

7 **REFERENCES**

7. REFERENCES

- Abdel-Wahab, N., Wicks, S.J., Mason, R.M. and Chantry, A. (2002) Decorin suppresses transforming growth factor-beta-induced expression of plasminogen activator inhibitor-1 in human mesangial cells through a mechanism that involves Ca²⁺-dependent phosphorylation of Smad2 at serine-240. *Biochem J*, **362**, 643-649.
- Abdollah, S., Macias-Silva, M., Tsukazaki, T., Hayashi, H., Attisano, L. and Wrana, J.L. (1997) TbetaRI phosphorylation of Smad2 on Ser465 and Ser467 is required for Smad2-Smad4 complex formation and signaling. *J Biol Chem*, **272**, 27678-27685.
- An, S., Zheng, Y. and Bleu, T. (2000) Sphingosine 1-phosphate-induced cell proliferation, survival, and related signaling events mediated by G protein-coupled receptors Edg3 and Edg5. *J Biol Chem*, **275**, 288-296.
- Anand-Apte, B., Zetter, B.R., Viswanathan, A., Qiu, R.G., Chen, J., Ruggieri, R. and Symons, M. (1997) Platelet-derived growth factor and fibronectin-stimulated migration are differentially regulated by the Rac and extracellular signal-regulated kinase pathways. *J Biol Chem*, **272**, 30688-30692.
- Anborgh, P.H., Seachrist, J.L., Dale, L.B. and Ferguson, S.S. (2000) Receptor/beta-arrestin complex formation and the differential trafficking and resensitization of beta2-adrenergic and angiotensin II type 1A receptors. *Mol Endocrinol*, **14**, 2040-2053.
- Anders, R.A., Arline, S.L., Dore, J.J. and Leof, E.B. (1997) Distinct endocytic responses of heteromeric and homomeric transforming growth factor beta receptors. *Mol Biol Cell*, **8**, 2133-2143.
- Anders, R.A. and Leof, E.B. (1996) Chimeric granulocyte/macrophage colony-stimulating factor/transforming growth factor-beta (TGF-beta) receptors define a model system for investigating the role of homomeric and heteromeric receptors in TGF-beta signaling. *J Biol Chem*, **271**, 21758-21766.
- Anliker, B. and Chun, J. (2004) Lysophospholipid G protein-coupled receptors. *J Biol Chem*, **279**, 20555-20558.
- Anzano, M.A., Roberts, A.B., Smith, J.M., Sporn, M.B. and De Larco, J.E. (1983) Sarcoma growth factor from conditioned medium of virally transformed cells is composed of both type alpha and type beta transforming growth factors. *Proc Natl Acad Sci U S A*, **80**, 6264-6268.
- Ashcroft, G.S. and Roberts, A.B. (2000) Loss of Smad3 modulates wound healing. *Cytokine Growth Factor Rev*, **11**, 125-131.
- Ashcroft, G.S., Yang, X., Glick, A.B., Weinstein, M., Letterio, J.L., Mizel, D.E., Anzano, M., Greenwell-Wild, T., Wahl, S.M., Deng, C. and Roberts, A.B. (1999) Mice lacking Smad3 show accelerated wound healing and an impaired local inflammatory response. *Nat Cell Biol*, **1**, 260-266.
- Attisano, L., Carcamo, J., Ventura, F., Weis, F.M., Massague, J. and Wrana, J.L. (1993) Identification of human activin and TGF beta type I receptors that form heteromeric kinase complexes with type II receptors. *Cell*, **75**, 671-680.
- Attisano, L., Wrana, J.L., Cheifetz, S. and Massague, J. (1992) Novel activin receptors: distinct genes and alternative mRNA splicing generate a repertoire of serine/threonine kinase receptors. *Cell*, **68**, 97-108.
- Bai, M. (2004) Dimerization of G-protein-coupled receptors: roles in signal transduction. *Cell Signal*, **16**, 175-186.
- Bandyopadhyay, B., Fan, J., Guan, S., Li, Y., Chen, M., Woodley, D.T. and Li, W. (2006) A "traffic control" role for TGFbeta3: orchestrating dermal and epidermal cell motility during wound healing. *J Cell Biol*, **172**, 1093-1105.
- Belcheva, M.M., Haas, P.D., Tan, Y., Heaton, V.M. and Coscia, C.J. (2002) The fibroblast growth factor receptor is at the site of convergence between mu-opioid receptor and growth factor signaling pathways in rat C6 glioma cells. *J Pharmacol Exp Ther*, **303**, 909-918.
- Beningo, K.A., Dembo, M., Kaverina, I., Small, J.V. and Wang, Y.L. (2001) Nascent focal adhesions are responsible for the generation of strong propulsive forces in migrating fibroblasts. *J Cell Biol*, **153**, 881-888.
- Boguslawski, G., Grogg, J.R., Welch, Z., Ciechanowicz, S., Sliva, D., Kovala, A.T., McGlynn, P., Brindley, D.N., Rhoades, R.A. and English, D. (2002) Migration of vascular smooth muscle cells induced by sphingosine 1-phosphate and related lipids: potential role in the angiogenic response. *Exp Cell Res*, **274**, 264-274.

- Bosse, Y., Thompson, C., Stankova, J. and Rola-Pleszczynski, M. (2006) Fibroblast growth factor 2 and transforming growth factor beta1 synergism in human bronchial smooth muscle cell proliferation. *Am J Respir Cell Mol Biol*, **34**, 746-753.
- Bouvier, M. (2001) Oligomerization of G-protein-coupled transmitter receptors. *Nat Rev Neurosci*, **2**, 274-286.
- Bradford, M.M. (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal Biochem*, **72**, 248-254.
- Brennan, F.M., Maini, R.N. and Feldmann, M. (1998) Role of pro-inflammatory cytokines in rheumatoid arthritis. *Springer Semin Immunopathol*, **20**, 133-147.
- Carrillo, J.J., Pediani, J. and Milligan, G. (2003) Dimers of class A G protein-coupled receptors function via agonist-mediated trans-activation of associated G proteins. *J Biol Chem*, **278**, 42578-42587.
- Cary, L.A., Han, D.C., Polte, T.R., Hanks, S.K. and Guan, J.L. (1998) Identification of p130Cas as a mediator of focal adhesion kinase-promoted cell migration. *J Cell Biol*, **140**, 211-221.
- Centrella, M., Horowitz, M.C., Wozney, J.M. and McCarthy, T.L. (1994) Transforming growth factor-beta gene family members and bone. *Endocr Rev*, **15**, 27-39.
- Chen, Y.G., Hata, A., Lo, R.S., Wotton, D., Shi, Y., Pavletich, N. and Massague, J. (1998) Determinants of specificity in TGF-beta signal transduction. *Genes Dev*, **12**, 2144-2152.
- Chen, Y.G., Liu, F. and Massague, J. (1997) Mechanism of TGFbeta receptor inhibition by FKBP12. *Embo J*, **16**, 3866-3876.
- Chiang, N., Serhan, C.N., Dahlen, S.E., Drazen, J.M., Hay, D.W., Rovati, G.E., Shimizu, T., Yokomizo, T. and Brink, C. (2006) The lipoxin receptor ALX: potent ligand-specific and stereoselective actions in vivo. *Pharmacol Rev*, **58**, 463-487.
- Chicheportiche, Y., Chicheportiche, R., Sizing, I., Thompson, J., Benjamin, C.B., Ambrose, C. and Dayer, J.M. (2002) Proinflammatory activity of TWEAK on human dermal fibroblasts and synoviocytes: blocking and enhancing effects of anti-TWEAK monoclonal antibodies. *Arthritis Res*, **4**, 126-133.
- Chun, J., Goetzl, E.J., Hla, T., Igarashi, Y., Lynch, K.R., Moolenaar, W., Pyne, S. and Tigyi, G. (2002) International Union of Pharmacology. XXXIV. Lysophospholipid receptor nomenclature. *Pharmacol Rev*, **54**, 265-269.
- Clark, R.A. (1993) Regulation of fibroplasia in cutaneous wound repair. *Am J Med Sci*, **306**, 42-48.
- Condeelis, J. (2001) How is actin polymerization nucleated in vivo? *Trends Cell Biol*, **11**, 288-293.
- Condeelis, J., Singer, R.H. and Segall, J.E. (2005) The great escape: when cancer cells hijack the genes for chemotaxis and motility. *Annu Rev Cell Dev Biol*, **21**, 695-718.
- Correia, J.J., Chacko, B.M., Lam, S.S. and Lin, K. (2001) Sedimentation studies reveal a direct role of phosphorylation in Smad3:Smad4 homo- and hetero-trimerization. *Biochemistry*, **40**, 1473-1482.
- Cuvillier, O., Pirianov, G., Kleuser, B., Vanek, P.G., Coso, O.A., Gutkind, S. and Spiegel, S. (1996) Suppression of ceramide-mediated programmed cell death by sphingosine-1-phosphate. *Nature*, **381**, 800-803.
- de Caestecker, M.P., Parks, W.T., Frank, C.J., Castagnino, P., Bottaro, D.P., Roberts, A.B. and Lechleider, R.J. (1998) Smad2 transduces common signals from receptor serine-threonine and tyrosine kinases. *Genes Dev*, **12**, 1587-1592.
- del Pozo, M.A., Price, L.S., Alderson, N.B., Ren, X.D. and Schwartz, M.A. (2000) Adhesion to the extracellular matrix regulates the coupling of the small GTPase Rac to its effector PAK. *Embo J*, **19**, 2008-2014.
- Devi, L.A. (2001) Heterodimerization of G-protein-coupled receptors: pharmacology, signaling and trafficking. *Trends Pharmacol Sci*, **22**, 532-537.
- Devreotes, P. and Janetopoulos, C. (2003) Eukaryotic chemotaxis: distinctions between directional sensing and polarization. *J Biol Chem*, **278**, 20445-20448.
- di Clemente, N., Wilson, C., Faure, E., Boussin, L., Carmillo, P., Tizard, R., Picard, J.Y., Vigier, B., Josso, N. and Cate, R. (1994) Cloning, expression, and alternative splicing of the receptor for anti-Mullerian hormone. *Mol Endocrinol*, **8**, 1006-1020.
- Di Fiore, P.P. and De Camilli, P. (2001) Endocytosis and signaling. an inseparable partnership. *Cell*, **106**, 1-4.
- Di Guglielmo, G.M., Le Roy, C., Goodfellow, A.F. and Wrana, J.L. (2003) Distinct endocytic pathways regulate TGF-beta receptor signalling and turnover. *Nat Cell Biol*, **5**, 410-421.
- Donati, C., Meacci, E., Nuti, F., Becciolini, L., Farnararo, M. and Bruni, P. (2005) Sphingosine 1-phosphate regulates myogenic differentiation: a major role for S1P2 receptor. *Faseb J*, **19**, 449-451.

