**Iron-sulfur Clusters Confer Vulnerability to Oxidative Stress.**

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Iron-sulfur clusters are versatile catalysts because iron and sulfur easily tolerate changes in redox state and coordination geometry. However, these same properties make them vulnerable to adventitious oxidants. A subclass of dehydratases employs solvent-exposed [4Fe-4S] clusters that can be inactivated in vitro by a variety of univalent biological oxidants, including superoxide, peroxynitrite, and hydrogen peroxide. The oxidized clusters are unstable, undergoing rearrangements that release the substrate-coordinating iron atom; enzyme activity is thereby lost. Previous studies showed that damage to these dehydratases creates the primary metabolic defects of superoxide-stressed cells. We are currently investigating the phenotypes of *E. coli* mutants that cannot scavenge $H_2O_2$. Because $H_2O_2$ is an inadvertent by-product of aerobic metabolism, micromolar levels accumulate in the medium of these mutants. These strains do not catabolize TCA-cycle intermediates well, which suggested that the $H_2O_2$ might inactivate [4Fe-4S] dehydratases. We have confirmed that very low concentrations of $H_2O_2$ oxidize the cluster of isopropylmalate isomerase, another dehydratase. Because iron atoms spill from these damaged clusters, the amount of intracellular free iron increases. This effect is important, because the freed iron reacts with $H_2O_2$ to generate hydroxyl radicals, which damage DNA. The cell addresses these problems in several ways. Damaged clusters are repaired by a still-undefined mechanism that is independent of the de novo cluster synthetic process. At the same time, Dps protein sequesters free iron and thereby minimizes DNA damage; in the absence of Dps, submicromolar levels of $H_2O_2$ are quickly lethal. These results reinforce the notion that while iron-sulfur clusters streamline metabolism, they also create a vulnerability to oxidants that must be addressed by the expression of defensive enzymes.