p115 RhoGEF, a GTPase Activating Protein for Gα₁₂ and Gα₁₃

Tohru Kozasa *et al.* <u>1998</u>

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Before this study ...

- GPCRs, heptahelical receptors, transduces signals for G proteins.
- Each heterotrimeric G protein has α , β , γ subunits.
- Ga subunits are groups into four subfamilies: G_s , G_i , $G_q \& G_{12}$.
- Rho, a small GTPase, mediates the formation of actin stress fibers and the assembly of focal adhesion complexes.



- Functional core (GTPase activating) of the RGS box contains nine alpha helices.
- P115 is a GEF specific for Rho.
- $G\alpha_{12}$ and $G\alpha_{13}$ activate Rho in vivo. A physical interaction between p115 and $G\alpha_{13}$ was detected.
- P115 RhoGEF stimulates only the intrinsic GTPase activity of $G\alpha_{12}$ and $G\alpha_{13}$, not other $G\alpha_{3}$.

RGS sequence alignments

	α1	α2	α3	* *	* * * 0	χ4
Rat RGS4 Mouse RGS2 Human GAIP Rat RGS12 Rat RGS14 Human p115 Mouse Lsc Human KIAA38 Drosophila DrhoGE	(59) WA (80) WA (87) WA (712) WA (64) WA (45) QF (43) QF (43) QF (310) J F	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	H E C G L A A F K A S K Y G L A A F R A S P A G R S V F R A D P V G V R Y F S D D P R G L A Y F T E R P A H L M A L L Q R P A H L M A L L Q R P A H L G V F L R E A E N V T F L A I	F L K S E - - Y S F L K S E - - - F C F L R T E - - - Y S F L R K E - - - F S F L R K E - - - F S F L R K E - - - F S H V A L Q - - - F E H V A L Q - - - F E H V A L Q - - - F E H V A L Q - - - F E H V A L Q - - - A	E E N I D F E E N I E F E E N M L F E E N I L F A E N V T F P G P L L C P G P L L C P S P L L F P A P L L F	N I S C E E Y K K I N L A C E D F K K T N L A C E D F K K T N L A C E C F S H V N Q A C E C F S H V N Q A C E R F Q Q I C L H A E M L G S L C L H A E M L S S L L L A E V Y Q Q A
			α5		,	** <u>*</u> α6
RGS4 RGS2 GAIP RGS12 RGS14 P115 Lsc KIAA38 DrhoGE	(102)1 $(123)1$ $(130)2$ $(755) PAI$ $(107) PAS$ $(88)3$ $(86)5$ $(86)5$ $(86)5$ $(86)5$ $(86)5$	K S P S K L S P K S P Q K L S S A N Q H V V D E H D K K E L S Y S D T K Q L A Q - G P K E A K K - G P K E A K K - S P K D S R S - T S K D M R K	K A K K I Y N E F I K A R K I Y T D F I K A R L I Y E D Y V R A R E I F S K F L E A H N I Y H E F L A F L D F Y H S F L A F L D F Y H S F L A F L D F Y H S F L A F L D F Y H S F L A F L D F Y H S F L W A Y E I H S T F L	S V Q A T E K E A P S I L S P C S K A T S S Q A L E K T A V L R - V P E K T A V L R - V P E K N A P L R - V K V P R A P L S W Y R	K E K E T P S P V P P N V A V P P S V A I P E M L Q I Q D E S L A I	N L D S C T R E I D F Q T K S L V S L D S R V R G V S L D S R V R G V S L D S Q A Q L V S D R Q A U S F L D R T R D L F L D R T R D L F L D S R L R N - K E L D S R L R N -
		x6		α7 * **	* α8	α9
RGS4 RGS2 GAIP RGS12 RGS14 P115 LSC KIAA38	(137) TSI (158) IA((165) INI (792) DDT (144) EET (130) ISI (128) ISI 0 (394) - SI	R N M L E P $Q N I Q E A$ $K M Q E P$ $I L N A P$ $V L A Q P$ $E D V Q - R R F$ $E D V Q - R R F$	T I T C F D E A Q K T S G C F T T A Q K S A H T F D D A Q L H P D M F K E Q Q L R P D M F R A Q Q L V Q E V V Q S Q Q V I Q E V V Q S Q Q A L C E A O E A A M P	K I F N L M E K D S R V Y S L M E N N S Q I Y T L M H R D S Q I Y T L M H R D S Q I F N L M K F D S Q I F N L M K F D S Q I F N L M K F D S Q I F N L M K F D S Q I F N L M K F D S Q I T O E Q I E D F R	Y R R F L K S Y P R F L E S Y P R F L S S Y T R F L K S Y A R F V K S S K R L M G I S K R L M G I	$ \begin{array}{c} \mathbf{S} \mathbf{R} \mathbf{F} \mathbf{Y} \mathbf{L} \mathbf{D} & (176) \\ \mathbf{S} \mathbf{E} \mathbf{F} \mathbf{Y} \mathbf{Q} \mathbf{D} & (197) \\ \mathbf{S} \mathbf{P} \mathbf{T} \mathbf{Y} \mathbf{R} \mathbf{A} & (204) \\ \mathbf{S} \mathbf{Q} \mathbf{L} \mathbf{Y} \mathbf{Q} \mathbf{E} & (830) \\ \mathbf{S} \mathbf{P} \mathbf{L} \mathbf{Y} \mathbf{Q} \mathbf{E} & (182) \\ \mathbf{M} \mathbf{T} \mathbf{P} \mathbf{W} \mathbf{E} \mathbf{Q} & (170) \\ \mathbf{M} \mathbf{T} \mathbf{P} \mathbf{W} \mathbf{E} \mathbf{Q} & (168) \\ \mathbf{G} \mathbf{S} \mathbf{L} \mathbf{Y} \mathbf{G} \mathbf{G} & (432) \\ \end{array} $
DrhoGE	F2 (1012)Y D H	VEILRTV:	FLRSRKRAKD	LISEODREFO	OKRTAGI	GTTYG (1053)