- Dudley, D.T., Pang, L., Decker, S.J., Bridges, A.J. and Saltiel, A.R. (1995) A synthetic inhibitor of the mitogen-activated protein kinase cascade. *Proc Natl Acad Sci U S A*, **92**, 7686-7689.
- Dutt, P., Jaffe, A.B., Merdek, K.D., Hall, A. and Toksoz, D. (2004) Galphaz inhibits serum response factor-dependent transcription by inhibiting Rho signaling. *Mol Pharmacol*, **66**, 1508-1516.
- Ehrlich, M., Shmueli, A. and Henis, Y.I. (2001) A single internalization signal from the di-leucine family is critical for constitutive endocytosis of the type II TGF-beta receptor. *J Cell Sci*, **114**, 1777-1786.
- Endo, A., Nagashima, K., Kurose, H., Mochizuki, S., Matsuda, M. and Mochizuki, N. (2002) Sphingosine 1-phosphate induces membrane ruffling and increases motility of human umbilical vein endothelial cells via vascular endothelial growth factor receptor and CrkII. *J Biol Chem*, **277**, 23747-23754.
- English, D., Welch, Z., Kovala, A.T., Harvey, K., Volpert, O.V., Brindley, D.N. and Garcia, J.G. (2000) Sphingosine 1-phosphate released from platelets during clotting accounts for the potent endothelial cell chemotactic activity of blood serum and provides a novel link between hemostasis and angiogenesis. *Faseb J*, **14**, 2255-2265.
- Evers, E.E., Zondag, G.C., Malliri, A., Price, L.S., ten Klooster, J.P., van der Kammen, R.A. and Collard, J.G. (2000) Rho family proteins in cell adhesion and cell migration. *Eur J Cancer*, **36**, 1269-1274.
- Faix, J. and Rottner, K. (2006) The making of filopodia. *Curr Opin Cell Biol*, **18**, 18-25.
- Fanayan, S., Firth, S.M. and Baxter, R.C. (2002) Signaling through the Smad pathway by insulin-like growth factor-binding protein-3 in breast cancer cells. Relationship to transforming growth factor-beta 1 signaling. *J Biol Chem*, **277**, 7255-7261.
- Fanayan, S., Firth, S.M., Butt, A.J. and Baxter, R.C. (2000) Growth inhibition by insulin-like growth factor-binding protein-3 in T47D breast cancer cells requires transforming growth factor-beta (TGF-beta) and the type II TGF-beta receptor. *J Biol Chem*, **275**, 39146-39151.
- Felsenfeld, D.P., Choquet, D. and Sheetz, M.P. (1996) Ligand binding regulates the directed movement of beta1 integrins on fibroblasts. *Nature*, **383**, 438-440.
- Felsenfeld, D.P., Schwartzberg, P.L., Venegas, A., Tse, R. and Sheetz, M.P. (1999) Selective regulation of integrin-cytoskeleton interactions by the tyrosine kinase Src. *Nat Cell Biol*, **1**, 200-206.
- Ferguson, S.S. (2001) Evolving concepts in G protein-coupled receptor endocytosis: the role in receptor desensitization and signaling. *Pharmacol Rev*, **53**, 1-24.
- Fieber, C.B., Eldridge, J., Taha, T.A., Obeid, L.M. and Muise-Helmericks, R.C. (2006) Modulation of total Akt kinase by increased expression of a single isoform: requirement of the sphingosine-1-phosphate receptor, Edg3/S1P3, for the VEGF-dependent expression of Akt3 in primary endothelial cells. *Exp Cell Res*, **312**, 1164-1173.
- Franzen, P., ten Dijke, P., Ichijo, H., Yamashita, H., Schulz, P., Heldin, C.H. and Miyazono, K. (1993) Cloning of a TGF beta type I receptor that forms a heteromeric complex with the TGF beta type II receptor. *Cell*, **75**, 681-692.
- Frolik, C.A., Wakefield, L.M., Smith, D.M. and Sporn, M.B. (1984) Characterization of a membrane receptor for transforming growth factor-beta in normal rat kidney fibroblasts. *J Biol Chem*, **259**, 10995-11000.
- Fujishiro, J., Kudou, S., Iwai, S., Takahashi, M., Hakamata, Y., Kinoshita, M., Iwanami, S., Izawa, S., Yasue, T., Hashizume, K., Murakami, T. and Kobayashi, E. (2006) Use of sphingosine-1-phosphate 1 receptor agonist, KRP-203, in combination with a subtherapeutic dose of cyclosporine A for rat renal transplantation. *Transplantation*, **82**, 804-812.
- Futerman, A.H. and Hannun, Y.A. (2004) The complex life of simple sphingolipids. *EMBO Rep*, **5**, 777-782.
- Galbraith, C.G., Yamada, K.M. and Sheetz, M.P. (2002) The relationship between force and focal complex development. *J Cell Biol*, **159**, 695-705.
- Garamszegi, N., Dore, J.J., Jr., Penheiter, S.G., Edens, M., Yao, D. and Leof, E.B. (2001) Transforming growth factor beta receptor signaling and endocytosis are linked through a COOH terminal activation motif in the type I receptor. *Mol Biol Cell*, **12**, 2881-2893.
- George, S.R., O'Dowd, B.F. and Lee, S.P. (2002) G-protein-coupled receptor oligomerization and its potential for drug discovery. *Nat Rev Drug Discov*, **1**, 808-820.
- Goetzl, E.J. and An, S. (1998) Diversity of cellular receptors and functions for the lysophospholipid growth factors lysophosphatidic acid and sphingosine 1-phosphate. *Faseb J*, **12**, 1589-1598.
- Goparaju, S.K., Jolly, P.S., Watterson, K.R., Bektas, M., Alvarez, S., Sarkar, S., Mel, L., Ishii, I., Chun, J., Milstien, S. and Spiegel, S. (2005) The S1P2 receptor negatively regulates platelet-derived growth factor-induced motility and proliferation. *Mol Cell Biol*, **25**, 4237-4249.

