Daedalus

Learning in middle life

The brain can learn; indeed, that is its main purpose. But with a mere ten billion cells it must use space with great economy. A whole lifetime of learning, language and experience must be packed in, all with almost instant recall. By contrast, a computer can easily store ten billion bits, but wastes nearly all of them.

This reminds Daedalus of last week's scheme to erase chosen bits of the brain. Botulinum toxin was injected into areas of skin, chosen by psychiatric acupuncturists to home in on selected brain areas. The toxin was encapsulated in small particles to travel slowly up the local nerve and reach the relevant brain area as the encapsulation decayed. The obsession, troublesome memory, complex or whatever, would be erased by the toxin for several months. One snag is that people with many obsessions and problems could lose data. The vacant cells would resemble a piece of empty brain tissue. Daedalus now reckons that, as it becomes available, the brain will seize this extra capacity avidly, and fill it with new data. The erased cells will more than recover. Even unlearning, the hardest feat of all, will become possible.

Unlearning and relearning are important these days. Increasingly, we move to new jobs and new partners; 'lifetime education' is widely advocated; several languages are now important. Yet we only have one small brain. How valuable to erase sizeable chunks of information, and fill the empty cells with new data! Our early formal education, for example, now irrelevant and largely overlaid with newer understanding, must still be in there somewhere, if only we could get it out.

So DREADCO is developing mid-life brain erasure. It could become as common as cosmetic surgery. Daedalus's volunteers will discover the most fruitful regions for forgetting, and the areas of skin that access them, by botulinum treatment. Such major innovations as the euro require huge acts of forgetting. New computer techniques are famously the province of the young, who do not have to unlearn the old stuff. Some businesses are so new that experience is a positive disadvantage. But now even the oldsters, with a lifetime's experience packed into their brains, could benefit. The selective amnesia of the botulinum treatment would enable them to learn new facts and skills. The dire verdict on so many politicians, "Where there's death there's hope", might not be so final.

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these proteins are not the same as those ubiquitinated proteins that actually regulate endocytosis.) Mammalian cells probably use ubiquitination, too³. Yet no obvious connections between ubiquitin and clathrin have been found, so it has been unclear how ubiquitinated membrane proteins are sorted into clathrin-coated pits.

This is one of the questions to which Polo *et al.*¹ provide a possible answer. But this is really an added extra — the main focus of their work was what determines how endocytosis-regulating proteins become labelled with just one rather than many ubiquitin molecules ('monoubiquitination' versus 'polyubiquitination'). This is a crucial distinction, because proteins that are tagged with longer ubiquitin chains (at least four ubiquitins) are destined for destruction: they are recognized by the proteasome, a large, barrel-shaped protein complex that destroys cytoplasmic proteins. Yet little is known about how this distinction is made. Polo *et al.* approached the problem by studying the mechanism by which proteins that regulate endocytosis, including eps15 and eps15R, are monoubiquitinated.

The authors started by mapping regions in eps15 and eps15R that are required for their monoubiquitination. They found that these regions overlap with a previously known sequence of amino acids called the ubiquitin-interacting motif (UIM)⁴. By mutating single amino acids within this motif, Polo *et al.* found that it is required both to allow these proteins to interact with ubiquitin, and for their monoubiquitination (although the motif is not itself ubiquitinated).

Ubiquitination is a complex process and usually requires three sequentially acting enzymes. The last enzyme in this series is a ubiquitin ligase, which transfers ubiquitin to the target protein. Polo *et al.* identified such an enzyme, Nedd4, that can add a single ubiquitin molecule to eps15. This enzyme has already been implicated in the ubiquitination of plasma-membrane proteins, including a sodium channel⁵, that are downregulated by endocytosis. But it seems that Nedd4, like its yeast relative Rsp5, might be involved in both monoubiquitination and polyubiquitination⁶. How does it 'decide' what to do? One possibility is that other proteins regulate Nedd4 and related ligases. Another possibility — one of two discussed by Polo *et al.*¹ — is that once a protein with a UIM is monoubiquitinated, the UIM binds to the ubiquitin group and prevents further modification. This mechanism may not apply to all monoubiquitinated proteins; they do not all have a UIM. Nevertheless, it is possible that a UIM on one protein could act in 'trans' by binding to the ubiquitin on another monoubiquitinated protein.

Interestingly, the eps15 protein can interact with adaptor proteins that are attached to clathrin-coated membrane pits. The fact

that it contains a UIM suggests that eps15 might also interact with other ubiquitinated plasma-membrane proteins, including receptors, that cannot themselves interact with clathrin, pulling those proteins into pits (Fig. 1). So eps15 might be one of the sought-after connections between ubiquitin molecules, used as endocytic signals on plasma-membrane proteins, and clathrin.

Eps15 and eps15R are not the only proteins involved in endocytosis — whether in internalization or in other steps — that contain a UIM. Two other examples are the epsin and Hrs proteins, which are also monoubiquitinated, as Polo *et al.*¹ show. Epsins interact directly with clathrin⁷ and are involved in internalization. Hrs is involved in recruiting clathrin to endosomes⁸, cellular compartments to which internalized material is targeted before moving further along the endocytic pathway. Epsins and Hrs share another characteristic: they both have domains that bind to specific lipids. Epsins have an 'ENTH' domain, which can bind to phosphatidylinositol-4,5-bisphosphate⁹, a lipid that can be generated at the plasma membrane. Hrs has a 'FYVE' domain that can bind to phosphatidylinositol-3-phosphate, which is generated on endosomes¹⁰. The use of many types of interaction — between different proteins, between proteins and lipids, and between proteins and ubiquitin — may be necessary to determine exactly where clathrin-coated vesicles form on cell membranes.

There is much still to be learned about monoubiquitination and UIMs. For example, these motifs might be involved in regulating the monoubiquitination of other proteins, such as cell-surface receptors. One can also speculate that monoubiquitination of a target UIM-containing protein leads that protein to release a ubiquitin-containing partner, freeing it to bind another protein. Monoubiquitination may also work like other protein modifications, such as phosphorylation, to induce a conformational change in the target protein, regulating its activity directly. And UIMs could allow the construction of larger protein networks, particularly as many proteins have more than one such motif. All of this remains to be seen: Polo *et al.*'s work¹ marks the beginning of an exciting quest.

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