孤兒G蛋白偶聯受體, GPCR109B及GPCR43,在藥物誘導K562人類血癌細胞株分化過程扮演不同角色 = Orphan G protein-coupled ...

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摘 要

G蛋白偶聯受體(G protein-coupled receptor, GPCR)為人類廣泛存在之蛋白質的一個族群，其扮演之角色主要為細胞訊息傳遞過程中之媒介者(Mediators)。當細胞表面GPCR受到專一或非專一性配體(Ligand)結合時，可刺激G蛋白並將訊息傳遞至下游，造成一連串的瀑布(cascade)效應。很多疾病的產生，即是因為GPCR功能的喪失或是藥物濫用後影響其訊息途徑所造成。困於目前對於大部分的GPCR在生理上之功能性尚未完全了解，實際用於治療的應用不多。若可結合特殊配體與受體之間之專一性作用，未來應用在開發新藥物治療或標靶治療(Taget Therapy)上的願景是可期待的。 G蛋白為細胞訊息傳遞中重要媒介角色，其可接受來自GPCR的一級訊號再將其轉變成二級訊號進一步傳遞下去。文獻預測GPCR109B及GPCR43此兩受體分別會影響下游G蛋白次單元Gαi及Gα11之訊息傳遞。本論文研究目的主要釐清此兩受體是否會影響血球細胞功能性基因表現的變化，而希望藉由了解此傳遞之路徑，試圖找出治療血癌或貧血等疾病的契機。 當過量表現GPCR109B後，添加其配體N-amino nicotinate作用，會明顯增加血小板生長因子(Platelet-derived growth factor, PDGF)表現；而GPCR43與其配體丙酸鹽（propionate）結合則會抑制PDGF的表現。血球巨核細胞分化因子(Tescalcin, TESC)在此兩受體中皆沒有顯著的差異。在GPCR109B過量表現時γ球蛋白有明顯的減少，但GPCR43則沒有顯著影響。而當延長細胞誘導時間後，在GPCR109B部份，Vimentin的表現量則有明顯的升高，GPCR43則是TESC有明顯的增加。綜合此結果結合細胞型態的判斷，暗示此兩受體訊息傳遞路徑可能是不同的，GPCR43可能會影響細胞走向巨核細胞分化途徑，而GPCR109B則可能與巨噬細胞分化有關聯。

關鍵詞 : G蛋白 ; 配體 ; 標靶治療 ; 巨噬細胞 ; 巨核細胞

目錄

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參考文獻

1. 黃聖懿。2008。血液腫瘤之標靶治療。台灣醫學12（1）:27-48。 2. 蘇金源。2005。2001 年生理醫學桂冠，細胞分裂的調控。(諾貝爾的榮耀-生理醫學桂冠，林榮崧)。212-219頁。天下遠見出版股有限公司。台北市，台灣。 3. 陳至丞。2004。血癌的認知。聲洋防癌之聲秋季號:11-17。 4. Abe, J., Fukuzawa, T. and Hirose, S. 2002. Cleavage of Ig-Hepta at a "SEA" module and at a conserved G protein-coupled receptor proteolytic site. J Biol Chem. 277:23391-8. 5. Altschul, R., Hoffer, R., Stephen, J. D. 1955. Arch. Biochem. 54, 558; Tavintharan, S., Kashyap, M. L. 2001. Curr. Atheroscler. Rep. 3, 74; Carlson, L. A. J. 2005. Int. Med. 258, 94. 6. Bale, T. L. and Vale, W. W. 2004. CRF and CRF receptors: role in stress responsivity and other behaviors. Annu Rev Pharmacol Toxicol. 44: 525-557. 7. Bernini, L.F. and Harteveld, C.L. 1998. Alpha-thalassaemia Baillieres Clin Haematol. 11: 53-90. 8. Bockaert, J. and Pin, J.P. 1999. Molecular tinkering of G protein-coupled receptors: an evolutionary success. EMBO J. 18:1723-1729. 9. Body, J. J. 2002. Calcitonin for the long-term prevention and treatment of postmenopausal osteoporosis. Bone. 30: 75S-79S. 10. Brunkhorst, B.A., Kraus E., Coppi M., Budnick M., Niederman R.1992. Infect. Immun. 60: 2957. 11. Brusa, G., Zuffa, E., Mancini, M., Benvenuti, M., Calonghi, N., Barbieri, E. and Santucci M. A. 2006. P210 Bcr-abl tyrosine kinase interaction with histone deacetylase 1 modifies histone H4 acetylation and chromatin structure of chronic myeloid leukemia haematopoietic progenitors. Br. J. Haematol. 132: 359-369. 12. Cabrele, C. and Beck-Sickinger, A. G.. 2000. Molecular characterization of the ligand-receptor interaction of the neuropeptide Y family. J. Pept. Sci. 6: 97-122. 