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EDITORIAL

Classic Spotlight: Electron Bifurcation, a Unifying Concept for Energy Conservation in Anaerobes

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In 1857, Louis Pasteur published the first of his many studies on fermentation, which he described as "life without air" (1). This seminal work on anaerobic physiology ushered in the modern age of microbiology; thus, it is ironic that the ensuing scientific revolution focused almost entirely on aerobic biology. Over the next 150 years, the metabolism and physiology that underpin aerobic life were firmly established, while questions regarding anaerobic metabolism often languished. This is especially true regarding the mechanisms of biological energy conservation in the absence of oxygen. Accordingly, our incomplete understanding of anaerobic energy conservation led to the idea that anaerobic organisms captured chemical energy inefficiently (i.e., they made less ATP than would be expected based on thermodymanic considerations), a concept that was directly contradicted by their relatively high growth yields (2). This conundrum led to a series of strained, and often contradictory, theories to explain the unusual physiology of metabolically diverse anaerobes.

However, a paper published in the *Journal of Bacteriology* in 2008 solved these dilemmas by introducing a concept that revolutionized our understanding of anaerobic metabolism: namely, flavin-based electron bifurcation (3). In this classic paper, Li et al. describe a new activity for an old enzyme, the crotonyl coenzyme A (crotonyl-CoA) reductase from *Clostridium kluyveri*. This soluble, cytoplasmic enzyme was shown to couple the previously observed exergonic reduction of crotonyl-CoA to the unsuspected and highly endergonic reduction of ferredoxin using NADH as the electron donor for both reactions. The low-potential ferredoxin produced in this reaction serves to capture potential energy that can subsequently be used to drive otherwise endergonic reactions, such as production of hydrogen at high partial pressures or generation of a membrane potential that can be used for ATP synthesis (4). This finding nicely explains the enigmatic characteristics of *C. kluyveri* that have long puzzled microbiologists. More importantly, the idea of coupling exergonic and endergonic reactions by flavin-containing cytoplasmic enzyme complexes was immediately seen to explain unanswered questions across a wide spectrum of anaerobic microbes. In short order, electron bifurcation was demonstrated in assorted fermenters, sulfate reducers, acetogens, and methanogens, where it plays diverse roles in CO_2 fixation, cofactor balancing, and hydrogen production (3, 5–9). Further, the reverse of the process, electron confurcation, appears to explain the ability of syntrophic bacteria to consume their substrates and produce hydrogen under conditions that are not thermodynamically favorable without a mechanism that couples the unfavorable reaction to a favorable one (10, 11). Indeed, this recent, but already classic, paper is in many ways a "unified field theory" for anaerobic energy conservation. There is little doubt that its profound impact will endure as we explore the microbes that inhabit the unique and ancient anoxic habitats first appreciated by Louis Pasteur.

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