Do Tyr/Trp redox pathways protect O_2-reducing C. Coelicolor laccase from oxidative damage?

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O2 reduction is one of the most important life-sustaining reactions in the biocatalysis field. The kinetically challenging task of reducing O2 to H2O requires the delivery of four electrons and four protons in a well-coordinated manner. The lack of electrons in the instance of 'catalytic action' might lead to the formation of highly reactive oxygen species (ROS), which at elevated levels are toxic to any biological environment. Although there has been substantial focus on the molecular mechanism of O2 reactions at the enzymatic active site, it is necessary to expand the viewpoint to the redox role of the entire protein matrix in the context of protection against oxidative damage. In this respect, Gray and Winkler recently demonstrated the presence of redox-active Tyr and Trp chains in O2- utilizing metalloenzymes, potentially providing conduits for transferring highly oxidizing holes away from protein active sites.[1] In the presented work, the hypothesis of the protective role of Tyr/Trp chains is explored in the example of *S. Coelicolor* laccase, in which the trinuclear center-proximal Tyr108 was shown to be involved in O2 reduction by donating an electron during catalytic turnover.[2] Accordingly, the Tyr/Trp redox pathways are identified, and their role in oxygen conversion is studied by means of site-directed mutagenesis, a UV-Vis, and EPR spectroscopy.[3] Involvement of Tyr/Trp chains in SLAC's catalysis may indicate a regulatory mechanism of the protein.

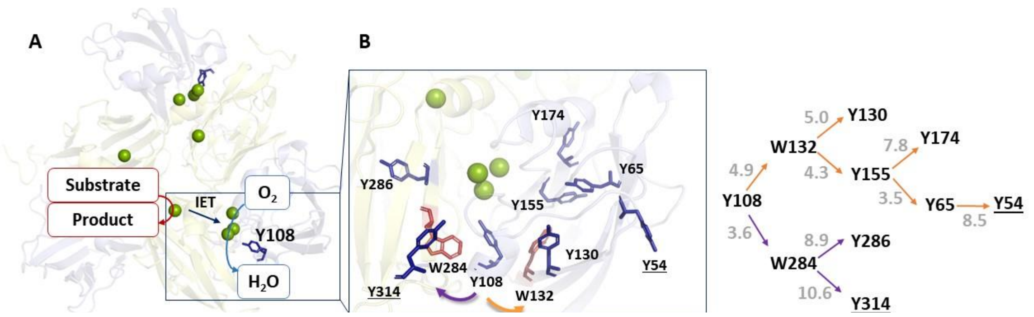

Figure 1. (A) Structure of small laccase (SLAC) PDB ID 3CG8 with copper ions and Tyr108 marked in green and blue, respectively. Substrate oxidation coupled to oxygen reduction is shown schematically. (B) Possible redox Tyr/Trp pathways: (I) Y108 → W284 …, (II) Y108 → W132 …, indicated by the purple and orange arrows, respectively. Numbers refer to the shortest atom-atom distances in Å.

[1]Gray, HB., Winkler, JR. *PNAS*, 112, 35, 10920, 2015.
[2]Gupta, A., Nederlof, I., Sottini, S., Tepper, Groenen, E., Thomassen, E. Canters, G. *JACS*, 134, 18213-16, 2012
[3] Kielb, P., Gray, HB, Winkler, JR, 2020 ChemRxiv preprint