- Graeler, M. and Goetzl, E.J. (2002) Activation-regulated expression and chemotactic function of sphingosine 1-phosphate receptors in mouse splenic T cells. *Faseb J.*, **16**, 1874-1878.
- Graler, M.H., Bernhardt, G. and Lipp, M. (1998) EDG6, a novel G-protein-coupled receptor related to receptors for bioactive lysophospholipids, is specifically expressed in lymphoid tissue. *Genomics*, **53**, 164-169.
- Graler, M.H., Grosse, R., Kusch, A., Kremmer, E., Gudermann, T. and Lipp, M. (2003) The sphingosine 1-phosphate receptor S1P4 regulates cell shape and motility via coupling to Gi and G12/13. *J Cell Biochem*, **89**, 507-519.
- Grande, M., Franzen, A., Karlsson, J.O., Ericson, L.E., Hedin, N.E. and Nilsson, M. (2002) Transforming growth factor-beta and epidermal growth factor synergistically stimulate epithelial to mesenchymal transition (EMT) through a MEK-dependent mechanism in primary cultured pig thyrocytes. *J Cell Sci*, **115**, 4227-4236.
- Hall, A. (1998) Rho GTPases and the actin cytoskeleton. *Science*, **279**, 509-514.
- Hall, R.A., Premont, R.T. and Lefkowitz, R.J. (1999) Heptahelical receptor signaling: beyond the G protein paradigm. *J Cell Biol*, **145**, 927-932.
- Hayes, S., Chawla, A. and Corvera, S. (2002) TGF beta receptor internalization into EEA1-enriched early endosomes: role in signaling to Smad2. *J Cell Biol*, **158**, 1239-1249.
- Herrlich, A., Daub, H., Knebel, A., Herrlich, P., Ullrich, A., Schultz, G. and Gudermann, T. (1998) Ligand-independent activation of platelet-derived growth factor receptor is a necessary intermediate in lysophosphatidic, acid-stimulated mitogenic activity in L cells. *Proc Natl Acad Sci U S A*, **95**, 8985-8990.
- Hla, T. and Maciag, T. (1990) An abundant transcript induced in differentiating human endothelial cells encodes a polypeptide with structural similarities to G-protein-coupled receptors. *J Biol Chem*, **265**, 9308-9313.
- Hobson, J.P., Rosenfeldt, H.M., Barak, L.S., Olivera, A., Poulton, S., Caron, M.G., Milstien, S. and Spiegel, S. (2001) Role of the sphingosine-1-phosphate receptor EDG-1 in PDGF-induced cell motility. *Science*, **291**, 1800-1803.
- Hsieh, H.L., Wu, C.B., Sun, C.C., Liao, C.H., Lau, Y.T. and Yang, C.M. (2006) Sphingosine-1-phosphate induces COX-2 expression via PI3K/Akt and p42/p44 MAPK pathways in rat vascular smooth muscle cells. *J Cell Physiol*, **207**, 757-766.
- Huang, J.S., Mukherjee, J.J. and Kiss, Z. (1999) Ethanol potentiates the mitogenic effects of sphingosine 1-phosphate by a zinc- and calcium-dependent mechanism in fibroblasts. *Arch Biochem Biophys*, **366**, 131-138.
- Hur, E.M. and Kim, K.T. (2002) G protein-coupled receptor signalling and cross-talk: achieving rapidity and specificity. *Cell Signal*, **14**, 397-405.
- Huse, M., Muir, T.W., Xu, L., Chen, Y.G., Kuriyan, J. and Massague, J. (2001) The TGF beta receptor activation process: an inhibitor- to substrate-binding switch. *Mol Cell*, **8**, 671-682.
- Igarashi, J., Erwin, P.A., Dantas, A.P., Chen, H. and Michel, T. (2003) VEGF induces S1P1 receptors in endothelial cells: Implications for cross-talk between sphingolipid and growth factor receptors. *Proc Natl Acad Sci U S A*, **100**, 10664-10669.
- Igarashi, J. and Michel, T. (2001) Sphingosine 1-phosphate and isoform-specific activation of phosphoinositide 3-kinase beta. Evidence for divergence and convergence of receptor-regulated endothelial nitric-oxide synthase signaling pathways. *J Biol Chem*, **276**, 36281-36288.
- Ilic, D., Furuta, Y., Kanazawa, S., Takeda, N., Sobue, K., Nakatsuji, N., Nomura, S., Fujimoto, J., Okada, M. and Yamamoto, T. (1995) Reduced cell motility and enhanced focal adhesion contact formation in cells from FAK-deficient mice. *Nature*, **377**, 539-544.
- Im, D.S., Heise, C.E., Ancellin, N., O'Dowd, B.F., Shei, G.J., Heavens, R.P., Rigby, M.R., Hla, T., Mandala, S., McAllister, G., George, S.R. and Lynch, K.R. (2000) Characterization of a novel sphingosine 1-phosphate receptor, Edg-8. *J Biol Chem*, **275**, 14281-14286.
- Imanishi, J., Kamiyama, K., Iguchi, I., Kita, M., Sotozono, C. and Kinoshita, S. (2000) Growth factors: importance in wound healing and maintenance of transparency of the cornea. *Prog Retin Eye Res*, **19**, 113-129.
- Inman, G.J., Nicolas, F.J., Callahan, J.F., Harling, J.D., Gaster, L.M., Reith, A.D., Laping, N.J. and Hill, C.S. (2002) SB-431542 is a potent and specific inhibitor of transforming growth factor-beta superfamily type I activin receptor-like kinase (ALK) receptors ALK4, ALK5, and ALK7. *Mol Pharmacol*, **62**, 65-74.
- Inoue, H., Nojima, H. and Okayama, H. (1990) High efficiency transformation of Escherichia coli with plasmids. *Gene*, **96**, 23-28.

REFERENCES

- Ishii, I., Friedman, B., Ye, X., Kawamura, S., McGiffert, C., Contos, J.J., Kingsbury, M.A., Zhang, G., Brown, J.H. and Chun, J. (2001) Selective loss of sphingosine 1-phosphate signaling with no obvious phenotypic abnormality in mice lacking its G protein-coupled receptor, LP(B3)/EDG-3. *J Biol Chem*, **276**, 33697-33704.
- Ishii, I., Ye, X., Friedman, B., Kawamura, S., Contos, J.J., Kingsbury, M.A., Yang, A.H., Zhang, G., Brown, J.H. and Chun, J. (2002) Marked perinatal lethality and cellular signaling deficits in mice null for the two sphingosine 1-phosphate (S1P) receptors, S1P(2)/LP(B2)/EDG-5 and S1P(3)/LP(B3)/EDG-3. *J Biol Chem*, **277**, 25152-25159.
- Itoh, F., Divecha, N., Brocks, L., Oomen, L., Janssen, H., Calafat, J., Itoh, S. and Dijke Pt, P. (2002a) The FYVE domain in Smad anchor for receptor activation (SARA) is sufficient for localization of SARA in early endosomes and regulates TGF-beta/Smad signalling. *Genes Cells*, **7**, 321-331.
- Itoh, R.E., Kurokawa, K., Ohba, Y., Yoshizaki, H., Mochizuki, N. and Matsuda, M. (2002b) Activation of rac and cdc42 visualized by fluorescent resonance energy transfer-based single-molecule probes in the membrane of living cells. *Mol Cell Biol*, **22**, 6582-6591.
- Jaillard, C., Harrison, S., Stankoff, B., Aigrot, M.S., Calver, A.R., Duddy, G., Walsh, F.S., Pangalos, M.N., Arimura, N., Kaibuchi, K., Zalc, B. and Lubetzki, C. (2005) Edg8/S1P5: an oligodendroglial receptor with dual function on process retraction and cell survival. *J Neurosci*, **25**, 1459-1469.
- Janda, E., Nevolo, M., Lehmann, K., Downward, J., Beug, H. and Grieco, M. (2006) Raf plus TGFbeta-dependent EMT is initiated by endocytosis and lysosomal degradation of E-cadherin. *Oncogene*, **25**, 7117-7130.
- Jolly, P.S., Bektas, M., Olivera, A., Gonzalez-Espinosa, C., Proia, R.L., Rivera, J., Milstien, S. and Spiegel, S. (2004) Transactivation of sphingosine-1-phosphate receptors by Fc epsilon RI triggering is required for normal mast cell degranulation and chemotaxis. *J Exp Med*, **199**, 959-970.
- Kawabata, M., Inoue, H., Hanyu, A., Imamura, T. and Miyazono, K. (1998) Smad proteins exist as monomers in vivo and undergo homo- and hetero-oligomerization upon activation by serine/threonine kinase receptors. *Embo J*, **17**, 4056-4065.
- Kawaguchi, Y., Nishimagi, E., Tochimoto, A., Kawamoto, M., Katsumata, Y., Soejima, M., Kanno, T., Kamatani, N. and Hara, M. (2006) Intracellular IL-1 α -binding proteins contribute to biological functions of endogenous IL-1 α in systemic sclerosis fibroblasts. *Proc Natl Acad Sci U S A*, **103**, 14501-14506.
- Keller, C.D., Rivera Gil, P., Tolle, M., van der Giet, M., Chun, J., Radeke, H.H., Schafer-Korting, M. and Kleuser, B. (2007) Immunomodulator FTY720 Induces Myofibroblast Differentiation via the Lysophospholipid Receptor S1P3 and Smad3 Signaling. *Am J Pathol*, **170**, 281-292.
- Kim, D.S., Kim, S.Y., Kleuser, B., Schafer-Korting, M., Kim, K.H. and Park, K.C. (2004) Sphingosine-1-phosphate inhibits human keratinocyte proliferation via Akt/protein kinase B inactivation. *Cell Signal*, **16**, 89-95.
- Kim, J.H., Kim, J.H., Song, W.K., Kim, J.H. and Chun, J.S. (2000) Sphingosine 1-phosphate activates Erk-1/-2 by transactivating epidermal growth factor receptor in rat-2 cells. *IUBMB Life*, **50**, 119-124.
- Kimura, T., Watanabe, T., Sato, K., Kon, J., Tomura, H., Tamama, K., Kuwabara, A., Kanda, T., Kobayashi, I., Ohta, H., Ui, M. and Okajima, F. (2000) Sphingosine 1-phosphate stimulates proliferation and migration of human endothelial cells possibly through the lipid receptors, Edg-1 and Edg-3. *Biochem J*, **348 Pt 1**, 71-76.
- Kiosses, W.B., Shattil, S.J., Pampori, N. and Schwartz, M.A. (2001) Rac recruits high-affinity integrin alphavbeta3 to lamellipodia in endothelial cell migration. *Nat Cell Biol*, **3**, 316-320.
- Klemke, R.L., Leng, J., Molander, R., Brooks, P.C., Vuori, K. and Cheresh, D.A. (1998) CAS/Crk coupling serves as a "molecular switch" for induction of cell migration. *J Cell Biol*, **140**, 961-972.
- Kohama, T., Olivera, A., Edsall, L., Nagiec, M.M., Dickson, R. and Spiegel, S. (1998) Molecular cloning and functional characterization of murine sphingosine kinase. *J Biol Chem*, **273**, 23722-23728.
- Kohno, T., Matsuyuki, H., Inagaki, Y. and Igarashi, Y. (2003) Sphingosine 1-phosphate promotes cell migration through the activation of Cdc42 in Edg-6/S1P4-expressing cells. *Genes Cells*, **8**, 685-697.
- Kolesnick, R.N. (1987) 1,2-Diacylglycerols but not phorbol esters stimulate sphingomyelin hydrolysis in GH3 pituitary cells. *J Biol Chem*, **262**, 16759-16762.

