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Candidate gene approaches reveal new target pathways for treating antibiotic-resistant gram-negative bacterial infections

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New antibiotics are needed because resistance has rendered many existing drugs ineffective. We discovered that the antifungal drug, ciclopirox, prevents growth of problematic, multidrug-resistant clinical isolates, although the drug target remains elusive. We showed that both sugar metabolism and free iron in the growth medium affect ciclopirox inhibition of *E. coli*. Additionally, iron-acquiring siderophore production in *P. aeruginosa* was increased in the presence of ciclopirox, implying a disruption of iron acquisition. We performed a literature search and identified 103 genes involved in specific iron-utilization and sugar metabolism pathways. To test for those that are affected by ciclopirox, we screened gene deletion strains for increased sensitivity to ciclopirox. We filtered out those gene deletions affected by any antibiotic based on the literature. Because ciclopirox can bind free iron, we screened our remaining 29 gene set for increased sensitivity to the iron chelator 1, 10-phenanthroline. This stratification resulted in 18 gene deletions with increased susceptibility to ciclopirox alone. Most of these genes encode proteins involved with the synthesis of the surface glycolipid enterobacterial common antigen, consistent with our laboratory's published work that shows ciclopirox alters glycolipid expression in the cell outer membrane. Other stratified genes encode proteins involved in the uptake of the siderophore enterobactin. We conclude that ciclopirox interferes in multiple pathways including the construction of glycolipids and iron acquisition. These data are an important step toward developing ciclopirox or new derivatives of ciclopirox, as drugs against multidrug-resistant gram-negative pathogens for which few therapeutic options exist currently.

Biography

Zachary C Conley completed his BS in Cellular and Molecular Biology at Westmont College in Santa Barbara, California. He is currently a PhD candidate studying antibiotic resistance in the laboratory of Dr. Lynn Zechiedrich in the Verna and Marrs McLean Department of Biochemistry and Molecular Biology at Baylor College of Medicine in Houston, Texas.

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