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The ABC-type efflux pump MacAB protects Salmonella enterica serovar typhimurium from oxidative stress

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Abstract

Multidrug efflux pumps are integral membrane proteins known to actively excrete antibiotics. The macrolide-specific pump MacAB, the only ABC-type drug efflux pump in Salmonella, has previously been linked to virulence in mice. The molecular mechanism of this link between macAB and infection is unclear. We demonstrate that macAB plays a role in the detoxification of reactive oxygen species (ROS), compounds that salmonellae are exposed to at various stages of infection. macAB is induced upon exposure to H2O2 and is critical for survival of Salmonella enterica serovar Typhimurium in the presence of peroxide. Furthermore, we determined that macAB is required for intracellular replication inside J774.A1 murine macrophages but is not required for survival in ROS-deficient J774.D9 macrophages. macAB mutants also had reduced survival in the intestine in the mouse colitis model, a model characterized by a strong neutrophilic intestinal infiltrate where bacteria may experience the cytotoxic actions of ROS. Using an Amplex red-coupled assay, macAB mutants appear to be unable to induce protection against exogenous H2O2 in vitro, in contrast to the isogenic wild type. In mixed cultures, the presence of the wild-type organism, or media preconditioned by the growth of the wild-type organism, was sufficient to rescue the macAB mutant from peroxide-mediated killing. Our data indicate that the MacAB drug efflux pump has functions beyond resistance to antibiotics and plays a role in the protection of Salmonella against oxidative stress. Intriguingly, our data also suggest the presence of a soluble anti-H2O2 compound secreted by Salmonella cells through a MacAB-dependent mechanism. IMPORTANCE The ABC-type multidrug efflux pump MacAB is known to be required for Salmonella enterica serovar Typhimurium virulence after oral infection in mice, yet the function of this pump during infection is unknown. We show that this pump is necessary for colonization of niches in infected mice where salmonellae encounter oxidative stress during infection. MacAB is required for growth in cultured macrophages that produce reactive oxygen species (ROS) but is not needed in macrophages that do not generate ROS. In addition, we show that MacAB is required to resist peroxide-mediated killing in vitro and for the inactivation of peroxide in the media. Finally, wild-type organisms, or supernatant from wild-type organisms grown in the presence of peroxide, rescue the growth defect of macAB mutants in H2O2. MacAB appears to participate in the excretion of a compound that induces protection against ROS-mediated killing, revealing a new role for this multidrug efflux pump.

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