- Koli, K., Hytytainen, M., Ryynanen, M.J. and Keski-Oja, J. (2005) Sequential deposition of latent TGF-beta binding proteins (LTBPs) during formation of the extracellular matrix in human lung fibroblasts. *Exp Cell Res*, **310**, 370-382.
- Kolodziej, P.A. and Young, R.A. (1991) Epitope tagging and protein surveillance. *Methods Enzymol*, **194**, 508-519.
- Kon, J., Sato, K., Watanabe, T., Tomura, H., Kuwabara, A., Kimura, T., Tamama, K., Ishizuka, T., Murata, N., Kanda, T., Kobayashi, I., Ohta, H., Ui, M. and Okajima, F. (1999) Comparison of intrinsic activities of the putative sphingosine 1-phosphate receptor subtypes to regulate several signaling pathways in their cDNA-transfected Chinese hamster ovary cells. *J Biol Chem*, **274**, 23940-23947.
- Konttinen, Y.T., Li, T.F., Hukkanen, M., Ma, J., Xu, J.W. and Virtanen, I. (2000) Fibroblast biology. Signals targeting the synovial fibroblast in arthritis. *Arthritis Res*, **2**, 348-355.
- Kostenis, E. (2004) Novel clusters of receptors for sphingosine-1-phosphate, sphingosylphosphorylcholine, and (lyso)-phosphatidic acid: new receptors for "old" ligands. *J Cell Biochem*, **92**, 923-936.
- Kretzschmar, M., Doody, J. and Massague, J. (1997) Opposing BMP and EGF signalling pathways converge on the TGF-beta family mediator Smad1. *Nature*, **389**, 618-622.
- Kretzschmar, M., Doody, J., Timokhina, I. and Massague, J. (1999) A mechanism of repression of TGFbeta/ Smad signaling by oncogenic Ras. *Genes Dev*, **13**, 804-816.
- Kupperman, E., An, S., Osborne, N., Waldron, S. and Stainier, D.Y. (2000) A sphingosine-1-phosphate receptor regulates cell migration during vertebrate heart development. *Nature*, **406**, 192-195.
- Laping, N.J., Grygielko, E., Mathur, A., Butter, S., Bomberger, J., Tweed, C., Martin, W., Fornwald, J., Lehr, R., Harling, J., Gaster, L., Callahan, J.F. and Olson, B.A. (2002) Inhibition of transforming growth factor (TGF)-beta1-induced extracellular matrix with a novel inhibitor of the TGF-beta type I receptor kinase activity: SB-431542. *Mol Pharmacol*, **62**, 58-64.
- Larkin, J.M., Donzell, W.C. and Anderson, R.G. (1986) Potassium-dependent assembly of coated pits: new coated pits form as planar clathrin lattices. *J Cell Biol*, **103**, 2619-2627.
- Larsen, K., Malmstrom, J., Wildt, M., Dahlqvist, C., Hansson, L., Marko-Varga, G., Bjermer, L., Scheja, A. and Westergren-Thorsson, G. (2006) Functional and phenotypical comparison of myofibroblasts derived from biopsies and bronchoalveolar lavage in mild asthma and scleroderma. *Respir Res*, **7**, 11.
- Lauffenburger, D.A. and Horwitz, A.F. (1996) Cell migration: a physically integrated molecular process. *Cell*, **84**, 359-369.
- Le Stunff, H., Mikami, A., Giussani, P., Hobson, J.P., Jolly, P.S., Milstien, S. and Spiegel, S. (2004) Role of sphingosine-1-phosphate phosphatase 1 in epidermal growth factor-induced chemotaxis. *J Biol Chem*, **279**, 34290-34297.
- Lee, H., Zahra, D., Vogelzang, A., Newton, R., Thatcher, J., Quan, A., So, T., Zwirner, J., Koentgen, F., Padkjaer, S.B., Mackay, F., Whitfeld, P.L. and Mackay, C.R. (2006a) Human C5aR knock-in mice facilitate the production and assessment of anti-inflammatory monoclonal antibodies. *Nat Biotechnol*.
- Lee, J.F., Ozaki, H., Zhan, X., Wang, E., Hla, T. and Lee, M.J. (2006b) Sphingosine-1-phosphate signaling regulates lamellipodia localization of cortactin complexes in endothelial cells. *Histochem Cell Biol*, **126**, 297-304.
- Lee, M.J., Thangada, S., Claffey, K.P., Ancellin, N., Liu, C.H., Kluk, M., Volpi, M., Sha'afi, R.I. and Hla, T. (1999) Vascular endothelial cell adherens junction assembly and morphogenesis induced by sphingosine-1-phosphate. *Cell*, **99**, 301-312.
- Lefkowitz, R.J. (1998) G protein-coupled receptors. III. New roles for receptor kinases and beta-arrestins in receptor signaling and desensitization. *J Biol Chem*, **273**, 18677-18680.
- Lefkowitz, R.J. and Whalen, E.J. (2004) beta-arrestins: traffic cops of cell signaling. *Curr Opin Cell Biol*, **16**, 162-168.
- Lepley, D., Paik, J.H., Hla, T. and Ferrer, F. (2005) The G protein-coupled receptor S1P2 regulates Rho/Rho kinase pathway to inhibit tumor cell migration. *Cancer Res*, **65**, 3788-3795.
- Li, J., Lee, G.I., Van Doren, S.R. and Walker, J.C. (2000) The FHA domain mediates phosphoprotein interactions. *J Cell Sci*, **113 Pt 23**, 4143-4149.
- Limaye, V., Li, X., Hahn, C., Xia, P., Berndt, M.C., Vadas, M.A. and Gamble, J.R. (2005) Sphingosine kinase-1 enhances endothelial cell survival through a PECAM-1-dependent activation of PI-3K/Akt and regulation of Bcl-2 family members. *Blood*, **105**, 3169-3177.

