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College *	College of Medicine
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Title of Research *	Activation of the RhoGEF PLEKHG2 (FLJ00018) by G Beta Gamma
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Introduction & Purpose *

Rho guanine nucleotide exchange factors (GEFs) catalyze the activation of the RhoGTPase family that induces numerous downstream effects, including cytoskeletal rearrangement and DNA transcription. PLEKHG2 is a novel G beta gamma-activated Rho guanine nucleotide exchange factor (GEF) which catalyzes the activation of the RhoGTPase family of proteins. Overexpression of PLEKHG2 has been associated with enhanced cell transformation and leukemia. Additionally, PLEKHG2 may mediate lysophosphatidic acid (LPA)-induced cell spreading. However; the mechanism of PLEKHG2 regulation has yet to be elucidated. In this study we aim to identify how LPA stimulation of G proteins activates PLEKHG2.

Experimental Design *

To assay activation of PLEKHG2, we used an SRE-based luciferase reporter, cotransfected with exogenous DNA to monitor GEF activity.

Results *

We found that PLEKHG2 activation via LPA is selectively mediated by G beta gamma subunits released from G proteins, as activation is completely abolished by scavengers of G beta gamma, G alpha T or the C-terminal tail of G protein-coupled receptor kinase 2. Interestingly, PLEKHG2 activation is only partially inhibited by Pertussis toxin, the G alpha q minigene, or the G alpha13 minigene that selectively uncouple the Gi/o, Gq/11, and G12/13 classes of G proteins, suggesting that activation of PLEKHG2 involves G beta gamma subunits released from multiple classes of G proteins. By comparing the activation of PLEKHG2 by different G beta isoforms, we further provided evidence that activation of PLEKHG2 is G beta isoform specific.

Conclusions *

Taken together, our data indicate that PLEKHG2 is a RhoGEF activated by selective G beta gamma isoforms released from multiple classes of G proteins. These findings lay the foundation for us to further elucidate the mechanism of PLEKHG2 activation and regulation, and its functions in both physiological and pathological settings, including leukocyte migration, wound healing, and breast cancer development.

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