

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.

## References

1. T. F. Gallagher, P. Pillet, *Adv. At. Mol. Opt. Phys.* **56**, 161 (2008).
2. G. Günter *et al.*, *Science* **342**, 954 (2013).
3. M. Müller, S. Diehl, G. Pupillo, P. Zoller, *Adv. At. Mol. Opt. Phys.* **61**, 1 (2012).
4. E. Collini, *Chem. Soc. Rev.* **42**, 4932 (2013).
5. D. Jaksch, J. I. Cirac, P. Zoller, R. Côté, M. D. Lukin, *Phys. Rev. Lett.* **85**, 2208 (2000).
6. M. Fleischhauer, A. Imamoglu, J. P. Marangos, *Rev. Mod. Phys.* **77**, 633 (2005).

10.1126/science.1247392

## BIOCHEMISTRY

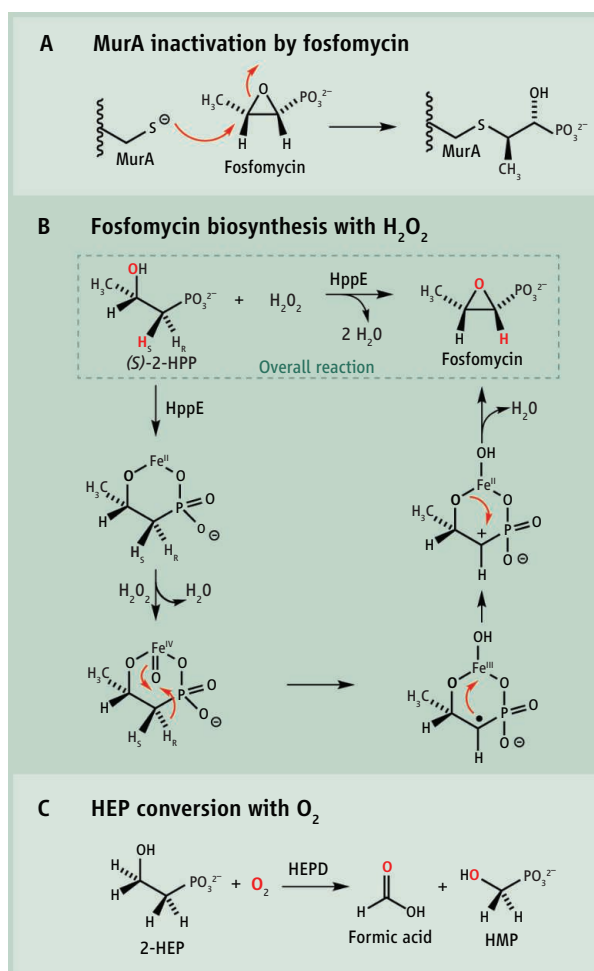
# Not an Oxidase, But a Peroxidase

Frank M. Raushel

**F**osfomycin (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 ( $H_2O_2$ ) rather than molecular oxygen ( $O_2$ ). 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.  $O_2$  was long thought to be the



A key step in the biosynthesis of the antibiotic fosfomycin requires hydrogen peroxide, rather than molecular oxygen as previously assumed.

**Oxidant action.** (A) The antibiotic fosfomycin acts by inactivating the enzyme MurA, which plays a key role in bacterial cell wall biosynthesis. (B) It was long thought that fosfomycin biosynthesis, which is catalyzed by the HppE enzyme, requires molecular oxygen ( $O_2$ ). Wang *et al.* propose an alternative mechanism in which  $H_2O_2$  serves as the oxidant. (C) The HEPD enzyme is structurally similar to HppE yet requires  $O_2$  as the oxidant.

is incorrect. The actual oxidant is  $H_2O_2$ , 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 ( $-CH_2-$ ) of the substrate is ultimately

ultimate recipient of the two electrons (5), but the reduction of  $O_2$  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  $O_2$ . Wang *et al.* now show that this view of the catalytic mechanism of epoxide formation by HppE

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  $O_2$  (4). This binding event initiated the reduction of  $O_2$  via transfer of electrons from the ferrous

Department of Chemistry, Texas A&M University, College Station, TX 77843, USA. E-mail: raushel@chem.tamu.edu