13. Cabrera-Vera, T. M., Vanhauwe, J., Thomas, T. O., Medkova, M., Preininger, A., Mazzoni, M. R. and Hamm, H. E. 2003. Insights into G protein structure, function, and regulation. Endocr Rev. 24: 765-781. 14. Cadigan, K., and Nusse, R. 1997. Wnt signaling: a common theme in animal development. Genes Dev. 11: 3286-3305. 15. Chang, J. C., Ye, L. and Kan, Y. W. 2006. Correction of the sickle cell mutation in embryonic stem cells. Proc Natl Acad Sci U S A. 103: 1036-1040. 16. Chang, J. G., Lin, C. P., Liu, T. C., Chiou, S. S., Chen, P. H., Lee, L. S., and Chen, T. P. 1994. Molecular basis of beta-thalassemia minor in Taiwan. Int J Hematol 59: 267-272. 17.Colvin, G.. A., Elfenbein, G.. J. 2003. The latest treatment advances for acute myelogenous leukemia. Med Health R I . 86 (8): 243 – 6. 18. Colucci-Guyon, E., Portier, M. M., Dunia, I., Paulin, D., Pournin, S. and Babinet, C. 1994. Mice lacking vimentin develop and reproduce without an obvious phenotype. Cell. 79:679-694. 19. Cummings, J. H., Macfarlane, G. T., Parenter, J. J. 1997. Enteral. Nutr. 21: 357. 20. Dann, C. E., Hsieh, J. C., Rattner, A., Sharma, D., Nathans, J. and Leahy, D. J. 2001. Insight into Wnt binding and signaling from the structures of two Frizzled cysteine-rich domains. Nature. 412: 86-90. 21. Drexler, H. G.., MacLeod, R. A. and Uphoff, C. C. 1999. Leukemia cell lines: in vitro models for the study of Philadelphia chromosome-positive leukemia. Leuk. Res. 23: 207-215. 22. Eftimiadi, C., Buzzi, E., Tonetti, M., Buffa, P., Buffa, D., van, M. T. Steenbergen, J., de Graaff, G. A., Botta, J. Infect. 1987. 14:43. 23. Foord, S. M., Jupe, S. and Holbrook, J. 2002. Bioinformatics and type II G-protein-coupled receptors. Biochem Soc Trans. 30: 473-479. 24. Francesco, F., Stefania, B., Alessandro, C., Dario, B., Silvio, B., Roberta , Z., Claudia, G., Gian, A. D. and Sergio, F. 2007. Genomic expression during human myelopoiesis. BMC Genomics. 10: 1186/1471-2164. 25. Franke, W. W. 1993. The intermediate filaments and associated proteins. In Guidebook to the Cytoskeletal and Motor Proteins (ed. T. Kreis and R. Vale). 137-143. 26. Fredriksson, R., Lagerstrom, M. C., Lundin, L. G., and Schioth, H. B. 2003. The G protein-coupled receptors in human gemone from five main families. Phylogenetic analysis, paralogon groups, and fingerprints. Mol Pharmacol. 63: 1256-1272. 27. Gardella, T. J. and Juppner, H. 2001. Molecular properties of G-protein of the PTH/PTHrP receptor. Trends Endocrinol Metab. 12: 210-217. 