the distribution of impurities did not grow with time. Thus, the environment as controlled by the laser fields had a strong influence on the observed energy transport.

It is likely that in future uses of these techniques, quantum-simulation studies can be performed in open quantum systems with controlled energy hopping and decoherence rates. The ratio of these rates determines whether the energy transport occurs in the classical or quantum regimes. If the energy hopping rate exceeds the measurement-induced decoherence rate, then quantum coherent energy transport occurs. It may be possible to control and lower the decoherence rate to allow for studies of coherent excitonic behavior, which may bring insights to theories on energy transport in complex molecular systems such as light-emitting organic systems and photosynthetic proteins.

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Fosfomycin (see the figure, panel A) is a deceptively simple antibiotic that is clinically effective for the treatment of gastrointestinal and lower urinary tract infections (1). The biological target of this compound is the bacterial enzyme MurA, which plays a key role in bacterial cell wall biosynthesis. On page 991 of this issue, Wang et al. (2) report that a key step in the biosynthesis of fosfomycin requires hydrogen peroxide (H₂O₂) rather than molecular oxygen (O₂). This discovery clarifies how the strained epoxide ring of fosfomycin is synthesized by bacteria and enhances understanding of the catalytic repertoire of iron-activated enzymes.

MurA catalyzes the transfer of the enolpyruvyl group from PEP to UDP-N-acetylglucosamine in an essential step of bacterial cell wall biosynthesis. Fosfomycin functions as a structural mimic of PEP. The highly strained epoxide ring of the antibiotic is attacked by a cysteine residue in the MurA active site to generate a covalent enzyme-fosfomycin adduct that renders the enzyme inactive (see the figure, panel A) (3). The pharmacological function of fosfomycin is thus dictated by the structural similarity to PEP and the inherent chemical reactivity of the strained epoxide ring.

In fosfomycin-producing organisms, the antibiotic is constructed in a five-step biosynthetic pathway (4). The epoxide group is assembled in the last step of this pathway from S-HPP. During the conversion of S-HPP to fosfomycin, catalyzed by the enzyme HppE, two electrons and two hydrogen atoms must be removed from the substrate. O₂ was long thought to be the ultimate recipient of the two electrons (5), but the reduction of O₂ to two water molecules requires four electrons. Therefore, two additional electrons from nicotinamide or flavin coenzymes were thought to be required for the activation of O₂. Wang et al. now show that this view of the catalytic mechanism of epoxide formation by HppE is incorrect. The actual oxidant is H₂O₂, and HppE is thus a peroxidase rather than an oxidase.

The three-dimensional x-ray structure of HppE shows that the active site is composed of a non–heme iron center (6). When the substrate, HPP, binds to the enzyme, it is coordinated to the iron center by the hydroxyl group and one of the oxygens from the phosphonate moiety (6). Isotopic labeling studies have revealed that one of the hydrogen atoms from the methylene group (-CH₂-) of the substrate is ultimately found in solvent water and that the epoxide oxygen of fosfomycin derives from the hydroxyl group of the substrate (7, 8).

In the originally proposed reaction mechanism, the iron center of the enzyme-substrate complex bound O₂ (4). This binding event initiated the reduction of O₂ via transfer of electrons from the ferrous
This discovery led to the proposal that the added \( \text{S}_2\text{O}_7^{2-} \) was reducing \( \text{O}_2 \) to \( \text{H}_2\text{O}_2 \) and that \( \text{H}_2\text{O}_2 \) might be the physiological oxidant for epoxide formation by HppE. This hypothesis proved to be correct. The reduction of \( \text{H}_2\text{O}_2 \) to water requires only two electrons, matching the two-electron requirement for the overall conversion of \( \text{S}-\text{HPP} \) to fosfomycin. With \( \text{H}_2\text{O}_2 \) as the added oxidant, one equivalent of fosfomycin is formed for every \( \text{H}_2\text{O}_2 \) used in the enzyme-catalyzed reaction.

Wang et al. propose that the \( \text{H}_2\text{O}_2 \)-assisted transformation proceeds via a multistep mechanism that includes an \( \text{Fe}^{IV} \) species and a carbocation intermediate (see the figure, panel B). Experimental support for a carbocation intermediate comes from the observation that HppE catalyzes an unusual 1,2-phosphono migration when \( \text{R}-\text{HPP} \) is used as a substrate during the formation of 1-oxopropan-2-ylphosphonate (9).

Now that it is known that the true oxidant is \( \text{H}_2\text{O}_2 \), proper steady-state and rapid-kinetic studies can be conducted to provide data that will be critical for determination of the rate-limiting steps for this unusual chemical reaction. Thus far, there is no direct spectroscopic evidence for the formation of the ferryl \( [\text{Fe}^{IV}=\text{O}] \) intermediate, although recent computational studies are consistent with the formation of this intermediate (10).

It is also unclear how HppE selectively uses \( \text{H}_2\text{O}_2 \) rather than \( \text{O}_2 \). The enzyme most structurally similar to HppE is HEPD, which converts HEP and \( \text{O}_2 \) to formate and HMP (see the figure, panel C). The structure of the non–heme iron center and the substrate-bound complex in the active site of HEPD is essentially identical to that of HppE (11). Yet, HEPD does not use \( \text{H}_2\text{O}_2 \) as a cosubstrate, and HppE does not use \( \text{O}_2 \) as a substrate (5). Further experimental and computational probes are needed to fully understand the structural and dynamic differences between these two enzymes that dictate why one enzyme functions as a peroxidase, whereas the other is a dioxygenase.

References

10.1126/science.1247233

NEUROSCIENCE

Synapses, Language, and Being Human

Philip Lieberman

Humans’ ability to cope with the challenges they meet in life is transmitted almost exclusively through the medium of language. We have yet to fully map out the circuits of the human brain, the genes acting on them, and the processes they control that yield this distinct human quality. However, the findings of Sia et al. (1), on page 987 of this issue, bring us a step closer. The authors have determined that a secreted protein called sushi repeat–containing protein X–linked 2 (SRPX2) promotes mammalian vocalization by controlling the formation of synapses in the mouse cerebral cortex. Expression of this protein is known to be repressed by the transcription factor foxhead box protein P2 (FOXP2), which has been implicated in human language acquisition. A link between these two factors and synaptogenesis may have played a role in the evolution of the neural circuits associated with human language and cognition, as well as the pathogenesis of language disorders.

FOXP2 has become a “gene of interest” in the mystery that surrounds the evolution of the human brain. It first came to notice in a study of the behavioral deficits of the members of a large extended family who had only one copy of the gene. These individuals had profound difficulties in talking, comprehending, and forming sentences, and had depressed scores on intelligence tests (2). Anomalies in their basal ganglia, subcortical structures deep in the brain, were also noted (3). FOXP2 is one of the few human genes that differ from its chimpanzee version. A series of mutations in FOXP2 has occurred in the last 500,000 years; the most recent one took place about 200,000 years ago, when modern humans appeared in Africa (4). When a form of FOXP2 shared by humans, Neandertals, and Denisovans (another extinct hominin species) was introduced into mouse pups, synaptic plasticity

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Not an Oxidase, But a Peroxidase
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Science 342, 943 (2013);
DOI: 10.1126/science.1247233

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