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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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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 an infection. 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, is one underlying cause of persistence. Indeed, HipA was the first *bona fide* persistence factor identified in this bacterium. HipA is a serine/threonine protein kinase. HipB is the transcription regulator of the hipBA operon and is critical in "neutralizing" HipA. Here, we shall present our 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 HipA inhibition through HipB binding and autophosphorylation-induced structural changes of HipA that are critical to initiate new 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 Medicine as the James B. Duke Professor of Biochemistry and Chair of the Department. He has published more than 125 papers and serves on the editorial boards of three journals. He was elected a fellow of the American Academy of Microbiology in 2007 and the American Association for the Advancement of Science in 2011.

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