28. Gray, J. X., Haino, M., Roth, M. J., Maguire, J. E., Jensen, P. N., Yarme, A., Stetler-Stevenson, M. A., Siebenlist, U. and Kelly, K. 1996. CD97 is a processed, seven-transmembrane, heterodimeric receptor associated with inflammation. J Immunol. 157: 5438-5447. 29. Gutierrez-Ford, C., et al. 2003. Characterization of tescalcin, a novel EF-hand protein with a single Ca2+-binding site: metal-binding properties, localization in tissues and cells, and effect on calcineurin. Biochemistry. 42:14553 – 14565. 30. Halayko, A. J., Salari, H. and Stephens, N. L. 1996. Markers of airway smooth muscle cell phenotype. Am J Physiol Lung Cell Mol Physiol. 270: L1040 – L1051. 31. Harmar, A. J. 2001. Family-B G-protein-coupled receptors. Genome Biol. 2: reviews3013.1 – reviews3013.10. 32. Heidaran, M. A., Pierce, J. H., Yu, J. C., et al. 1991. Role of alpha beta receptor heterodimer formation in beta platelet-derived growth factor (PDGF) receptor activation by PDGF-AB. J. Biol. Chem. 266 (30): 20232 – 7. 33. Hermans, E., and Challiss, R. A. 2001. Structural, signalling and regulatory properties of the group I metabotropic glutamate receptor: prototypic family C G protein-coupled receptors. Biochem J. 359: 465-84. 34. Hoare, S. R. 2005. Mechanisms of peptide and nonpeptide ligand binding to Class B G-protein-coupled receptors. Drug Discov Today. 10: 417-427. 35. Hodsman, A. B., Bauer, D. C., Dempster, D. W., Dian, L., Hanley, D.A., Harris, S. T., Kendler, D. L., McClung, M. R., Miller, P. D., Plszynski, W. P., Orwoll, E. and Yuen, C. K. 2005. Parathyroid mormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev. 26: 688-703. 36. Huang, H. C. and Klein, P. S. 2004. The Frizzled family: receptors for multiple signal transduction pathways. Genome Biol. 5: 234 37. Ichtchenko, K., Bittner, M. A., Krasnoperov, V., Little, A. R., Chepurny, O., Holz, R. W. and Petrenko, A. G. 1999. A novel ubiquitously expressed alpha-latrotoxin receptor is a member of the CIRL family of G-protein-coupled receptors. J. Biol. Chem. 274: 5491-5498. 38. Johansson, B., Eriksson, A., Virtanen, I. and Thornell, L.E. 1997. Intermediate filament proteins in adult human arteries. Anat Rec. 247: 439 – 448. 39. Kang, C. D., Do, I. R., Kim, K. W., Ahn, B. K., Kim, S. H., Chung, B. S., Jhun, B. H. and Yoo, M. A. 1999. Role of Ras/ERK- dependent pathway in the erythroid differentiation of K562 cells. Exp. Mol. Med. 31: 76-82. 40. Klabunde, T., and Hessler, G. 2002. Drug design strategies for targeting G-protein-coupled receptors. Chembiochem 3: 928-944. 41. Kolakowski, L. F., Jr. 1994. GCRDb: a G-protein-coupled receptor database.

