

Pseudomonas aeruginosa Uses Dihydrolipoamide Dehydrogenase (Lpd) to Bind to the Human Terminal Pathway Regulators Vitronectin and Clusterin to Inhibit Terminal Pathway Complement Attack.

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Abstract

The opportunistic human pathogen *Pseudomonas aeruginosa* controls host innate immune and complement attack. Here we identify Dihydrolipoamide dehydrogenase (Lpd), a 57 kDa moonlighting protein, as the first *P. aeruginosa* protein that binds the two human terminal pathway inhibitors vitronectin and clusterin. Both human regulators when bound to the bacterium inhibited effector function of the terminal complement, blocked C5b-9 deposition and protected the bacterium from complement damage. *P. aeruginosa* when challenged with complement active human serum depleted from vitronectin was severely damaged and bacterial survival was reduced by over 50%. Similarly, when in human serum clusterin was blocked by a mAb, bacterial survival was reduced by 44%. Thus, demonstrating that *Pseudomonas* benefits from attachment of each

human regulator and controls complement attack. The Lpd binding site in vitronectin was localized to the C-terminal region, i.e. to residues 354-363. Thus, Lpd of *P. aeruginosa* is a surface exposed moonlighting protein that binds two human terminal pathway inhibitors, vitronectin and clusterin and each human inhibitor when attached protected the bacterial pathogen from the action of the terminal complement pathway. Our results showed insights into the important function of Lpd as a complement regulator binding protein that might play an important role in virulence of *P. aeruginosa*.

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