## Glossary

HEP, 2-hydroxyethyl-1-phosphonate

HEPD, HEP dioxygenase

HMP, hydroxymethyl phosphonate

HppE, S-HPP epoxidase

MurA, uridine diphosphate (UDP)-*N*-acetylglucosamine enolpyruvyl transferase

NADH, nicotinamide adenine dinucleotide, H

PEP, phospho(enol)pyruvate

S-HPP, (S)-2-hydroxypropyl-1-phosphonate

UDP, uridine diphosphate

[Fe(II)] iron and externally added NADH to ultimately form the ferryl [Fe(IV)=O] oxidation state (4). However, there are problems with this mechanism. The crystal structure of HppE provided no support for the binding of a companion reductase protein for the transfer of external electrons from either nicotinamide or reduced flavin cofactors (6). Furthermore, the steady-state rate of product formation catalyzed by HppE with O<sub>2</sub> and external reductants is extremely slow (~0.01 s<sup>-1</sup>). The very slow rate of epoxide formation prompted Wang *et al.* to search for alternative reductants to NADH. They subsequently found that addition of dithionite (S<sub>2</sub>O<sub>4</sub><sup>2-</sup>) increased the rate of fosfomycin formation up to 1000 times.

This discovery led to the proposal that the added S<sub>2</sub>O<sub>4</sub><sup>2-</sup> was reducing O<sub>2</sub> to H<sub>2</sub>O<sub>2</sub> and that H<sub>2</sub>O<sub>2</sub> might be the physiological oxidant for epoxide formation by HppE. This hypothesis proved to be correct. The reduction of H<sub>2</sub>O<sub>2</sub> to water requires only two electrons, matching the two-electron requirement for the overall conversion of S-HPP to fosfomycin. With H<sub>2</sub>O<sub>2</sub> as the added oxidant, one equivalent of fosfomycin is formed for every H<sub>2</sub>O<sub>2</sub> used in the enzyme-catalyzed reaction.

Wang *et al.* propose that the H<sub>2</sub>O<sub>2</sub>-assisted transformation proceeds via a multistep mechanism that includes an 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 R-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 H<sub>2</sub>O<sub>2</sub>, 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 [Fe(IV)=O] intermediate, although recent computational studies are consistent with the formation of this intermediate (10).

It is also unclear how HppE selectively uses H<sub>2</sub>O<sub>2</sub> rather than O<sub>2</sub>. The enzyme most structurally similar to HppE is HEPD, which converts HEP and O<sub>2</sub> 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 H<sub>2</sub>O<sub>2</sub> as a cosubstrate, and HppE does not use O<sub>2</sub> 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

1. M. E. Falagas, A. C. Kastoris, D. E. Karageorgopoulos, P. I. Rafailidis, *Int. J. Antimicrob. Agents* **34**, 111 (2009).
2. C. Wang *et al.*, *Science* **342**, 991 (2013); 10.1126/science.1240373.
3. J. L. Marquardt *et al.*, *Biochemistry* **33**, 10646 (1994).
4. T. Hidaka *et al.*, *Mol. Gen. Genet.* **249**, 274 (1995).
5. P. Liu *et al.*, *J. Am. Chem. Soc.* **123**, 4619 (2001).
6. L. J. Higgins, F. Yan, P. Liu, H. W. Liu, C. L. Drennan, *Nature* **437**, 838 (2005).
7. F. Hammerschmidt, H. Kählig, *J. Org. Chem.* **56**, 2364 (1991).
8. F. Hammerschmidt, *J. Chem. Soc. Perkin Trans.* **18**, 1993 (1991).
9. W. C. Chang *et al.*, *Nature* **496**, 114 (2013).
10. A. Milaczewska, E. Broclawik, T. Borowski, *Chemistry* **19**, 771 (2013).
11. R. M. Cicchillo *et al.*, *Nature* **459**, 871 (2009).

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 mamma-

lian 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

Two factors that controls synapse formation in mammalian brain are associated with human language acquisition.

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

Cognitive and Linguistic Sciences, Brown University, 190 Thayer Street, Providence, RI 02912, USA. E-mail: phil-ip\_lieberman@brown.edu



## Not an Oxidase, But a Peroxidase

Frank M. Raushel  
*Science* **342**, 943 (2013);  
DOI: 10.1126/science.1247233

*This copy is for your personal, non-commercial use only.*

If you wish to distribute this article to others, you can order high-quality copies for your colleagues, clients, or customers by [clicking here](#).

Permission to republish or repurpose articles or portions of articles can be obtained by following the guidelines [here](#).

**The following resources related to this article are available online at [www.sciencemag.org](http://www.sciencemag.org) (this information is current as of April 23, 2015):**

**Updated information and services**, including high-resolution figures, can be found in the online version of this article at:

<http://www.sciencemag.org/content/342/6161/943.full.html>

A list of selected additional articles on the Science Web sites **related to this article** can be found at:

<http://www.sciencemag.org/content/342/6161/943.full.html#related>

This article **cites 11 articles**, 1 of which can be accessed free:

<http://www.sciencemag.org/content/342/6161/943.full.html#ref-list-1>

This article appears in the following **subject collections**:

Biochemistry

<http://www.sciencemag.org/cgi/collection/biochem>