Receptors Channels. 2: 1-7. 42. Krystal G., Lam V., Dragowska W., Takahshi C., Appei J., Gontier A., Jenkins A., Lam H., Quon L., and Lansdorp P. 1994. Transformation growth factor β 1 is an inducer of erythroid differentiation. J. Exp. Med. 180: 851-860. 43. Klabunde, T. and Hessler, G. 2002. Drug design strategies for targeting G-protein-coupled receptors. Chembiochem. 3: 928-944. 44. Krasnoperov, V. G., et al. 1997. alpha-Latrotoxin stimulates exocytosis by the interaction with a neuronal G-protein-coupled receptor. Neuron. 18: 925-37. 45. Krystal, G., Lam. V., Dragowska, W., Takahshi, C., Appei, J., Gontier, A., Jenkins, A., Lam, H., Quon, L. and Lansdorp, P. 1994. Transformation growth factor β 1 is an inducer of erythroid differentiation. J. Exp. Med. 180: 851-860. 46. Kwakkenbos, M. J., Kop, E. N., Stacey, M., Matmati, M., Gordon, S., Lin, H. H. and Hamann, J. 2004. The EGF-TM7 family: a postgenomic view. Immunogenetics. 55: 655-666. 47. Lee, S., ianjun, C., Guolin, Z., Run, Z. S., Gerard, G. B., Masha, K., Xijin, G., Miao, S., Nimanthi, J., Yeong, C. K., Neelmini, E., Stefan, K., Bohlander, M. M., Justin, K., Ozden, O., Richard, A. L., Michelle, M. L., Eric, D. G., Jeffery, T., Theodore, K., Piu, P. L., San, M. W. and Janet, D. R. 2005. 48. Lee, S., Chen, J., Zhou, G., Shi, R. Z., Bouffard, G. G., Kocherginsky, M., Ge, X., Sun, M., Jayathilaka, N., Kim, Y. C., et al. 2006. Gene expression profiles in acute myeloid leukemia with common translocations using SAGE. Proc. Natl. Acad. Sci. U S A. 103: 1030-1035. 49. Levay, K. and Slepak, V. Z. 2007. Tescalcin is an essential factor in megakaryocytic differentiation associated with Ets family gene expression. J. Clin. Invest. 117:2672 – 2683. 50. Leupin, N., Kuhn, A., Hugli, B., Grob, T. J., Jaggi, R., Tobler, A., Delorenji, M. and Fey, M. F. 2006. Gene expression profiling reveals consistant differences between clinical samples of human leukemias and their model cell lines. British, J. Haemotol. 135: 520-523. 51. Li, X., Liu, Y., Kay, C.M., Muller-Esterl, W. and Fliegel, L. 2003. The Na+/H+ exchanger cytoplasmic tail: structure, function, and interactions with tescalcin. Biochemistry. 42:7448 – 7456. 52. Lozzio, C. B. and Lozzio, B. B. 1975. Human chronic myelogenous leukemia cell-line with positive Philadelphia chromosome. Blood. 45: 321-334. 53. Lum, L. and Beachy P. A. 2004. The Hedgehog response network: sensors, switches, and routers. Science. 304: 1755-1759. 54. Leupin, N., Kuhn, A., Hugli, B., Grob, J.J., Jaggi, R., Tobler, A., Delorenqi, M. and Fey, M.F. 2006. Gene expression profiling reveals consistant differences between clinical samples of human leukemias and their model cell lines. British J. Haemotol. 135: 520-523. 55. Lorenzen, A., Stannek, C., Lang, H., Andrianov, V., Kalvinsh, I., Schwabe, U. M. 2001. Pharmacol. 59, 349. 56. Mailander, J., Muller-Esterl, W. and Dedio, J. 2001. Human homolog of mouse tescalcin associates with Na(+)/H(+) exchanger type-1. FEBS Lett. 507:331 – 335. 57. Malbon, C. C., Wang, H., and Moon, R. T. 2001. Wnt signaling and heterotrimeric G-proteins: strange bedfellows or a classic reonace? Biochem Biophys Res Commun. 287: 589-593. 58. Matsui, T., Heidaran, M., Miki, T., et al. 1989. Isolation of a novel receptor cDNA establishes the existence of two PDGF receptor genes. Science. 243(4892): 800-4. 59. Miyashita, T. and Reed, J. C. 1995. Tumor suppressor p53 is a direct transcriptional activator of the human bax gene. Cell. 80: 293-299. 60. Monplaisir, N., Merault, G., Poyart, C., Rhoda, M. D., Craescu, C., Vidaud, M., Galacteros, F., Blouquit, Y. and Rosa, J. 1986. 61. Moon, R. T., Brown, J. D. and Torres M. 1997. WNTs modulate cell fate and behavior during vertebrate development. Trends Genet. 13: 157-162. 