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# Cytochrome *bd* Oxidase and Hydrogen Peroxide Resistance in *Mycobacterium tuberculosis*

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Cytochrome *bd* oxidase is a prokaryotic respiratory oxidase, phylogenetically unrelated to the well-known heme-copper oxidases, which catalyzes the reduction of O<sub>2</sub> to 2H<sub>2</sub>O. Apart from having a role in energy metabolism, this enzyme plays other key functions relevant to physiology and, particularly, to adaptation to stress conditions (reference 1 and references therein). The enzyme is encoded in several pathogens, and its expression was found to correlate positively with virulence in some bacteria. In *Mycobacterium tuberculosis*, a transient upregulation of cytochrome *bd* was observed *in vivo* during the transition from acute to chronic infection of mouse lungs, as was reduced virulence of a mutant strain defective in the cytochrome *bd*-associated transporter *CydC* (2). Stimulation of *M. tuberculosis* cytochrome *bd* expression was also observed in response to hypoxia and upon exposure to nitric oxide (NO) (2), a cytotoxic molecule produced by the immune system in response to microbial infection. All together, these data enforce the growing evidence that cytochrome *bd* plays an important role in counteracting the hostile conditions created by the immune system to fight microbial pathogens, although the molecular mechanisms through which the enzyme enhances bacterial resistance have been only partially clarified.

Based on mutagenesis experiments, Small and coworkers recently reported in *mBio* (3) that disruption of cytochrome *c* maturation (CCM) in *M. tuberculosis* results in both overexpression of cytochrome *bd* oxidase (with no effects on bacterial persistence during chronic mouse infection) and, intriguingly, hyper-resistance to H<sub>2</sub>O<sub>2</sub>. The higher resistance to H<sub>2</sub>O<sub>2</sub> was shown to be catalase independent, suggesting a different route for H<sub>2</sub>O<sub>2</sub> degradation/detoxification. Also based on the original observation that *Escherichia coli* cytochrome *bd*-deficient mutants are hypersusceptible to H<sub>2</sub>O<sub>2</sub> (4, 5), Small et al. proposed a protective function against H<sub>2</sub>O<sub>2</sub> for *M. tuberculosis* cytochrome *bd*.

We wish to highlight that this conclusion was recently reached for cytochrome *bd*-I from *E. coli* by Borisov et al. (6), based, this time, on the direct experimental demonstration that, over and above its O<sub>2</sub>-consuming activity, the enzyme, either purified or overexpressed in a catalase-deficient *E. coli* strain, displays a remarkable catalase activity that is insensitive to NO. Even if at present the molecular mechanism underlying this activity of *E. coli* cytochrome *bd*-I is not known with certainty, the ability of the

enzyme to promptly degrade H<sub>2</sub>O<sub>2</sub> was found to be sensitive to cyanide, as well as to the redox state of the enzyme, pointing to heme *b*<sub>595</sub> as the site where H<sub>2</sub>O<sub>2</sub> catalysis takes place. These recent observations are fully consistent with the hypothesis that cytochrome *bd* oxidases play a role in bacterial physiology, conferring resistance to oxidative- and nitrosative-stress conditions (1).

Based on the recent work by Borisov et al. on *E. coli* cytochrome *bd*-I (6), we think that it is important to test whether cytochrome *bd* from *M. tuberculosis* is also endowed with a high catalase activity, thereby explaining the hyper-resistance to H<sub>2</sub>O<sub>2</sub> observed by Small et al. (3) upon cytochrome *bd* overexpression.

## REFERENCES

1. Giuffrè A, Borisov VB, Mastronicola D, Sarti P, Forte E. 2012. Cytochrome *bd* oxidase and nitric oxide: from reaction mechanisms to bacterial physiology. *FEBS Lett.* 586:622–629.
2. Shi L, Sohaskey CD, Kana BD, Dawes S, North RJ, Mizrahi V, Gennaro ML. 2005. Changes in energy metabolism of *Mycobacterium tuberculosis* in mouse lung and under *in vitro* conditions affecting aerobic respiration. *Proc. Natl. Acad. Sci. U. S. A.* 102:15629–15634.
3. Small JL, Park SW, Kana BD, Ioerger TR, Sacchettini JC, Ehrst S. 2013. Perturbation of cytochrome *c* maturation reveals adaptability of the respiratory chain in *Mycobacterium tuberculosis*. *mBio* 4(5):e00475-13. doi: 10.1128/mBio.00475-13.
4. Wall D, Delaney JM, Fayet O, Lipinska B, Yamamoto T, Georgopoulos C. 1992. *arc*-dependent thermal regulation and extragenic suppression of the *Escherichia coli* cytochrome *d* operon. *J. Bacteriol.* 174:6554–6562.
5. Lindqvist A, Membrillo-Hernandez J, Poole RK, Cook GM. 2000. Roles of respiratory oxidases in protecting *Escherichia coli* K12 from oxidative stress. *Antonie Van Leeuwenhoek* 78:23–31.
6. Borisov VB, Forte E, Davletshin A, Mastronicola D, Sarti P, Giuffrè A. 2013. Cytochrome *bd* oxidase from *Escherichia coli* displays high catalase activity: an additional defense against oxidative stress. *FEBS Lett.* 587: 2214–2218.

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