- Lin, H.Y., Wang, X.F., Ng-Eaton, E., Weinberg, R.A. and Lodish, H.F. (1992) Expression cloning of the TGF-beta type II receptor, a functional transmembrane serine/threonine kinase. *Cell*, **68**, 775-785.
- Lin, J., Liu, J., Wang, Y., Zhu, J., Zhou, K., Smith, N. and Zhan, X. (2005) Differential regulation of cortactin and N-WASP-mediated actin polymerization by missing in metastasis (MIM) protein. *Oncogene*, **24**, 2059-2066.
- Liu, F., Ventura, F., Doody, J. and Massague, J. (1995) Human type II receptor for bone morphogenic proteins (BMPs): extension of the two-kinase receptor model to the BMPs. *Mol Cell Biol*, **15**, 3479-3486.
- Liu, H., Sugiura, M., Nava, V.E., Edsall, L.C., Kono, K., Poulton, S., Milstien, S., Kohama, T. and Spiegel, S. (2000a) Molecular cloning and functional characterization of a novel mammalian sphingosine kinase type 2 isoform. *J Biol Chem*, **275**, 19513-19520.
- Liu, Y., Wada, R., Yamashita, T., Mi, Y., Deng, C.X., Hobson, J.P., Rosenfeldt, H.M., Nava, V.E., Chae, S.S., Lee, M.J., Liu, C.H., Hla, T., Spiegel, S. and Proia, R.L. (2000b) Edg-1, the G protein-coupled receptor for sphingosine-1-phosphate, is essential for vascular maturation. *J Clin Invest*, **106**, 951-961.
- Lo, R.S. and Massague, J. (1999) Ubiquitin-dependent degradation of TGF-beta-activated smad2. *Nat Cell Biol*, **1**, 472-478.
- Long, J.S., Natarajan, V., Tigyi, G., Pyne, S. and Pyne, N.J. (2006) The functional PDGFbeta receptor-S1P1 receptor signaling complex is involved in regulating migration of mouse embryonic fibroblasts in response to platelet derived growth factor. *Prostaglandins Other Lipid Mediat*, **80**, 74-80.
- Lu, M., Munger, J.S., Steadale, M., Busald, C., Tellier, M. and Schnapp, L.M. (2002a) Integrin alpha8beta1 mediates adhesion to LAP-TGFbeta1. *J Cell Sci*, **115**, 4641-4648.
- Lu, Z., Murray, J.T., Luo, W., Li, H., Wu, X., Xu, H., Backer, J.M. and Chen, Y.G. (2002b) Transforming growth factor beta activates Smad2 in the absence of receptor endocytosis. *J Biol Chem*, **277**, 29363-29368.
- Lundeen, K.A., Sun, B., Karlsson, L. and Fourie, A.M. (2006) Leukotriene B4 receptors BLT1 and BLT2: expression and function in human and murine mast cells. *J Immunol*, **177**, 3439-3447.
- Luo, K. and Lodish, H.F. (1996) Signaling by chimeric erythropoietin-TGF-beta receptors: homodimerization of the cytoplasmic domain of the type I TGF-beta receptor and heterodimerization with the type II receptor are both required for intracellular signal transduction. *Embo J*, **15**, 4485-4496.
- Luo, K. and Lodish, H.F. (1997) Positive and negative regulation of type II TGF-beta receptor signal transduction by autophosphorylation on multiple serine residues. *Embo J*, **16**, 1970-1981.
- Luttrell, L.M. (2006) Transmembrane signaling by G protein-coupled receptors. *Methods Mol Biol*, **332**, 3-49.
- Maceyka, M., Payne, S.G., Milstien, S. and Spiegel, S. (2002) Sphingosine kinase, sphingosine-1-phosphate, and apoptosis. *Biochim Biophys Acta*, **1585**, 193-201.
- Maceyka, M., Sankala, H., Hait, N.C., Le Stunff, H., Liu, H., Toman, R., Collier, C., Zhang, M., Satin, L.S., Merrill, A.H., Jr., Milstien, S. and Spiegel, S. (2005) SphK1 and SphK2, sphingosine kinase isoenzymes with opposing functions in sphingolipid metabolism. *J Biol Chem*, **280**, 37118-37129.
- Macias-Silva, M., Abdollah, S., Hoodless, P.A., Pirone, R., Attisano, L. and Wrana, J.L. (1996) MADR2 is a substrate of the TGFbeta receptor and its phosphorylation is required for nuclear accumulation and signaling. *Cell*, **87**, 1215-1224.
- MacLennan, A.J., Carney, P.R., Zhu, W.J., Chaves, A.H., Garcia, J., Grimes, J.R., Anderson, K.J., Roper, S.N. and Lee, N. (2001) An essential role for the H218/AGR16/Edg-5/LP(B2) sphingosine 1-phosphate receptor in neuronal excitability. *Eur J Neurosci*, **14**, 203-209.
- Malek, D., Gust, R. and Kleuser, B. (2006) 17-Beta-estradiol inhibits transforming-growth-factor-beta-induced MCF-7 cell migration by Smad3-repression. *Eur J Pharmacol*, **534**, 39-47.
- Malek, R.L., Toman, R.E., Edsall, L.C., Wong, S., Chiu, J., Letterle, C.A., Van Brocklyn, J.R., Milstien, S., Spiegel, S. and Lee, N.H. (2001) Nrg-1 belongs to the endothelial differentiation gene family of G protein-coupled sphingosine-1-phosphate receptors. *J Biol Chem*, **276**, 5692-5699.
- Massague, J. (1998) TGF-beta signal transduction. *Annu Rev Biochem*, **67**, 753-791.
- Massague, J. (1999) Wounding Smad. *Nat Cell Biol*, **1**, E117-119.
- Massague, J. and Chen, Y.G. (2000) Controlling TGF-beta signaling. *Genes Dev*, **14**, 627-644.
- Matsuura, I., Wang, G., He, D. and Liu, F. (2005) Identification and characterization of ERK MAP kinase phosphorylation sites in Smad3. *Biochemistry*, **44**, 12546-12553.

- McPherson, P.S., Kay, B.K. and Hussain, N.K. (2001) Signaling on the endocytic pathway. *Traffic*, **2**, 375-384.
- Meacci, E., Cencetti, F., Donati, C., Nuti, F., Farnararo, M., Kohno, T., Igarashi, Y. and Bruni, P. (2003) Down-regulation of EDG5/S1P2 during myogenic differentiation results in the specific uncoupling of sphingosine 1-phosphate signalling to phospholipase D. *Biochim Biophys Acta*, **1633**, 133-142.
- Merlot, S. and Firtel, R.A. (2003) Leading the way: Directional sensing through phosphatidylinositol 3-kinase and other signaling pathways. *J Cell Sci*, **116**, 3471-3478.
- Meyer zu Heringdorf, D., Lass, H., Alemany, R., Laser, K.T., Neumann, E., Zhang, C., Schmidt, M., Rauen, U., Jakobs, K.H. and van Koppen, C.J. (1998) Sphingosine kinase-mediated Ca²⁺ signalling by G-protein-coupled receptors. *Embo J*, **17**, 2830-2837.
- Miao, H.Q. and Klagsbrun, M. (2000) Neuropilin is a mediator of angiogenesis. *Cancer Metastasis Rev*, **19**, 29-37.
- Millard, T.H., Sharp, S.J. and Machesky, L.M. (2004) Signalling to actin assembly via the WASP (Wiskott-Aldrich syndrome protein)-family proteins and the Arp2/3 complex. *Biochem J*, **380**, 1-17.
- Milligan, G. (2001) Oligomerisation of G-protein-coupled receptors. *J Cell Sci*, **114**, 1265-1271.
- Minguillon, J., Moráncho, B., Kim, S.J., López-Botet, M. and Aramburu, J. (2005) Concentrations of cyclosporin A and FK506 that inhibit IL-2 induction in human T cells do not affect TGF-beta1 biosynthesis, whereas higher doses of cyclosporin A trigger apoptosis and release of preformed TGF-beta1. *J Leukoc Biol*, **77**, 748-758.
- Miura, S., Takeshita, T., Asao, H., Kimura, Y., Murata, K., Sasaki, Y., Hanai, J.I., Beppu, H., Tsukazaki, T., Wrana, J.L., Miyazono, K. and Sugamura, K. (2000a) Hgs (Hrs), a FYVE domain protein, is involved in Smad signaling through cooperation with SARA. *Mol Cell Biol*, **20**, 9346-9355.
- Miura, Y., Yatomi, Y., Rile, G., Ohmori, T., Satoh, K. and Ozaki, Y. (2000b) Rho-mediated phosphorylation of focal adhesion kinase and myosin light chain in human endothelial cells stimulated with sphingosine 1-phosphate, a bioactive lysophospholipid released from activated platelets. *J Biochem (Tokyo)*, **127**, 909-914.
- Mizejewski, G.J. (1999) Role of integrins in cancer: survey of expression patterns. *Proc Soc Exp Biol Med*, **222**, 124-138.
- Morales-Ruiz, M., Lee, M.J., Zollner, S., Gratton, J.P., Scotland, R., Shiojima, I., Walsh, K., Hla, T. and Sessa, W.C. (2001) Sphingosine 1-phosphate activates Akt, nitric oxide production, and chemotaxis through a Gi protein/phosphoinositide 3-kinase pathway in endothelial cells. *J Biol Chem*, **276**, 19672-19677.
- Moustakas, A., Souchelnytskyi, S. and Heldin, C.H. (2001) Smad regulation in TGF-beta signal transduction. *J Cell Sci*, **114**, 4359-4369.
- Muramatsu, M., Yan, J., Eto, K., Tomoda, T., Yamada, R. and Arai, K. (1997) A chimeric serine/threonine kinase receptor system reveals the potential of multiple type II receptors to cooperate with transforming growth factor-beta type I receptor. *Mol Biol Cell*, **8**, 469-480.
- Murata, N., Sato, K., Kon, J., Tomura, H., Yanagita, M., Kuwabara, A., Ui, M. and Okajima, F. (2000) Interaction of sphingosine 1-phosphate with plasma components, including lipoproteins, regulates the lipid receptor-mediated actions. *Biochem J*, **352 Pt 3**, 809-815.
- Nelson, R.D., Gracyk, J.M., Fiegel, V.D., Herron, M.J. and Chenoweth, D.E. (1981) Chemotactic deactivation of human neutrophils: protective influence of phenylbutazone. *Blood*, **58**, 752-758.
- Nicholson-Dykstra, S., Higgs, H.N. and Harris, E.S. (2005) Actin dynamics: growth from dendritic branches. *Curr Biol*, **15**, R346-357.
- Nickl-Jockschat, T., Arslan, F., Doerfelt, A., Bogdahn, U., Bosserhoff, A. and Hau, P. (2007) An imbalance between Smad and MAPK pathways is responsible for TGF-beta tumor promoting effects in high-grade gliomas. *Int J Oncol*, **30**, 499-507.
- Ohmori, T., Yatomi, Y., Okamoto, H., Miura, Y., Rile, G., Satoh, K. and Ozaki, Y. (2001) G(i)-mediated Cas tyrosine phosphorylation in vascular endothelial cells stimulated with sphingosine 1-phosphate: possible involvement in cell motility enhancement in cooperation with Rho-mediated pathways. *J Biol Chem*, **276**, 5274-5280.
- Okamoto, H., Takuwa, N., Yokomizo, T., Sugimoto, N., Sakurada, S., Shigematsu, H. and Takuwa, Y. (2000a) Inhibitory regulation of Rac activation, membrane ruffling, and cell migration by the G protein-coupled sphingosine-1-phosphate receptor EDG5 but not EDG1 or EDG3. *Mol Cell Biol*, **20**, 9247-9261.

