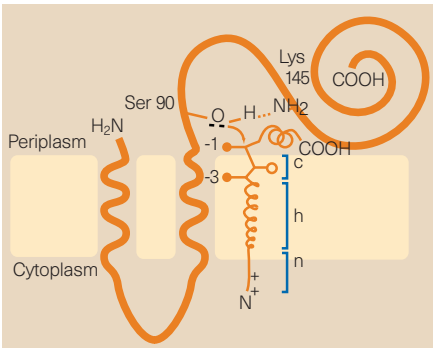

Figure 1 **The signal peptidase of *Escherichia coli*, the structure of which has been solved by Paetzel *et al.*[1]. Two amino-terminal transmembrane helices anchor the protein in the inner membrane, and the catalytic carboxy-terminal domain is partly immersed in the outer leaflet of the bilayer. Serine-90 (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