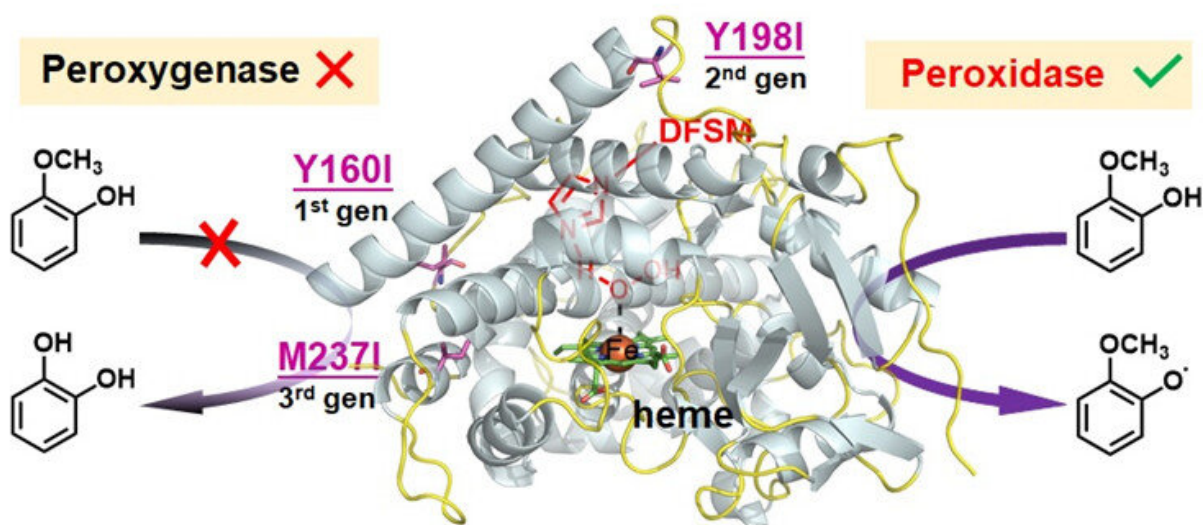


Converting P450 peroxygenase into peroxidase via mechanism-guided protein engineering

July 13 2021, by Li Yuan



Functional conversion of peroxygenase to peroxidase in DFSM-facilitated P450BM3- H₂O₂ system. Credit: Ma Nana

Enzyme catalysis is a promising green solution for producing pharmaceuticals, fine chemicals, and biofuels. However, exploring their catalytic promiscuity to expand and enhance the capabilities of enzymes remains challenging.

A research team led by Dr. Cong Zhiqi from the Qingdao Institute of

Bioenergy and Bioprocess Technology (QIBEBT) of the Chinese Academy of Sciences (CAS) applied a protein engineering strategy of mutating redox-sensitive residues that enables the peroxygenase system to achieve efficient peroxidase activity.

The study was published in *ACS Catalysis* on June 28.

In their previous study, the researchers reported a unique H₂O₂-dependent cytochrome P450 system driven by a dual-functional small molecule (DFSM), which exhibited highly efficient peroxygenase function rather than peroxidase activity. "However, the catalytic peroxidase functionality of P450s has not yet been fully explored," said Dr. Cong.

To expand the catalytic promiscuity of the DFSM-facilitated P450-H₂O₂ system, the researchers analysed three possible catalytic pathways in the system, and inferred that the intrinsic competitive oxidation of redox-sensitive residues may be the main reason to prevent its peroxidase function.

They identified hotspots of redox-sensitive residues, and then used a small number of logically chosen amino acids to exchange the residues at the hotspots.

After combining several-round iterative mutations of redox-sensitive residues at different sites, the researchers realized peroxidase function of the DFSM-facilitated P450-H₂O₂ system with efficient one-electron oxidation activity toward various substrates. This system attained the best peroxidase activity of any P450 reported to date, and rivaled most natural peroxidases.

The collaborative simulation study with Dr. WANG Binju of Xiamen University showed the possibility for the origin of [peroxidase](#) activity in

the DFSM-facilitated P450BM3-H₂O₂ system from either the removal of the redox-sensitive residues to eliminate their competitive oxidations or the alteration of substrate orientation after protein engineering.

"The study provides new insights and strategies relevant for expanding the catalytic promiscuity of P450s through combining the effects of protein engineering and exogenous molecules," said Dr. Cong.

More information: Nana Ma et al, Switching an Artificial P450 Peroxygenase into Peroxidase via Mechanism-Guided Protein Engineering, *ACS Catalysis* (2021). [DOI: 10.1021/acscatal.1c02698](https://doi.org/10.1021/acscatal.1c02698)

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