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CueO: a multicopper oxidase involved in bacterial copper homeostasis.

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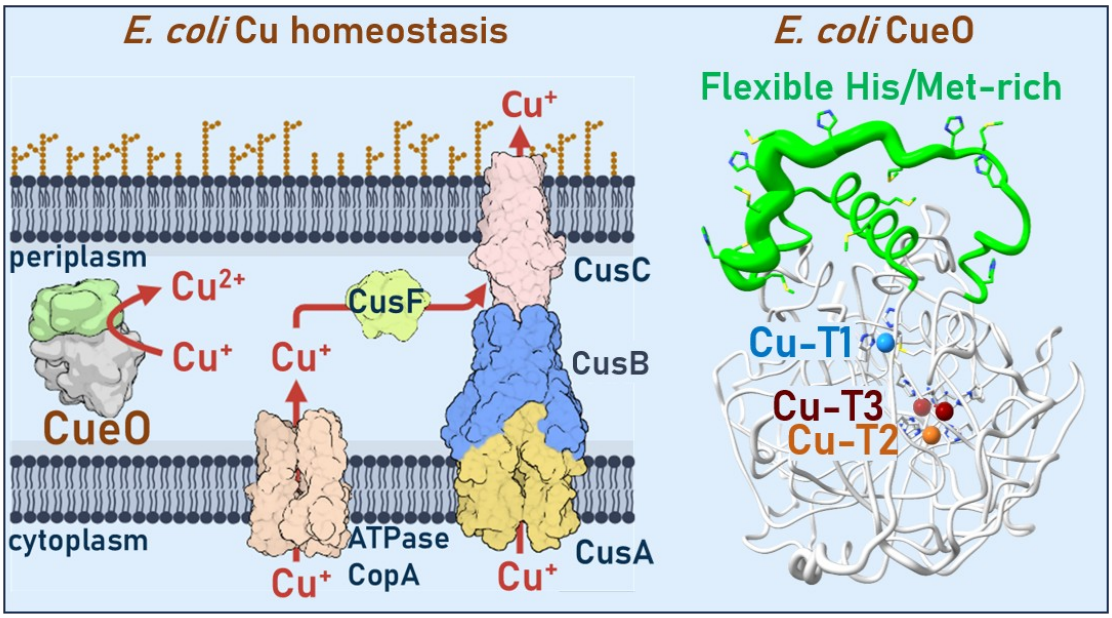
Bacterial copper homeostasis relies on multicopper oxidases such as CueO, which catalyze the oxidation of toxic cuprous ions (Cu^{+}) into the less reactive cupric form (Cu^{2+}).[1] A defining feature of many CueO enzymes is the presence of a flexible histidine/methionine-rich (His/Met-rich) insertion, whose functional role has remained debated. Recently, we have demonstrated that this domain is not essential for cuprous oxidation under conditions of high copper availability but instead facilitates copper acquisition when Cu^{+} is strongly chelated, acting as a transient copper-binding platform.[2]

Comparative structural and functional analyses of CueO homologs revealed that variations in the size and composition of the His/Met-rich insertion modulate catalytic efficiency, with larger domains enhancing activity under copper-limiting conditions.[3] These findings established the His/Met-rich insertion as an adaptive element tuning enzyme performance to environmental copper availability. Subsequent electrochemical and biochemical investigations further quantified the interplay between copper chelation strength, substrate accessibility, and catalytic turnover, confirming that the contribution of the flexible domain becomes critical when bioavailable copper is limited.[4]

More recent we identified an additional transient copper-binding site involved in enzyme metalation, providing new insight into the maturation process of multicopper oxidases.[5] Together, these results define a coherent structure-function framework in which auxiliary copper-binding regions dynamically regulate copper acquisition and detoxification in bacteria.



References
(1) Mazurenko, I., Adachi, T., Ezraty, B., Ilbert, M., Sowa, K., & Lojou, E. (2022). *Current Opinion in Electrochemistry*
(2) Contaldo, U., Savant-Aira, D., Vergnes, A., Becam, J., Biaso, F., Ilbert, M., Aussel, L., Ezraty, B., Lojou, E., Mazurenko, I. (2024). *Proceedings of the National Academy of Sciences,* 121(42), e2402862121.
(3) Contaldo, U., Santucci, P., Vergnes, A., Leone, P., Becam, J., Biaso, F., Ilbert, M., Ezraty, B., Lojou, E., Mazurenko, I. (2025). *JACS Au,* 5(4), 1833–1844.
(4) Saska, V., Santucci, P., de Poulpiquet, A., Gasparutto, D., Contaldo, U., Mazurenko, I., & Lojou, E. (2025). *Bioelectrochemistry*, 166, 109051.
(5) Santucci, P., Biaso, F., Becam, J., Dubard, L., Ilbert, M., Ezraty, B., Mazurenko, I., Lojou, E., Contaldo, U. (2026). *Journal of Inorganic Biochemistry*, 278