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Sphingosine 1-phosphate activation of EGFR as a novel target for meningitic *Escherichia coli* penetration of the blood brain barrier

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Central nervous system (CNS) infection continues to be an important cause of mortality and morbidity, necessitating new approaches for investigating its pathogenesis and prevention of the disease. *Escherichia coli* is the most common Gram-negative bacillary organism causing meningitis, which develops following penetration of the blood brain barrier (BBB). By chemical library screening, we identified epidermal growth factor receptor (EGFR) as a contributor to *E. coli* invasion of the BBB *in vitro* and *in vivo*. Here, we obtained the direct evidence that CNS-infecting *E. coli* exploited sphingosine 1-phosphate (S1P) for EGFR activation in its penetration of the BBB. We found that S1P was upstream of EGFR and participated in EGFR transactivation through EGFR-related ligand HB-EGF and blockade of S1P function through targeting sphingosine kinase and S1P receptor inhibited EGFR activation as well as *E. coli* invasion of the BBB. We further found that both S1P and EGFR activations in response to meningitic *E. coli* involve the same *E. coli* proteins (OmpA, FimH, NlpI) and that S1P and EGFR promoted *E. coli* invasion of the BBB by activating the downstream c-Src. These findings indicate that S1P and EGFR represent the novel host targets for meningitic *E. coli* penetration of the BBB and counteracting such targets provide a novel approach for controlling *E. coli* meningitis in the era of increasing resistance to conventional antibiotics.

Biography

Xiangru Wang has completed his PhD from Department of Preventive Veterinary Medicine, School of Veterinary Medicine, Huazhong Agriculture University. He has been awarded scholarship under the State Scholarship Fund for the exchange study overseas as a joint PhD Visiting Scholar at Johns Hopkins University School of Medicine from October 2012 to April 2014, working on the CNS-infecting bacterial penetration of the blood-brain barrier. He is presently a Research Member in State Key Laboratory of Agricultural Microbiology, China and has published more than 10 research articles in reputed journals in the field of veterinary.

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