SUMOylation. Alternatively, kainate could induce a specific signal-transduction pathway to trigger SUMOylation, as the involvement of PKC in kainate-induced KAR endocytosis might suggest[4]. Finally, the carboxy-terminal domain of GluR6 binds to scaffolding proteins such as Pick1 and syntenin. SUMOylation could interfere with these interactions, thus promoting KAR endocytosis by dislodging it from its anchors at the cell surface and/or enhancing its interaction with members of the endocytic pathway.

What about functional consequences? SUMOylation-mediated endocytosis of synaptic KARs is known to occur under physiological conditions, because the SUMO inhibitor SENP1 induces an increase in spontaneous miniature excitatory postsynaptic currents. So, could the SUMOylation of KARs be involved in synaptic plasticity? Alternatively, given that KARs are involved in neuronal death due to receptor overactivation (excitotoxicity)[3], Martin *et al.*[1] propose that SUMOylation-induced endocytosis could help protect neurons from excitotoxic stress.

The findings of Martin *et al.* add SUMOylation to the list of post-translational molecular mechanisms that regulate glutamate-receptor trafficking, such as phosphorylation and ubiquitination, and indicate its possible involvement in synaptic plasticity. The challenge is to sort out the interplay between these mechanisms, and to unravel the precise physiological context in which they control receptor numbers and function. ■

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ORGANIC CHEMISTRY

Molecular cross-talk

Alexander Greer

There is a long way to go before artificial enzymes can reproduce the functions of the real things. The advent of systems that generate and respond to signals may bring that ideal a step closer.

Molecules are often used as signals in biological systems, triggering reactions to various stimuli. Enzymes in plants, for example, liberate electronically excited oxygen — known as singlet oxygen — in response to stress, eliciting protective responses from other biomolecules[1,2]. Such chemical cross-talk has now been demonstrated in a synthetic system, as reported by Natarajan *et al.*[3] in the *Journal of the American Chemical Society*. They have designed an artificial enzyme that generates singlet oxygen and releases it into the surrounding solution. The oxygen then diffuses to another, remote artificial enzyme, where it is trapped and reacts with acceptor molecules.

Artificial enzymes have been around since the 1980s, when chemists discovered that the hydrophobic interior environment of enzymes could be mimicked by large 'host' molecules that encapsulate small 'guest' molecules[4]. But despite the great ingenuity applied to the design of the hosts, these systems were primitive compared with natural, highly evolved enzyme pockets. One big problem was devising recognition and capturing strategies for molecules of sufficient quality to accurately direct guests to the artificial-enzyme sites — such exquisite control is essential for reproducing the functions of natural enzymes. An understanding of molecular host–guest binding has slowly developed so that, for example, we now appreciate how non-covalent interactions can immobilize guests in a process known as constrictive binding[5]. It is also possible to tailor the size and shape of hosts, so that their geometry can direct chemical reactions to selected sites in a guest molecule[6,7].

Natarajan *et al.* have used such ideas in their study[3]. They trapped two different guest molecules into separate hosts, permanently isolating them from each other (Fig. 1, overleaf). The first guest was a photosensitizer — a compound that readily transfers light energy to other molecules, so promoting them into excited states. The second isolated guest was an alkene, which acts as an oxygen acceptor. The encapsulated photosensitizer absorbs light and — if the host is open to allow oxygen into its cavity — converts ground-state oxygen into singlet oxygen, which then escapes into the bulk solution. Some of the singlet oxygen reaches the separate alkene-containing hosts, where it reacts with the guest molecule. Because the alkene-containing hosts hold their guests in a particular orientation within the cavity, some parts of the alkene are more accessible to chemical attack than others. The singlet oxygen therefore predominantly attacks the alkene at the most accessible position, yielding mostly one product. In the absence of the host, the singlet oxygen attacks the alkene at several positions, so that a mixture of compounds forms, with no major product[8].

Despite the effectiveness of this reaction system, surprisingly little is known about the dynamics of the artificial enzymes. For example, how does the oxygen enter the cavities? The hosts are actually dimeric complexes, in which two bowl-shaped subunits are held together by weak intermolecular forces to form capsules[9]. The structural integrity of these capsules is therefore not fixed, because they are not rigidly bound together by covalent bonds. The authors suggest[3] that the alkene-containing host probably opens up to allow singlet oxygen in, rather than the oxygen somehow penetrating the walls of the closed capsule (which would be a much slower process than that observed).

Some details of the opening and closing process may be gleaned from previous studies on capsules in which the two halves are held together with covalent bonds[5]. These indicate that the gating mechanism is akin to the movement of French doors — where a couple of small flaps hinge apart to create an opening — rather than a more severe deformation that prises apart the entire host. This is reminiscent of gating in certain natural enzymes, such as HIV-1 protease, in which a flap over the active site can flip-flop for the exclusion or inclusion of guests[10,11]. Future work in this area would undoubtedly benefit from a computational analysis of how the structure swings open. An assessment of the attack trajectories of the singlet oxygen would also help in the design of other artificial enzymes that attempt to control the exact position of a reaction in a molecule[12].

