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Phosphorylation of Rac1 at threonine 108 by ERK in response to EGF: A novel mechanism to regulate Rac1 function

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Abstract

Accumulating evidence has implicated Rho GTPases including Rac1 in many aspects of cancer development, especially in metastasis. The regulatory cycle of Rho GTPases is normally controlled by three distinct families of proteins, guanine nucleotide exchange factors (GEFs), GTPase-activating proteins (GAPs), and guanine nucleotide dissociation inhibitors (GDIs). However, recent findings suggest that phosphorylation might further contribute to the tight regulation of Rho GTPases. Interestingly, sequence analysis of Rac1 shows that Rac1 T108 within the 106PNTP109 motif is likely an ERK phosphorylation site and Rac1 also has an ERK docking site 183KKRKRKCLLL192 (D-site) at C-terminus. Indeed we show here that when expressed in COS-7 cells, GFP-tagged Rac1 interacts with ERK and this interaction is mediated by its D-site. GFP-Rac1 is threonine phosphorylated in response to EGF, but mutant Rac1 with the mutation of T108 to alanine (A) (GFP-Rac1T108A) is not threonine phosphorylated. Moreover, in vitro ERK kinase assay shows that pure active ERK phosphorylate both purified His-tagged Rac1 and GST-tagged Rac1, but not mutant GST-Rac1T108A. We further show that Rac1 T108 phosphorylation decreases its activity, possibly due to inhibiting its interaction with PLC-□1. T108 phosphorylation also targets Rac1 to the nucleus and hinds Rac1's ability to mediate EGF-induced cell migration. We conclude that Rac1 T108 is phosphorylated by ERK in response to EGF, which plays an important role in regulating Rac1 activity and function.

Biography

Dr. Zhixiang Wang, got his PhD at Simon Fraser University, Canada in 1993. He is now a full professor at the Department of Medical Genetics, Faculty of Medicine and Dentistry, University of Alberta. He has published more than 50 papers in reputed journals and has been serving as reviewer or board/panel members for various journal and funding agencies.