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Vitamin C and *Mycobacterium tuberculosis* Persisters

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We read with great interest the article by Vilchèze and coworkers regarding vitamin C-mediated enhancement of killing of *Mycobacterium tuberculosis* by first-line antituberculosis drugs in the murine model (1). In this elegant experiment, vitamin C alone was not found to have any antituberculosis activity. However, using high-dose vitamin C, potentiation of bactericidal activity of isoniazid and rifampin in combination was observed.

Earlier on, Vilchèze and coworkers suggested the induction of the Fenton reaction as an explanation for the beneficial adjunctive activity of vitamin C against *M. tuberculosis* (2). Indeed, such prooxidant activity has been shown in mycobacteria under different study conditions (3, 4). Oxidative stress intuitively may induce the formation of dormant mycobacterial persisters. On the other side of the coin, there have also been recent reports reiterating the antioxidative property of vitamin C, counteracting the development of dormancy in mycobacterial species. In an experiment that used *Mycobacterium smegmatis*, the nonpathogenic surrogate of *M. tuberculosis*, it has been shown that vitamin C at a high concentration could inhibit the synthesis of guanosine pentaphosphate [(p)ppGpp], a pivotal regulator in the dormancy response of mycobacteria to stress, resulting in compromised long-term survival and biofilm formation in the bacilli (5). By using a network-based approach for analysis of gene expression, vitamin C was shown to trigger multifaceted and robust adaptation responses in *Mycobacterium tuberculosis*, embracing both oxidative and antioxidative activities, and, thus, possibly a bidirectional propensity for the formation of mycobacterial persisters (4). In this same study, vitamin C was found to exhibit synergism with pyrazinamide against *M. tuberculosis* through tackling the dormant organisms and inhibiting the development of rifampin-tolerant and isoniazid-tolerant persisters in intracellular infection models. These findings, apparently more in keeping with the antioxidative activity of vitamin C, corroborate those of Vilchèze and coworkers regarding the use of cysteine or other small thiols with isoniazid or rifampin in preventing the development of drug-tolerant or drug-resistant bacilli in *M. tuberculosis* cultures in the presence of oxidative stress (6).

We have recently hypothesized the contributory role of oxidative stress, or, more broadly, disturbance of redox homeostasis, regarding the adverse outcomes of tuberculosis associated with diabetes mellitus or HIV infection, especially the risks of reactivated tuberculosis after treatment. In these two diseases comorbid to tuberculosis, with oxidative stress inherent to their pathogenesis, it appears that a biologically plausible mechanism central to the hypothesis is the redox stress-associated propensity for the development of dormant *M. tuberculosis* persisters with tolerance to antituberculosis drugs, leading to difficulty in mycobacterial eradication (7, 8). Thus, our hypoth-

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esis is quite in line with the findings of the above-mentioned studies. Interestingly, in a recent study involving the treatment of *M. tuberculosis* clinical cultures with hydrogen peroxide, bacilli with reduced cell envelope thickness and accumulation of intracytoplasmic lipid inclusions were observed with a higher frequency, apparently supporting the induction of mycobacterial persisters with oxidative stress (9). Clearly, more research is required to delineate the role of vitamin C in the clinical management of tuberculosis, especially pertaining to the optimal dosage to achieve therapeutic effects without toxicity.

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