states with densely-packed vortices. However, the same samples also provide good conditions for frustrated loop formation.

Further experiments on mesoscopic discs will teach us about vortex physics in conventional superconductors, and may enable us to observe some of the unusual vortex structures expected in unconventional superconductors. These miniature superconductors may also become important technological materials, largely because of their magnetic properties, and new devices may be designed to exploit these quantum coherence phenomena. □

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Protein transport

Life and death of a signal peptide

Gunnar von Heijne

Signal peptides target proteins for secretion in both prokaryotic and eukaryotic cells. A deceptively simple-looking amino-terminal extension on the newly synthesized polypeptide chain, the signal peptide takes part in an array of protein–protein and protein–lipid interactions. The result is initiation of protein translocation through a proteinaceous channel — the translocon — in the bacterial inner membrane, or in the endoplasmic reticulum (ER) of eukaryotic cells. After fulfilling its mission, the signal peptide receives its *coup de grâce* from the signal peptidase, a membrane-bound enzyme that liberates the mature protein from this now useless appendage.

Thanks to the work of Paetzel *et al.*[1], who report the crystal structure of a bacterial signal peptidase on page 186 of this issue, we now have a glimpse of how this unusual enzyme can cleave the signal peptide so precisely as it emerges from the relative safety of the membrane. Not only do we see a new protease fold and a strikingly hydrophobic surface patch that positions the active site relative to the lipid bilayer, but the structure of the bacterial enzyme can also be used as a template to model other signal peptidases, and will be of great interest for designing new antibiotics.

Signal peptides have a common structure: a short, positively charged amino-terminal region (n-region); a central hydrophobic region (h-region); and a more polar carboxy-terminal region (c-region) containing the site that is cleaved by the signal peptidase (Fig. 1, overleaf). It has been obvious all along that many of the interactions between the signal peptide and other molecules must be hydrophobic in nature, but only recently has the structural basis for at least

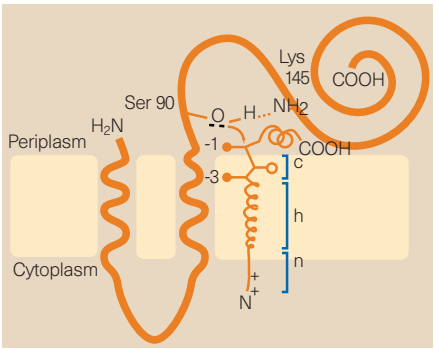

Figure 1 **The signal peptidase of *Escherichia coli*, the structure of which has been solved by Paetzel *et al.*[1]. Two amino-terminal transmembrane helices anchor the protein in the inner membrane, and the catalytic carboxy-terminal domain is partly immersed in the outer leaflet of the bilayer. Serine-90 (Ser 90) is the acylating nucleophile and lysine-145 (Lys 145) acts as the general base in both the acylation and deacylation steps of catalysis. Small residues in positions −1 and −3 in the signal peptide bind to the S1 and S3 specificity pockets in the enzyme. The h-region is helical, whereas the c-region must be in an extended conformation to be accessible for cleavage.**

some of these interactions become apparent.

As the signal peptide emerges from the ribosome, it is first recognized by a ribonucleoprotein complex, the signal recognition particle (SRP). The subunit that binds the signal peptide has a hydrophobic surface groove lined by flexible methionine side chains, and it seems perfectly designed to adapt to the highly variable h-region[2]. By virtue of its affinity for the membrane-bound SRP receptor, the SRP ensures that the nascent protein is delivered to the translocon. Here, the signal peptide is scrutinized a second time, and it is eventually inserted in a lipid-exposed location between two transmembrane helices of the Sec61α protein[3,4]. In the ER translocon, this insertion step correlates with the establishment of a tight seal between the ribosome and the translocation channel[5]. As seen by electron microscopy[6], the nascent chain runs in a closed, continuous tunnel from the ribosomal P-site through the large ribosomal subunit and then through the translocation channel, finally emerging in the lumen of the ER. In *Escherichia coli*, where proteins are translocated after they have dissociated from the ribosome, the SecA protein seals the channel from the cytoplasmic side and helps move the nascent chain through the translocon[7]. An X-ray structure of the SecA protein has been shown at meetings, but so far has not been published.

At this point, the signal peptide spans the membrane with its carboxy-terminal end facing the ER lumen (or, in *E. coli*, the periplasm). Although still associated with the translocon, it is also exposed to membrane lipids and its h-region has a helical conformation[3]. Enter the signal peptidase. Its job: to skim the lumenal (or periplasmic) surface of the membrane, looking for suitably exposed signal-peptide cleavage sites. Paetzel and colleagues' structure of the periplasmic domain of the *E. coli* enzyme[1] tells us how this is accomplished.

First, an extended hydrophobic patch surrounds the active site, suggesting that this part of the enzyme is immersed in the outer leaflet of the lipid bilayer. Second, the structure of the active site readily explains the requirement for small residues such as alanine in positions −1 and −3, upstream of the cleavage site, and also shows that the c-region must be in an extended conformation. The h-region thus, presumably, positions the c-region near the lipid head-groups, within reach of the signal peptidase. This may also explain why signal peptidase does not cleave transmembrane helices in integral membrane proteins, or signal peptides with artificially lengthened h-regions[8]. Such helices generally extend across the lipid head-group region, so they do not present the required extended conformation.

This is where the story could end — the last mopping up is taken care of by various oligopeptidases, which digest the signal peptide into free amino acids. But biology would not be so interesting if it didn't always come up with the unexpected. Certain signal peptides leak back into the cell where they bind to proteins such as calmodulin[9], or they are presented to the immune system by molecules of the major histocompatibility complex on the surface of the cell[10]. So, some signal peptides probably have a second signalling function, distinct from their role in targeting.

We are experiencing a new wave of structural and biochemical work on protein targeting, which is finally showing us the intimate details of the life and death of signal peptides and the machineries that they put in motion. The key is the h-region — a simple stretch of about ten hydrophobic residues that primes the SRP, unlocks the translocon and positions the signal peptide for cleavage. The messenger is the message. □

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Chronology

Friday XIII

This is the Friday the Thirteenth Club, meeting in Paris in 1930 to dance underneath a ladder and carry open umbrellas indoors. Being a rational reader of *Nature*, you surely applaud this contemptuous attitude towards superstition, so you won't be at all concerned by the following sinister tale.

In 1582, Pope Gregory XIII introduced a new calendar to replace the old Julian system, whose inaccuracies had made Easter slip slowly through the seasons. To bring the festivals back to their old positions, ten days disappeared from October 1582. Some people thought the days were being stolen from them.

But rebuilding and resetting the calendar had a more subtle effect. The Gregorian cycle of 400 years contains exactly 20,871 weeks, and hidden in the calendar's machinery is a bias towards certain days of the week landing on certain dates in the month. The 13th is more likely to be a Friday than any other day (Brown, B. H. *Amer. Math. Monthly* 40, 607; 1933).

Bernard Yallop now points out that with a personal computer it is possible to look for such peculiarities "without resorting to mathematics" (*Spectrum* October, 66; 1998). His table shows for example that there are 688 Friday-the-thirteenths every 400 years, but only 684 Thursdays; and a month (like a week) is most likely to begin on a Sunday.

HULTON GETTY

Did the Friday the Thirteenth Club know of their good fortune in having these extra opportunities to carouse? I only hope they didn't meet a sticky end before finding out.

Stephen Battersby