Singlet oxygen is highly reactive, and is rapidly quenched in water to form stable, ground-state oxygen. To maximize the amount of singlet oxygen that reaches the target sites in Natarajan and colleagues' system[3], two approaches can be envisaged: the oxygen molecules could be stabilized in some way that enables them to diffuse a greater distance before being quenched, or protective channels could be provided between hosts to prevent quenching. But quenching reactions might actually be useful, as they can steer the attack of singlet oxygen onto substrates, so directing the orientation of chemical groups in the reaction product[13]; singlet oxygen might quench on one side of a molecule, but react chemically on the other. Incorporating such control

50 YEARS AGO

Two sharply divergent points of view are held with regard to children's films. The Soviet bloc and most of Europe believe that children at the cinema should be sheltered from the actualities of life. They should be provided with cartoon or puppet films which show them a fairy-tale world of fantasy or else with films with a direct moral purpose such as "stressing the value of human labour". On the other hand, the Americans, who do not make special children's films, believe that children are essentially little adults and are perfectly ready to take adult screen entertainment. Neither of these divergent points of view is accepted in Britain, where it is believed that, to get the greatest pleasure and profit in the cinema, children should see specially produced films within their understanding and experience, and these should be mainly realistic... Children are really interested only in children like themselves or in attractive animals; they have little interest in adults and few cowboys would be popular if deprived of their horses. However, very old people who are approaching their second childhood compel attention.

From *Nature* 18 May 1957.

100 YEARS AGO

The problem of establishing a connection between the mineral ingredients of the tea plant and the quality and strength of the tea is under investigation, with a prospect of obtaining definite results. From a study of the methods of preparing Oolong tea in Formosa, it is concluded that the quality and characteristics are due to an aroma produced by faint oxidation in drying and a slight scorching during roasting of the leaf, as well as to the mild decomposition caused by a fungus, and it is suggested that the fungus acting on the legumin in the leaf produces flavouring bodies similar to the action of moulds in cheese.

From *Nature* 16 May 1907.

50 & 100 YEARS AGO

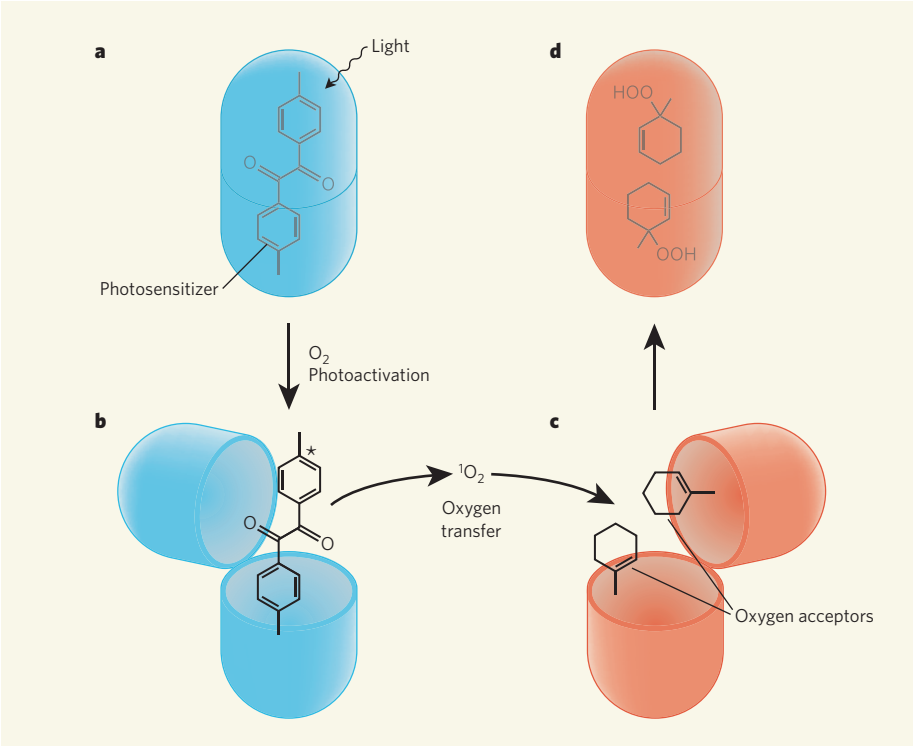

Figure 1 | Chemical correspondence. Natarajan *et al.*[3] have devised an artificial system that mimics chemical signalling between enzymes. **a**, A photosensitizer molecule is trapped in an artificial enzyme pocket and irradiated with light. **b**, The light energy promotes the photosensitizer into an excited electronic state (indicated by the asterisk), which in turn excites oxygen molecules if the enzyme pocket is open. **c**, The excited oxygen, $^1O_2$, diffuses through the surrounding solution until it reaches an open pocket of another enzyme that contains oxygen acceptor molecules. **d**, Because the acceptor molecules bind into the enzyme pocket in a particular orientation, the excited oxygen reacts only at the most accessible site of those molecules.

into enzyme-mimics that use singlet oxygen might help them target specific sites in their substrates.

Natarajan and colleagues' report[3] forms part of a growing body of work examining chemical cross-talk. Their study is carried out entirely in solution, but an interesting related area examines the transportation of molecules between solid materials, which may be more relevant to the mechanisms used by proteins for trapping molecules and responding to chemical signals. Singlet oxygen can diffuse in polymer films[14] or be taken up by acceptor molecules connected to solid supports (such as resins, or porous inorganic materials known as zeolites). Resin-to-resin reactions are quite useful because they can transfer a variety of chemical signals through solution[15], including inherently unstable molecules such as singlet oxygen and cyclobutadiene (a reactive hydrocarbon). This challenges the preconception that only stable molecules can act as chemical signals.

There is no denying that synthetic enzymes will require huge improvements if they are to compete with their biological equivalents. Problems still awaiting exploration include the incorporation of allosteric features — binding sites other than the main cavity — into artificial hosts, and the introduction of cooperative dialogue between hosts that might enhance chemical trapping, as occurs in nature. But as a first step in the advanced development of artificial enzymes, Natarajan and colleagues' work[3] on chemical signalling will certainly create a lot of cross-talk between chemists. ■

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