62. Moriguchi, T., Haraguchi, K., Ueda, N., Okada, M., Furuya, T. and Akiyama, T. 2004. DREG, a developmentally regulated G protein-coupled receptor containing two conserved proteolytic cleavage sites. Genes Cells. 9: 549-560. 63. Nakao, S., Fujii, A., Niederman, R. Infect. 1992. Immun. 60: 5307. 64. Nauck, M. A., Baller, B. and Meier, J. J. 2004. Gastric inhibitory polypeptide and lucagon-like peptide-1 in the pathogenesis of type 2 diabetes. Diabetes 53 Suppl 3 : S190-6. 65. Nechiporuk, T., Urness, L. D. and Keating, M. T. 2001. ETL, a novel seven-transmembrane receptor that is developmentally regulated in the heart. ETL is a member of the secretin family and belongs to the epidermal growth factor-seven-transmembrane subfamily. J. Biol. Chem. 276: 4150-4157. 66. Neer, E. J. 1995. Heterotrimeric G proteins: organizers of transmembrane signals. Cell. 80: 249-257. 67. Obermann, H., Samalecos, A., Osterhoff, C., Schroder, B., Heller, R., and Kirchhoff, C. 2003. HE6, a two-subunit heptahelical receptor associated with apical membranes of efferent and epididymal duct epithelia. Mol. Reprod Dev. 64:13-26. 68. Offermanns, S. 2006. Trends Pharmacol. Sci., 27, 384. 69. Philip, J. S., Martin, C. C., Peter, J. W., Carleton, R. S., Huong, T. D., Cameron, C. P., Ruoping, C., Susan, Y. T., Jeremy, G. R., Daniel, T. C. and Graeme Semple. 2007. 3-Nitro-4-amino benzoic acids and 6-amino nicotinic acids are highly selective agonists of GPR109b. Bioorganic & Medicinal Chemistry Letters. 17: 6619 – 6622. 70. Perera, E. M., et al. 2001. Tescalcin, a novel gene encoding a putative EF-hand Ca2+-binding protein, Co19a3, and renin are expressed in the mouse testis during the early stages of gonadal differentiation. Endocrinology. 142: 455-463. 71. Pelleymounter, M. A., Joppa, M., Ling, N. and Foster A. C. 2002. Pharmacological evidence supporting a role for central corticotropin-releasing factor(2) receptors in behavioral, but not endocrine, response to environmental stress. J. Pharmacol Exp. Ther. 302: 145-152. 72. Perrin, M. H., Fischer, W. H., Kunitake, K. S., Craig, A. G., Koerber, S. C., Cervini, L. A., Rivier, J. E., Groppe, J. C, Greenwald, J., Moller Nielsen, S. and Vale, W. W. 2001. Expression, purfication, and characterization of a soluble form of the first extracellular domain of the human type 1 corticotropin releasing factor receptor. J. Biol. Cham. 276: 31528-31534. 73. Pin, J. P., Kniazeff, J., Goudet, C., Bessis, A. S., Liu, J., Galvez, T., Acher, F., Rondard, P. and Prezeau, L. 2004. The activation mechanism of class-C G-protein coupled receptors. Biol Cell. 96: 335-342. 74. Ponting, C. P., Hofmann, K. and Bork, P. 1999. A latrophilin/CL-1-like GPS domain in polycystin-1. Curr. Biol. 9: 585-588. 75. Radhika, V. and Dhanasekaran, N. 2001. Transforming G proteins. Oncogene. 20: 1607-1614. 76. Rens-Domiano, S. and Hamm, H. E. 1995. Structural and functional relationships of heterotrimeric G-proteins. FASEB J. 9: 1059-1066. 77. Safaya, S., Ibrahim, A. and Rieder, R. F. 1994. Augmentation of gamma-globin gene promoter activity by carboxylic acids and components of the human beta-globin locus control region. Blood. 84: 3929-3935; Sarnaik, S.A. 2005. Thalassemia and related hemoglobinopathies. Indian J. Pediatr. 72: 319-324. 78. Stehle, H. W., Leblebicioglu, B., Walters, J. D., Periodontol, J. 2001.72: 1059. 79. Skinner, P. J., Cherrier, M. C., Webb, P. J., Sage, C. R., Dang, H. T., Pride, C. C., Chen, R., Tamura, S. Y., Richman, J. G., Connolly, D. T., et al. 2007. 3-Nitro-4-amino benzoic acids and 6-amino nicotinic acids are highly selective agonists of GPR109b. Bioorg Med Chem Lett. 17: 6619-6622. 80. Soga, T., Kamohara, M., Takasaki, J. M., Shun-Ichiro, S., Tetsu, O., Takahide, H., Hideki, M. A., Matsushime, H., Furuichi, K. Biochem. 2003.

