error, this region must have been lost relatively late in evolution. If this domain does indeed restrict polymerization then MACs in trout should not contain multiple C9 molecules. In thrombospondin this domain is found on a part of the polypeptide chain involved in trimer formation, encouraging the interpretation that these regions in the complement proteins could be involved in forming the stoichiometric C5b-8 complex but they could prevent the polymerization that is characteristic of only C9 and perforin.

The largest terminal component of complement that has been cloned is C7. After the thrombospondin domain, this has two further cysteine-rich domains at the carboxy terminus, which are found in a large family of C3- and C4-binding proteins. This homology was not reported in the original paper¹⁰ but both domains (residues 546-606 and 607-668) contain 15 out of 21 of the consensus amino acids for this family of sequences¹⁵. These sequences could neatly account for binding of the terminal complement components to C5b, which is an integral part of the terminal complex but resembles C3 and C4 in sequence. Acquisition of these C4 binding-protein-like domains explains how the early complement pathway, which opsonizes bacteria and produces inflammatory intermediates, has come together in evolution with the terminal pathway that provides a mechanism for membrane attack. Coupling the two pathways gives a specific stimulus to regulate the action of the humoral cytolytic proteins, analogous to the stimulus provided by effector-target cell interaction for perforin release.

The finding that perforin has a high degree of homology over a short part of the molecule, rather than an overall homology with the terminal complement components, should greatly help us to understand how cytolysis occurs. The mosaic character of these proteins, with many independently folding domains, means that the function of each region can now be ascertained by constructing chimaeric proteins. At the mechanistic level the questions can also now be more precisely formulated. How is the transition from a soluble protein to an integral membrane protein achieved? In perforin the presence of the same amphipathic helix thought to be used for membrane insertion in the terminal complement components strongly supports a two-step model. This involves an initial binding close to the membrane and then a refolding of the membrane-inserting domain to expose the hydrophobic patches¹⁴. It is still unexplained why this region allows the cytolytic proteins to bind to membranes with such avidity. Perhaps only site-directed mutagenesis can answer this question.

Perforin requires calcium for insertion into the membrane, which might facilitate

the initial binding of the protein in the proximity of the lipid bilayer. The carboxy-terminal domain of perforin¹ has some highly acidic regions which could account for calcium binding, although it has no recognizable calmodulin-like feature. For C9 the initial interaction occurs with the C5b-8 complex but, because we now know that this is composed of C9-like molecules, we are no nearer to explaining how the first membrane attachment occurs. The argument, which predated cloning, about exposure of hydrophobic regions directing the C5b-7 complex to the membrane no longer holds water, for none of the complement components is particularly hydrophobic and exposure of hydrophobic domains is anyway more likely to lead to aggregation rather than membrane insertion.

The proximity of the C5 convertase to the membrane surface is most likely to be equivalent to the calcium attachment of perforin but it is still possible that C6 or C7 has some additional mechanism for membrane attachment potentiated by formation of the C5b-7 complex. One possibility not yet investigated is the presence of covalently bound lipid. It is intriguing that there is a short region of the C7 sequence between the thrombospondin and C4 binding-protein-like repeats (asterisk in figure) that shows some similarity with the lipid-linked membrane binding domain of the complement regulatory protein, decay accelerating factor¹⁶.

The sequences of perforin and the terminal components of complement have provided many surprises. They are interesting proteins, not only because of their importance in immune defence but also because they provide a model for the molecular interaction of proteins with lipid bilayers. From the evolutionary point of view, it seems that the essential features of membrane attachment, membrane insertion and polymerization found in perforin have also been used to generate a series of specialized cytolytic molecules in the terminal complement proteins by the acquisition of protein domains conferring new properties. □

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Keith Stanley is in the European Molecular Biology Laboratory, Postfach 10.2209, D-6900 Heidelberg, FRG; Paul Luzzio is in the EMBL on leave from the University of Cambridge.

Daedalus

Ocean currents

MUCH of the power needed to propel a ship goes into overcoming viscous drag. The water shrew solves this problem very neatly. Its oily fur repels water so perfectly that the creature as it swims is enveloped in a seamless silvery skin of entrained air and never even gets wet.

So Daedalus is devising a way of coating a ship's hull with a similar layer of drag-reducing gas. His ingenious strategy is to generate the gas directly on the hull surface by electrolysis, using the hull as an electrode. This will cover it with a uniform sheet of tiny bubbles, ideally suited as a captive overcoat. DREADCO's electrochemists are studying various electrode surfaces, from shiny and sticky finishes to rough, pitted or micro-bristly ones, seeking the best bubble-retaining characteristics. The final material should cling tenaciously to its bubbles, losing them only slowly by agglomeration and escape. So it will draw only a modest current, just enough to make up these gradual gas losses. In effect, it will be insulated from the water by its own gas coating. Only where the water breaks through this film will current flow: the resulting sudden burst of electrolysis will quickly push the water back again and break the circuit.

Any electrolytic cell needs two electrodes. So Daedalus's electrolytic vessel will be divided down the centre into two mutually insulated halves, port and starboard, with a potential of a few volts maintained between them by on-board turbine generators. The cathodic side will release hydrogen while the anodic side, in salt-water at least, will disengage oxygen and a little chlorine. (Both sides should powerfully discourage marine organisms.)

As a final brilliant touch, Daedalus will use his electrolytic drag-reduction system to propel his craft. The current will pass transversely beneath its keel, from port to starboard through the water. So Daedalus will mount big permanent magnets amidships, their fields penetrating the water vertically downwards. By standard motor action, they will force the current-carrying water astern, thus driving the ship ahead. Smaller control fields will deflect the water sideways to provide steering.

A ship coupled so elegantly to the water all around it would be wonderfully agile, manoeuvring in total silence with no turbulence at all. With negligible propulsive or viscous losses, it should also be amazingly economical on fuel. Mechanically simple and with no sonic signature, it should appeal to navies, too. Its small electrochemical losses, its weakly alkaline and chlorinated wake, and its complete inability to navigate by magnetic compass, are only minor drawbacks. David Jones