Department of Microbiology

MICROBIOLOGY FACULTY CANDIDATE

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Role of nickel and molecular hydrogen in campylobacters, and use of nickel chelation as antimicrobial therapy

ABSTRACT

Nickel (Ni) is an essential metal cofactor for at least ten different microbial enzymes, including nickel-iron [Ni-Fe] hydrogenases, which are enzymes that either oxidize or produce molecular hydrogen (H2). Several human pathogens, including campylobacters, are able to access the large amounts of H2 produced by colonic microbiota, to use it as an energy source for aerobic or anaerobic respiration. In Campylobacter concisus, a pathogen found throughout the entire oral-gastro-intestinal tract, H2 metabolism is particularly intriguing, as the gas is required for microaerobic growth, but not for anaerobic growth. Using a mutagenesis approach that had not been previously used in campylobacters, I was able to solve this apparent conundrum and determine the respective role of two different [Ni-Fe] hydrogenases in C. concisus. However, more work is needed to fully understand H2 metabolism in campylobacters, a group with very diverse hydrogenase content (number, type of hydrogenases, H2-oxidizing vs H2-producing, [Ni-Fe] vs [Fe-Fe], etc.)

Since there are no known animal or human Ni-enzymes, nickel chelation therapy represents a promising new antimicrobial approach. The Ni-specific chelator dimethylglyoxime (DMG) was found in our lab to be bacteriostatic against multidrug resistant strains of Salmonella and Klebsiella sp., by inhibiting their [Ni-Fe] hydrogenases and urease, respectively. A similar effect of DMG (i.e., bacteriostatic) was observed toward Campylobacter jejuni. Unexpectedly, DMG was found to be bactericidal in presence of copper (Cu). Both the cytoplasmic Ni-binding chaperone SlyD and the twin arginine translocation (Tat)-dependent periplasmic copper oxidase CueO were shown to play a central role in the Cu-DMG hypersensitivity phenotype. Injection of Cu-DMG into Galleria mellonella before C. jejuni inoculation significantly increased the insect survival rate compared to the control group. In chickens, oral administration of DMG or Cu-DMG decreased and even abolished C. jejuni colonization in some cases, compared to both water-only and Cu-only control groups. The latter finding is important, since campylobacteriosis is the leading bacterial foodborne infection, and chicken meat constitutes the major foodborne source.

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404D Biological Sciences Building