Biophys. Res. Commun. 303: 364. 81. Soudijn, W., van Wijngaarden, I., Jzerman, A. P. 2007. Med. Res. Rev. 27:417. 82. Stacey, M., et al. 2002. EMR4, a novel epidermal growth factor (EGF)-TM7 molecule up-regulated in activated mouse macrophages, binds to a putative cellular ligand on B lymphoma cell line A20. J. Biol. Chem. 277: 29283-93. 83. Strosberg, A. D. 1993. Structure, function, and regulation of adrenergic receptors. Protein Sci. 2: 1198-1209. 84. Svedmyr, N., Harthon, L., Lundholm, L. 1969. Clin. Pharmacol. Ther. 10, 559. 85. Tada, T. and Tada, M. 2001. Toti/pluripotential stem cells and epigenetic modifications. Cell Struct Funct. 26: 149-160. 86. Valgeirsdottirl, S. 1998. PDGF induces reorganization of vimentin filaments. JCS. 111: 1973-1980. 87. Van de Klundert, F. A. J. M., Raats, J. M. H. and Bloemendal, H. 1993. Intermediate filaments: regulation of gene expression and assembly. Eur. J. Biochem. 214: 351-366. 88. Venter, J.C., et al. 2001. The sequence of the human genome. Science. 291: 1304-51. 89. Von Wangenheim, K. H., Schofield, R., Kyffin S. and Klein, B. 1977. Studies on erythorid-committed precursor cells in the policy-thaemic mouse. Biomed. 27: 337-340. 90. Wang, et al. 2006. Role of vimentin in smooth muscle force development. Physiol Cell Physiol. 291: 483-489. 91. Wise, A., Foord, S. M., Fraser, N. J., Barnes, A. A., Elshourbagy, N., Eilert, M., Ignar, D. M., Murdock, P. R., Steplewski, K., Green, A., Brown, A. J., Dowell, S. J., Szekeres, P. G., Hassall, D. G., Marshall, F. H., Wilson, S., Pike, N. B. J. 2003. Biol. Chem. 278: 9869. 92. Xiao-Dong, C., Chun-Hui, H., Xue-Jun, Z., Heng-Yue, X., Wei-Ying, Z., Lei, Y., Shu-Bing, Z. and Ruo-Lan, Q. 2004. Effects of Huangqi (Hex) on Inducing Cell Differentiation and Cell Death in K562 and HEL Cells. Acta Biochimica et Biophysica Sinica. 36:211-217. 93. Yonezawa, T., Yosuke, K., Yoshiaki, O. 2006. Short-chain fatty acids induce acute phosphorylation of the p38 mitogen-activated protein kinase/heat shock protein 27 pathway via GPR43 in the MCF-7 human breast cancer cell line. Cellular Signalling. 19: 185-193. 94. Zhang, Y., Schmidt, R. J., Foxworthy, P., Emkey, R., Oler, J. K., Large, T. H., Wang, H., Su, E. W., Mosior, M. K., Eacho, P. I., Cao, G. 2005. Biochem. Biophys. Res. Commun., 334, 729.