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Towards a mechanistic understanding of the roles of HipA and HipB in bacterial multidrug tolerance and persistence

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Abstract

During exponential growth of *Escherichia coli*, one cell per ~1,000,000 becomes dormant. Dormancycan lead to multidrug tolerance, as many antibiotics work by attacking the machinery associated with cell wall biosynthesis, DNA replication or translation thereby leading to corrupted products that result in cell death. These dormant cells,called persisters,are not actively using these molecular machines and hence are not killed. Further exacerbating their intrinsic multidrug tolerance, persisters occupy biofilms, which provide another layer of protection, as the immune system of the host cannot penetrate these structures. After drug removal, persisters can reawaken to become fully functional and dividing planktonic cells that can restart aninfection.Thus, persisters underlie our inability to eradicate many bacterial infections.Although persistence was first described nearly 70 years ago, the molecular mechanisms by which bacterial cells become persistent are only now becoming clear. In *E.coli* the Toxin-Antitoxin pair, HipA and HipB, areone underlying cause of persistence. Indeed, HipA was the first *bona fide* persistence factor identified in this bacterium. HipA is a serine/threonineprotein kinase.HipB is the transcription regulator of the *hipBA* operon and is critical in "neutralizing" HipA.Here we shall presentour recent structural and biochemical studies on HipB, HipA and autophosphorylated HipA. These data reveal the mechanisms of differential HipB-*hipBA* operator binding, potential HipA substrates and the mechanisms of HipAinhibition through HipB binding and autophosphorylation-induced structural changes of HipA that are critical to initiatenew cell growth and reinfection.

Biography

Richard G. Brennan received his Ph.D.in Biochemistry from the University of Wisconsin at Madison in 1984 and carried out his postdoctoral studies with Brian Matthews at the University of Oregon.Recently he joined the Department of Biochemistry at Duke University School of Medicineas the James B. Duke Professor of Biochemistry and Chair of the Department. Dr. Brennan has published more than 125 papers and serveson the editorial boards of three journals. Dr. Brennan was elected a Fellow of the American Academy of Microbiology in 2007 and the American Association for the Advancement of Science in 2011.