- Okamoto, H., Yatomi, Y., Ohmori, T., Satoh, K., Matsumoto, Y. and Ozaki, Y. (2000b) Sphingosine 1-phosphate stimulates G(i)- and Rho-mediated vascular endothelial cell spreading and migration. *Thromb Res*, **99**, 259-265.
- Oklu, R. and Hesketh, R. (2000) The latent transforming growth factor beta binding protein (LTBP) family. *Biochem J*, **352 Pt 3**, 601-610.
- Olivera, A., Kohama, T., Edsall, L., Nava, V., Cuvillier, O., Poulton, S. and Spiegel, S. (1999) Sphingosine kinase expression increases intracellular sphingosine-1-phosphate and promotes cell growth and survival. *J Cell Biol*, **147**, 545-558.
- Olivera, A. and Rivera, J. (2005) Sphingolipids and the balancing of immune cell function: lessons from the mast cell. *J Immunol*, **174**, 1153-1158.
- Olivera, A., Rosenfeldt, H.M., Bektas, M., Wang, F., Ishii, I., Chun, J., Milstien, S. and Spiegel, S. (2003) Sphingosine kinase type 1 induces G12/13-mediated stress fiber formation, yet promotes growth and survival independent of G protein-coupled receptors. *J Biol Chem*, **278**, 46452-46460.
- Penheiter, S.G., Mitchell, H., Garamszegi, N., Edens, M., Dore, J.J., Jr. and Leof, E.B. (2002) Internalization-dependent and -independent requirements for transforming growth factor beta receptor signaling via the Smad pathway. *Mol Cell Biol*, **22**, 4750-4759.
- Pettus, B.J., Kitatani, K., Chalfant, C.E., Taha, T.A., Kawamori, T., Bielawski, J., Obeid, L.M. and Hannun, Y.A. (2005) The coordination of prostaglandin E2 production by sphingosine-1-phosphate and ceramide-1-phosphate. *Mol Pharmacol*, **68**, 330-335.
- Pierce, K.L., Maudsley, S., Daaka, Y., Luttrell, L.M. and Lefkowitz, R.J. (2000) Role of endocytosis in the activation of the extracellular signal-regulated kinase cascade by sequestering and nonsequestering G protein-coupled receptors. *Proc Natl Acad Sci U S A*, **97**, 1489-1494.
- Pierreux, C.E., Nicolas, F.J. and Hill, C.S. (2000) Transforming growth factor beta-independent shuttling of Smad4 between the cytoplasm and nucleus. *Mol Cell Biol*, **20**, 9041-9054.
- Pollard, T.D. and Borisy, G.G. (2003) Cellular motility driven by assembly and disassembly of actin filaments. *Cell*, **112**, 453-465.
- Prenzel, N., Zwick, E., Daub, H., Leserer, M., Abraham, R., Wallasch, C. and Ullrich, A. (1999) EGF receptor transactivation by G-protein-coupled receptors requires metalloproteinase cleavage of proHB-EGF. *Nature*, **402**, 884-888.
- Radeke, H.H., von Wenckstern, H., Stoidtner, K., Sauer, B., Hammer, S. and Kleuser, B. (2005) Overlapping signaling pathways of sphingosine 1-phosphate and TGF-beta in the murine Langerhans cell line XS52. *J Immunol*, **174**, 2778-2786.
- Raffetto, J.D., Mendez, M.V., Marien, B.J., Byers, H.R., Phillips, T.J., Park, H.Y. and Menzoian, J.O. (2001) Changes in cellular motility and cytoskeletal actin in fibroblasts from patients with chronic venous insufficiency and in neonatal fibroblasts in the presence of chronic wound fluid. *J Vasc Surg*, **33**, 1233-1241.
- Roberts, A.B., Anzano, M.A., Lamb, L.C., Smith, J.M. and Sporn, M.B. (1981) New class of transforming growth factors potentiated by epidermal growth factor: isolation from non-neoplastic tissues. *Proc Natl Acad Sci U S A*, **78**, 5339-5343.
- Roberts, A.B. and Derynck, R. (2001) Meeting report: signaling schemes for TGF-beta. *Sci STKE*, **2001**, PE43.
- Roberts, A.B., Frolik, C.A., Anzano, M.A. and Sporn, M.B. (1983) Transforming growth factors from neoplastic and nonneoplastic tissues. *Fed Proc*, **42**, 2621-2626.
- Roberts, A.B., Piek, E., Bottinger, E.P., Ashcroft, G., Mitchell, J.B. and Flanders, K.C. (2001) Is Smad3 a major player in signal transduction pathways leading to fibrogenesis? *Chest*, **120**, 43S-47S.
- Rodbell, M. (1997) The complex regulation of receptor-coupled G-proteins. *Adv Enzyme Regul*, **37**, 427-435.
- Rodriguez, O.C., Schaefer, A.W., Mandato, C.A., Forscher, P., Bement, W.M. and Waterman-Storer, C.M. (2003) Conserved microtubule-actin interactions in cell movement and morphogenesis. *Nat Cell Biol*, **5**, 599-609.
- Rosenfeldt, H.M., Hobson, J.P., Maceyka, M., Olivera, A., Nava, V.E., Milstien, S. and Spiegel, S. (2001a) EDG-1 links the PDGF receptor to Src and focal adhesion kinase activation leading to lamellipodia formation and cell migration. *Faseb J*, **15**, 2649-2659.
- Rosenfeldt, H.M., Hobson, J.P., Milstien, S. and Spiegel, S. (2001b) The sphingosine-1-phosphate receptor EDG-1 is essential for platelet-derived growth factor-induced cell motility. *Biochem Soc Trans*, **29**, 836-839.
- Runyan, C.E., Schnaper, H.W. and Poncelet, A.C. (2005) The role of internalization in transforming growth factor beta1-induced Smad2 association with Smad anchor for receptor activation

