

HEALTH RESEARCH ABSTRACT SUBMISSIONS

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Name *	Caitlin Runne
Email *	Caitlin-Runne@uiowa.edu
Educational Level *	PhD Candidate
If Selected Other	
College *	College of Medicine
Department *	Pharmacology
Title of Research *	Function and Regulation of a G Beta Gamma Stimulated RhoGEF, PLEKHG2
Other Authors *	Songhai Chen (UI, Carver College of Medicine, Department of Pharmacology, Advisor)

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. Overexpression of RhoGEFs is linked to several human diseases, including cardiovascular disease and cancer, due to aberrant cell growth and migration associated with enhanced RhoGTPase activation. PLEKHG2 is a novel RhoGEF that was recently identified to be activated by the beta gamma dimer of the heterotrimeric G proteins. Upregulation of PLEKHG2 has been associated with cell transformation and leukemia. However; the mechanism of regulation and the exact function of PLEKHG2 remain to be elucidated.

Experimental Design *

To perform our assays, we used a luciferase reporter cotransfected with exogenous DNA to monitor RhoGEF activity.

Results *

We have found that, in contrast to the majority of known RhoGEFs, PLEKHG2 activation is mediated specifically by agonists of G protein coupled receptors (GPCRs), such as lysophosphatidic acid, but not by growth factors, including epidermal growth factor (EGF) and insulin-like growth factor (IGF). PLEKHG2 activation is completely abolished by the scavengers of G-beta gamma, G-alpha-T and the C-terminal tail of G protein-coupled receptor kinase 2 (GRK2ct), but only partially inhibited by Pertussis toxin (PTx), implicating the involvement of G-beta gamma dimers released from both PTx –sensitive (Gi/o) and –insensitive G proteins. By comparing the activation of PLEKHG2 by different G-beta isoforms, we provided evidence that activation of PLEKHG2 involves a conserved region shared by G-beta1- 4, but not by G-beta5 and a splice variant of G-beta3, G-beta3s.

Conclusions *

Taken together, our data indicate that PLEKHG2 is a RhoGEF selectively activated by G-beta gamma 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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