GTPase activity stimulates by p115 RhoGEF



GTPase activity stimulates by the NH₂-terminus of p115 RhoGEF



Specific Gα inhibits p115 RhoGEF GAP activity



RGS sequence alignments

		α1	_α2		α3		* * *	* *	α4
Rat RGS4 Mouse RGS2 Human GAIP Rat RGS12 Rat RGS14 Human p115 Mouse Lsc Human KIAA380 Drosophila DrhoGEF2	(59) (80) (87) (712) (64) (45) 43) 310) 924)	W A E W A Q W A V W A Q Q F Q Q F Q I F Q P F N	S L E N A F D E S F D K S F E R S F E R S L E Q S L E Q D L E K N L T R	L I N H E C L L A S K Y L M H S P A L L Q D P V L L Q D P R V K R R P A V K R R P A L K S R P A L L - E A E	G L A A F K G L A A F R G R S V F R G V R Y F S G L A Y F T H L M A L L H L M A L L H L G V F L N V T F L A	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Y S E F C E F S E F S A F E P F E P A D P S N S D P	E N I D F E N I E F E N M L F E N I L F G P L L C G P L L C S P L L F A P L L F	W I S C E E Y K K I W L A C E D F K K T W L A C E E L K A E W Q A C E C F S H V W Q A C E R F Q Q I C L H A E M L G S L C L H A E M L S S L Y L C A E V Y Q Q A
			_	α	5	_			** <u>*</u> α6
RGS4 RGS2 GAIP RGS12 RGS14 p115 Lsc KIAA380 DrhoGEF2	(102) (123) (130) (755) (107) (88) (86) (353) (969)	K K A P A H P A S C	SPSK SPQK NQHV DKKE DTKQ GPKE SPKD TSKD	L S P K A K L S S K A R V D E K A R L S Y R A R L A Q E A H A K K A F L A K K A F L S R S L G K M R K W A Y	K I Y N E F K I Y T D F L I Y E D Y E I F S K F D F Y H E F D F Y H S F D F Y H S F D F Y H S T D I W N I F E I H S T F	I SV	- Q A T K - E A P K - L S P K - K A T T - Q A L S R - V P V R - V P V R - V K I S W Y R Q * *	E E P P P P P N V A P P S V A P E M L Q D E S L A * 0.8	V N L D S C T R E E I N I D F Q T K S L V S L D S R V R E G V N I D S Q A Q L A V N I D R Q A W L S F E L D R T R A D L F E L D R T R P D L A E I D S R L R N - R E V D N V L Q L E
RGS4 RGS2 GAIP RGS12 RGS14 p115 Lsc KIAA380 DrhoGEF2	(137) (158) (165) (792) (144) (130) (128) (394) (1012)	T S R I A Q I N K D D I E E V I S E I S E - S E Y D K	N M L E N I Q E K M Q E L N A - L A Q - D V Q - D V Q - D A - V E I L	P T I T - A T S G - P S A H - P H P D - P R P D R R F V Q E R R F I Q E R G V L C E R T V F L R	C F D E A Q C C F T T A Q C T F D D A Q C M F K E Q Q C V Q C S Q Q C V V Q S Q Q C A Q E A A M C S R K R A K C	K K I F N L M H K R V Y S L M H L Q I Y T L M H L Q I F N L M H V A V G R Q L H A A V S R Q L H P E I Q E Q I H D L I S E Q L H	K D S Y N N S Y F D S Y F D S Y D F R S D F R S D F R S I D Y R T E E F Q Q	R R F L K P R F L E P R F L S T R F L K A R F V K K R L M G K R L M G K R T L G K R T A G	S R F Y L D (176) S E F Y Q D (197) S P T Y R A (204) S Q L Y Q E (830) S P L Y Q E (182) M T P W E Q (170) M T P W E Q (168) L G S L Y G (432) L G T I Y G (1053)