- (SARA) and Smad2-dependent signaling in human mesangial cells. *J Biol Chem*, **280**, 8300-8308.
- Ryu, Y., Takuwa, N., Sugimoto, N., Sakurada, S., Usui, S., Okamoto, H., Matsui, O. and Takuwa, Y. (2002) Sphingosine-1-phosphate, a platelet-derived lysophospholipid mediator, negatively regulates cellular Rac activity and cell migration in vascular smooth muscle cells. *Circ Res*, **90**, 325-332.
- Sadahira, Y., Ruan, F., Hakomori, S. and Igarashi, Y. (1992) Sphingosine 1-phosphate, a specific endogenous signaling molecule controlling cell motility and tumor cell invasiveness. *Proc Natl Acad Sci U S A*, **89**, 9686-9690.
- Saha, D., Datta, P.K. and Beauchamp, R.D. (2001) Oncogenic ras represses transforming growth factor-beta /Smad signaling by degrading tumor suppressor Smad4. *J Biol Chem*, **276**, 29531-29537.
- Sahai, E. (2005) Mechanisms of cancer cell invasion. *Curr Opin Genet Dev*, **15**, 87-96.
- Sandulache, V.C., Parekh, A., Li-Korotky, H.S., Dohar, J.E. and Hebda, P.A. (2006) Prostaglandin E2 differentially modulates human fetal and adult dermal fibroblast migration and contraction: implication for wound healing. *Wound Repair Regen*, **14**, 633-643.
- Sanna, M.G., Liao, J., Jo, E., Alfonso, C., Ahn, M.Y., Peterson, M.S., Webb, B., Lefebvre, S., Chun, J., Gray, N. and Rosen, H. (2004) Sphingosine 1-phosphate (S1P) receptor subtypes S1P1 and S1P3, respectively, regulate lymphocyte recirculation and heart rate. *J Biol Chem*, **279**, 13839-13848.
- Sato, M., Markiewicz, M., Yamanaka, M., Bielawska, A., Mao, C., Obeid, L.M., Hannun, Y.A. and Trojanowska, M. (2003) Modulation of transforming growth factor-beta (TGF-beta) signaling by endogenous sphingolipid mediators. *J Biol Chem*, **278**, 9276-9282.
- Sauer, B., Vogler, R., von Wenckstern, H., Fujii, M., Anzano, M.B., Glick, A.B., Schafer-Korting, M., Roberts, A.B. and Kleuser, B. (2004a) Involvement of Smad signaling in sphingosine 1-phosphate-mediated biological responses of keratinocytes. *J Biol Chem*, **279**, 38471-38479.
- Sauer, B., Vogler, R., Zimmermann, K., Fujii, M., Anzano, M.B., Schafer-Korting, M., Roberts, A.B. and Kleuser, B. (2004b) Lysophosphatidic acid interacts with transforming growth factor-beta signaling to mediate keratinocyte growth arrest and chemotaxis. *J Invest Dermatol*, **123**, 840-849.
- Schwartz, M.A. and Shattil, S.J. (2000) Signaling networks linking integrins and rho family GTPases. *Trends Biochem Sci*, **25**, 388-391.
- Sekelsky, J.J., Newfeld, S.J., Raftery, L.A., Chartoff, E.H. and Gelbart, W.M. (1995) Genetic characterization and cloning of mothers against dpp, a gene required for decapentaplegic function in *Drosophila melanogaster*. *Genetics*, **139**, 1347-1358.
- Selbie, L.A. and Hill, S.J. (1998) G protein-coupled-receptor cross-talk: the fine-tuning of multiple receptor-signalling pathways. *Trends Pharmacol Sci*, **19**, 87-93.
- Shi, Y. (2001) Structural insights on Smad function in TGFbeta signaling. *Bioessays*, **23**, 223-232.
- Shi, Y. and Massague, J. (2003) Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell*, **113**, 685-700.
- Sillman, A.L., Quang, D.M., Farboud, B., Fang, K.S., Nuccitelli, R. and Isseroff, R.R. (2003) Human dermal fibroblasts do not exhibit directional migration on collagen I in direct-current electric fields of physiological strength. *Exp Dermatol*, **12**, 396-402.
- Singer, A.J. and Clark, R.A. (1999) Cutaneous wound healing. *N Engl J Med*, **341**, 738-746.
- Song, C.Z., Tian, X. and Gelehrter, T.D. (1999) Glucocorticoid receptor inhibits transforming growth factor-beta signaling by directly targeting the transcriptional activation function of Smad3. *Proc Natl Acad Sci U S A*, **96**, 11776-11781.
- Song, H.J., Choi, T.S., Chung, F.Y., Park, S.Y., Ryu, J.S., Woo, J.G., Min, Y.S., Shin, C.Y. and Sohn, U.D. (2006) Sphingosine 1-phosphate-induced signal transduction in cat esophagus smooth muscle cells. *Mol Cells*, **21**, 42-51.
- Sorensen, S.D., Nicole, O., Peavy, R.D., Montoya, L.M., Lee, C.J., Murphy, T.J., Traynelis, S.F. and Hepler, J.R. (2003) Common signaling pathways link activation of murine PAR-1, LPA, and S1P receptors to proliferation of astrocytes. *Mol Pharmacol*, **64**, 1199-1209.
- Souchelnytskyi, S., Tamaki, K., Engstrom, U., Wernstedt, C., ten Dijke, P. and Heldin, C.H. (1997) Phosphorylation of Ser465 and Ser467 in the C terminus of Smad2 mediates interaction with Smad4 and is required for transforming growth factor-beta signaling. *J Biol Chem*, **272**, 28107-28115.
- Souchelnytskyi, S., ten Dijke, P., Miyazono, K. and Heldin, C.H. (1996) Phosphorylation of Ser165 in TGF-beta type I receptor modulates TGF-beta1-induced cellular responses. *Embo J*, **15**, 6231-6240.

- Spiegel, S. and Kolesnick, R. (2002) Sphingosine 1-phosphate as a therapeutic agent. *Leukemia*, **16**, 1596-1602.
- Spiegel, S. and Merrill, A.H., Jr. (1996) Sphingolipid metabolism and cell growth regulation. *Faseb J*, **10**, 1388-1397.
- Srinivasan, S., Wang, F., Glavas, S., Ott, A., Hofmann, F., Aktories, K., Kalman, D. and Bourne, H.R. (2003) Rac and Cdc42 play distinct roles in regulating PI(3,4,5)P3 and polarity during neutrophil chemotaxis. *J Cell Biol*, **160**, 375-385.
- Subauste, M.C., Pertz, O., Adamson, E.D., Turner, C.E., Junger, S. and Hahn, K.M. (2004) Vinculin modulation of paxillin-FAK interactions regulates ERK to control survival and motility. *J Cell Biol*, **165**, 371-381.
- Sugimoto, N., Takuwa, N., Okamoto, H., Sakurada, S. and Takuwa, Y. (2003) Inhibitory and stimulatory regulation of Rac and cell motility by the G12/13-Rho and Gi pathways integrated downstream of a single G protein-coupled sphingosine-1-phosphate receptor isoform. *Mol Cell Biol*, **23**, 1534-1545.
- Sukocheva, O., Wadham, C., Holmes, A., Albanese, N., Verrier, E., Feng, F., Bernal, A., Derian, C.K., Ullrich, A., Vadas, M.A. and Xia, P. (2006) Estrogen transactivates EGFR via the sphingosine 1-phosphate receptor Edg-3: the role of sphingosine kinase-1. *J Cell Biol*, **173**, 301-310.
- Taha, T.A., Argraves, K.M. and Obeid, L.M. (2004) Sphingosine-1-phosphate receptors: receptor specificity versus functional redundancy. *Biochim Biophys Acta*, **1682**, 48-55.
- Takuwa, Y. (2002) Subtype-specific differential regulation of Rho family G proteins and cell migration by the Edg family sphingosine-1-phosphate receptors. *Biochim Biophys Acta*, **1582**, 112-120.
- Tani, M., Sano, T., Ito, M. and Igarashi, Y. (2005) Mechanisms of sphingosine and sphingosine 1-phosphate generation in human platelets. *J Lipid Res*, **46**, 2458-2467.
- Tanimoto, T., Jin, Z.G. and Berk, B.C. (2002) Transactivation of vascular endothelial growth factor (VEGF) receptor Flk-1/KDR is involved in sphingosine 1-phosphate-stimulated phosphorylation of Akt and endothelial nitric-oxide synthase (eNOS). *J Biol Chem*, **277**, 42997-43001.
- ten Dijke, P., Ichijo, H., Franzen, P., Schulz, P., Saras, J., Toyoshima, H., Heldin, C.H. and Miyazono, K. (1993) Activin receptor-like kinases: a novel subclass of cell-surface receptors with predicted serine/threonine kinase activity. *Oncogene*, **8**, 2879-2887.
- ten Dijke, P., Miyazono, K. and Heldin, C.H. (2000) Signaling inputs converge on nuclear effectors in TGF-beta signaling. *Trends Biochem Sci*, **25**, 64-70.
- Timar, J., Raso, E., Dome, B., Ladanyi, A., Banfalvi, T., Gilde, K. and Raz, A. (2002) Expression and function of the AMF receptor by human melanoma in experimental and clinical systems. *Clin Exp Metastasis*, **19**, 225-232.
- Traub, L.M. (2003) Sorting it out: AP-2 and alternate clathrin adaptors in endocytic cargo selection. *J Cell Biol*, **163**, 203-208.
- Tsukazaki, T., Chiang, T.A., Davison, A.F., Attisano, L. and Wrana, J.L. (1998) SARA, a FYVE domain protein that recruits Smad2 to the TGFbeta receptor. *Cell*, **95**, 779-791.
- Turner, C.E. (2000) Paxillin and focal adhesion signalling. *Nat Cell Biol*, **2**, E231-236.
- Turner, C.E., West, K.A. and Brown, M.C. (2001) Paxillin-ARF GAP signaling and the cytoskeleton. *Curr Opin Cell Biol*, **13**, 593-599.
- Van Brocklyn, J.R., Lee, M.J., Menzelev, R., Olivera, A., Edsall, L., Cuvillier, O., Thomas, D.M., Coopman, P.J., Thangada, S., Liu, C.H., Hla, T. and Spiegel, S. (1998) Dual actions of sphingosine-1-phosphate: extracellular through the Gi-coupled receptor Edg-1 and intracellular to regulate proliferation and survival. *J Cell Biol*, **142**, 229-240.
- Van Brocklyn, J.R., Young, N. and Roof, R. (2003) Sphingosine-1-phosphate stimulates motility and invasiveness of human glioblastoma multiforme cells. *Cancer Lett*, **199**, 53-60.
- Vogler, R., Sauer, B., Kim, D.S., Schafer-Korting, M. and Kleuser, B. (2003) Sphingosine-1-phosphate and its potentially paradoxical effects on critical parameters of cutaneous wound healing. *J Invest Dermatol*, **120**, 693-700.
- Vogt, P.M., Lehnhardt, M., Wagner, D., Jansen, V., Krieg, M. and Steinau, H.U. (1998) Determination of endogenous growth factors in human wound fluid: temporal presence and profiles of secretion. *Plast Reconstr Surg*, **102**, 117-123.
- Wakefield, L.M., Smith, D.M., Masui, T., Harris, C.C. and Sporn, M.B. (1987) Distribution and modulation of the cellular receptor for transforming growth factor-beta. *J Cell Biol*, **105**, 965-975.
- Wang, F., Van Brocklyn, J.R., Edsall, L., Nava, V.E. and Spiegel, S. (1999) Sphingosine-1-phosphate inhibits motility of human breast cancer cells independently of cell surface receptors. *Cancer Res*, **59**, 6185-6191.

