HEALTH RESEARCH ABSTRACT SUBMISSIONS #37

Name *	Caitlin Runne
Email *	Caitlin-runne@uiowa.edu
Educational Level *	PhD Candidate
If Selected Other	
College *	College of Pharmacy
Department *	Pharmacology
Title of Research *	Regulation of PLEKHG2, A Novel GBY-Activated RhoGEF
Other Authors *	Sun, Xiao Yun Tang, Songhai Chen

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 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 βγ 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 studies, we used a combination of luciferase reporter assays and co-immunoprecipitation assays to assess the molecular regulation of PLEKHG2 by Gβγ.

Results *

We found that PLEKHG2 activation is selectively mediated by Gβγ subunits, as activation is completely abolished by scavengers of Gβγ. By comparing the ability of PLEKHG2 to be activated by different forms of Gβ, we found that PLEKHG2 can be activated by Gβ1-4, but not Gβ5. However, co-immunoprecipitation of PLEKHG2 and Gβ1 or Gβ5 indicates that PLEKHG2 can form a complex with both isoforms. These data suggest that activation of PLEKHG2 by Gβγ involves critical residues conserved between Gβ1-4, but not Gβ5. Additional studies found that activation of PLEKHG2 involves Gβγ binding to the N-terminus of PLEKHG2, as truncation of the PLEKHG2 N-terminus abolished its activation by Gβγ. In contrast, truncation of the PLEKHG2 C-terminus led to enhanced PLEKHG2 activity, even in the absence of Gβγ stimulation, suggesting that the activity of PLEKHG2 may be autoinhibited by its C-terminus.

Conclusions *	Our data suggest that Gβγ activates PLEKHG2 by binding to its N-terminus, thereby releasing an autoinhibition mediated by the C-terminus. These mechanistic studies give us a foundation for further elucidating the functional role of PLEKHG2 in leukocyte and/or cancer cell migration.

Created
4 Apr 2012
10:20:36 AM

PUBLICPOLICYCENTER