Phagocytic cells possess a complex and unique system for the generation of superoxide anion (O_2^-). However, due to the acidic nature of the phagosomal vacuole, O_2^- is rapidly converted to hydrogen peroxide (H_2O_2) by spontaneous dismutation. These reactive oxygen reduction species are of well documented importance in the microbicidal and inflammatory response (1). H_2O_2 is believed to be particularly important because (*a*) it can traverse bacterial membranes to gain access to an intracellular milieu where it can cause DNA damage and oxidation of respiratory chain components and (*b*) H_2O_2 can lead to formation of more reactive "down-stream" oxidative species: H_2O_2 can react with Fe^{2+} or other reduced transition metals (e.g., Cu^+) in a Fenton reaction to form the hydroxyl radical ($HO^\bullet$); H_2O_2 can react with myeloperoxidase (or other peroxidases) in the presence of a halide such as chloride to form OCl^-; OCl^- derived from H_2O_2 can react with O_2^- to form $HO^\bullet$ (2). Last, H_2O_2 can react with HOCl to form the highly reactive singlet oxygen ($^1O_2$). Therefore, H_2O_2 is likely a critical threat to microbial survival.

How do microbes (and by extrapolation humans) reduce the stress imposed by exposure to H_2O_2? Two fundamental mechanisms have been extensively studied. First, the heme enzyme catalase catabolizes H_2O_2 to oxygen and water. Some (but not all) microbes have both cytoplasmic and periplasmic catalase isoenzymes encoded by separate genes and regulated by positive regulatory loci such as *oxyR*. Second, microbes are able to utilize several DNA repair systems in response to H_2O_2-mediated DNA damage. While many DNA repair systems have been described, only a few have been closely linked to oxidative stress. These include (but are not limited to) those involved in recombination repair (*recA*, *-BC*, *recF*, *recN*), excision repair (*xth*, exonuclease III), and DNA polymerization/3′→5′ exonuclease (*polA1*) (3, 4).

How can we compare the relative importance of catalase and DNA repair systems during exposure to H_2O_2? First, investigators have looked at the effects of exogenous H_2O_2 in studies conducted in vitro. In seminal work by Imlay and Linn (3, 4), *E. coli* demonstrated a bimodal sensitivity to H_2O_2 such that exaggerated microbial killing was observed at very low (1–3 mM, mode I) or very high (> 30 mM, mode II) H_2O_2 concentrations. Mutations in DNA repair genes enhanced mode I killing of *E. coli* by 2–4 logs and mode II killing by 1–3 logs. Catalase deficiency increased mode I killing by ~ 1.5 logs and mode II killing by 1 log (4). These latter observations must be further interpreted in light of the more recent work of Ma and Eaton (5) who have noted the greatest protection of catalase at higher bacterial density. These investigators concluded that at increased cellular density, H_2O_2 has poor access to individual cells. However, during bacterial growth as colonies on nutrient agar, the edge of each colony is actively growing while those on the interior are in stationary or death phase. Most bacteria in late log or stationary phase express their highest catalase activity and therefore demonstrate greatest resistance to H_2O_2.

Provocative observations with bacteria grown in vitro in the form of colonies often receive further consideration in more physiological models using mammalian cells or whole animals. In this issue of *The Journal*, Buchmeier et al., (6) used mutants of *S. typhimurium* to examine the contributions of *recA* and catalase to virulence. The results seem to demonstrate greater importance for *recA* than catalase during macrophage phagocytosis and growth of *S. typhimurium* in vivo. Indeed, because a *recA* mutant (6, 7) (but not a catalase-deficient mutant) demonstrated reduced survival in BALB/c mice, the authors concluded that *S. typhimurium* was likely exposed to low concentrations of H_2O_2 in vivo and grew at low cell density. Otherwise, it might be assumed, catalase deficiency would have proven of greater importance.

While provocative, these ideas deserve further scrutiny. First, microbial catalase is not necessarily unimportant during phagocytosis or growth in vivo. Many catalase deficient microbes (e.g., *S. aureus*, *E. coli*, *N. gonorrhoeae*) demonstrate increased susceptibility to neutrophil attack. Indeed, during phagocytosis of catalase-deficient *E. coli*, a greater production of the highly destructive $HO^\bullet$ can be demonstrated (8). Catalase deficiency may also lead to reduced virulence in some animal or tissue culture models (9). Second, *recA* (and other virulence genes studied) often serve functions beyond DNA repair evoked by oxidative stresses such as H_2O_2. Depending on the bacterial species, *recA* has been involved in competence for transformation, pilin antigenic variation, expression of bacterial chemoattractant formyl-methionyl-leucylphenylalanine, and other functions. Therefore, the assumption that *recA* sensitivity to H_2O_2 actually defined the degree of oxidative stress experienced by *S. typhimurium* in vivo may not ultimately prove correct. In addition, a *recA* mutation does not necessarily assure reduced bacterial virulence. For example, *recA* mutants of *Brucella abortis* (a well studied intracellular pathogen) demonstrated persistent infection in BALB/c mice (10).

Given these caveats, we believe observations about oxidative stress and bacterial virulence are important. First, they help us to better understand the pathogenesis of infectious diseases, and their prevention and treatment. Second, studies of bacterial DNA protection/repair systems can be expected to lend themselves to the understanding of human disease in important (and perhaps unpredictable) ways. For example, a defect in a human mismatch repair (analogous to *mutL* in bacteria and fungi) has been linked to hereditary colon cancer (11). Reactive oxygen species have already been shown to play a role in several human disease states including inflammation, heart disease, rheumatoid arthritis, ALS (Lou Gehrig's disease), ischemia reperfusion injury, Bloom's and Purtcher's syndromes, adult respiratory distress syndrome, mutations, cancer, and aging (12). It seems likely to us that the balance between DNA repairs systems such as *recA* and antioxidant enzymes such as catalase, so extensively studied in bacterial systems, will ultimately prove relevant in human disease as well.

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