- Watanabe, H., de Caestecker, M.P. and Yamada, Y. (2001) Transcriptional cross-talk between Smad, ERK1/2, and p38 mitogen-activated protein kinase pathways regulates transforming growth factor-beta-induced aggrecan gene expression in chondrogenic ATDC5 cells. *J Biol Chem*, **276**, 14466-14473.
- Waters, C.M., Long, J., Gorshkova, I., Fujiwara, Y., Connell, M., Belmonte, K.E., Tigyi, G., Natarajan, V., Pyne, S. and Pyne, N.J. (2006) Cell migration activated by platelet-derived growth factor receptor is blocked by an inverse agonist of the sphingosine 1-phosphate receptor-1. *Faseb J*, **20**, 509-511.
- Watterson, K., Sankala, H., Milstien, S. and Spiegel, S. (2003) Pleiotropic actions of sphingosine-1-phosphate. *Prog Lipid Res*, **42**, 344-357.
- Webb, D.J., Parsons, J.T. and Horwitz, A.F. (2002) Adhesion assembly, disassembly and turnover in migrating cells -- over and over and over again. *Nat Cell Biol*, **4**, E97-100.
- Weiss, F.U., Daub, H. and Ullrich, A. (1997) Novel mechanisms of RTK signal generation. *Curr Opin Genet Dev*, **7**, 80-86.
- Welch, H.C., Coadwell, W.J., Stephens, L.R. and Hawkins, P.T. (2003) Phosphoinositide 3-kinase-dependent activation of Rac. *FEBS Lett*, **546**, 93-97.
- Wells, R.G., Yankelev, H., Lin, H.Y. and Lodish, H.F. (1997) Biosynthesis of the type I and type II TGF-beta receptors. Implications for complex formation. *J Biol Chem*, **272**, 11444-11451.
- Wen, X., Li, Y., Hu, K., Dai, C. and Liu, Y. (2005) Hepatocyte growth factor receptor signaling mediates the anti-fibrotic action of 9-cis-retinoic acid in glomerular mesangial cells. *Am J Pathol*, **167**, 947-957.
- Wicks, S.J., Lui, S., Abdel-Wahab, N., Mason, R.M. and Chantry, A. (2000) Inactivation of smad-transforming growth factor beta signaling by Ca(2+)-calmodulin-dependent protein kinase II. *Mol Cell Biol*, **20**, 8103-8111.
- Wieser, R., Wrana, J.L. and Massague, J. (1995) GS domain mutations that constitutively activate T beta R-I, the downstream signaling component in the TGF-beta receptor complex. *Embo J*, **14**, 2199-2208.
- Windh, R.T., Lee, M.J., Hla, T., An, S., Barr, A.J. and Manning, D.R. (1999) Differential coupling of the sphingosine 1-phosphate receptors Edg-1, Edg-3, and H218/Edg-5 to the G(i), G(q), and G(12) families of heterotrimeric G proteins. *J Biol Chem*, **274**, 27351-27358.
- Worthy lake, R.A. and Burridge, K. (2003) RhoA and ROCK promote migration by limiting membrane protrusions. *J Biol Chem*, **278**, 13578-13584.
- Wrana, J.L., Attisano, L., Wieser, R., Ventura, F. and Massague, J. (1994) Mechanism of activation of the TGF-beta receptor. *Nature*, **370**, 341-347.
- Wu, G., Chen, Y.G., Ozdamar, B., Gyuricza, C.A., Chong, P.A., Wrana, J.L., Massague, J. and Shi, Y. (2000) Structural basis of Smad2 recognition by the Smad anchor for receptor activation. *Science*, **287**, 92-97.
- Wu, R.Y., Zhang, Y., Feng, X.H. and Derynck, R. (1997) Heteromeric and homomeric interactions correlate with signaling activity and functional cooperativity of Smad3 and Smad4/DPC4. *Mol Cell Biol*, **17**, 2521-2528.
- Xin, C., Ren, S., Kleuser, B., Shabahang, S., Eberhardt, W., Radeke, H., Schafer-Korting, M., Pfeilschifter, J. and Huwiler, A. (2004) Sphingosine 1-phosphate cross-activates the Smad signaling cascade and mimics transforming growth factor-beta-induced cell responses. *J Biol Chem*, **279**, 35255-35262.
- Xu, J., Wang, F., Van Keymeulen, A., Herzmark, P., Straight, A., Kelly, K., Takuwa, Y., Sugimoto, N., Mitchison, T. and Bourne, H.R. (2003a) Divergent signals and cytoskeletal assemblies regulate self-organizing polarity in neutrophils. *Cell*, **114**, 201-214.
- Xu, L., Alarcon, C., Col, S. and Massague, J. (2003b) Distinct domain utilization by Smad3 and Smad4 for nucleoporin interaction and nuclear import. *J Biol Chem*, **278**, 42569-42577.
- Xu, L., Chen, Y.G. and Massague, J. (2000) The nuclear import function of Smad2 is masked by SARA and unmasked by TGFbeta-dependent phosphorylation. *Nat Cell Biol*, **2**, 559-562.
- Xue, C., Wyckoff, J., Liang, F., Sidani, M., Violini, S., Tsai, K.L., Zhang, Z.Y., Sahai, E., Condeelis, J. and Segall, J.E. (2006) Epidermal growth factor receptor overexpression results in increased tumor cell motility in vivo coordinately with enhanced intravasation and metastasis. *Cancer Res*, **66**, 192-197.
- Yakymovych, I., Ten Dijke, P., Heldin, C.H. and Souchelnytskyi, S. (2001) Regulation of Smad signaling by protein kinase C. *Faseb J*, **15**, 553-555.
- Yamada, M., Banno, Y., Takuwa, Y., Koda, M., Hara, A. and Nozawa, Y. (2004) Overexpression of phospholipase D prevents actinomycin D-induced apoptosis through potentiation of

- phosphoinositide 3-kinase signalling pathways in Chinese-hamster ovary cells. *Biochem J*, **378**, 649-656.
- Yamaguchi, H. and Condeelis, J. (2006) Regulation of the actin cytoskeleton in cancer cell migration and invasion. *Biochim Biophys Acta*.
- Yamaguchi, H., Kitayama, J., Takuwa, N., Arikawa, K., Inoki, I., Takehara, K., Nagawa, H. and Takuwa, Y. (2003) Sphingosine-1-phosphate receptor subtype-specific positive and negative regulation of Rac and haematogenous metastasis of melanoma cells. *Biochem J*, **374**, 715-722.
- Yamashita, H., Kitayama, J., Shida, D., Yamaguchi, H., Mori, K., Osada, M., Aoki, S., Yatomi, Y., Takuwa, Y. and Nagawa, H. (2005) Sphingosine 1-Phosphate Receptor Expression Profile in Human Gastric Cancer Cells: Differential Regulation on the Migration and Proliferation. *J Surg Res*.
- Yamashita, H., ten Dijke, P., Franzen, P., Miyazono, K. and Heldin, C.H. (1994) Formation of hetero-oligomeric complexes of type I and type II receptors for transforming growth factor-beta. *J Biol Chem*, **269**, 20172-20178.
- Yamazaki, Y., Kon, J., Sato, K., Tomura, H., Sato, M., Yoneya, T., Okazaki, H., Okajima, F. and Ohta, H. (2000) Edg-6 as a putative sphingosine 1-phosphate receptor coupling to Ca(2+) signaling pathway. *Biochem Biophys Res Commun*, **268**, 583-589.
- Yanagisawa, J., Yanagi, Y., Masuhiro, Y., Suzawa, M., Watanabe, M., Kashiwagi, K., Toriyabe, T., Kawabata, M., Miyazono, K. and Kato, S. (1999) Convergence of transforming growth factor-beta and vitamin D signaling pathways on SMAD transcriptional coactivators. *Science*, **283**, 1317-1321.
- Yao, D., Ehrlich, M., Henis, Y.I. and Leof, E.B. (2002) Transforming growth factor-beta receptors interact with AP2 by direct binding to beta2 subunit. *Mol Biol Cell*, **13**, 4001-4012.
- Yatomi, Y., Igarashi, Y., Yang, L., Hisano, N., Qi, R., Asazuma, N., Satoh, K., Ozaki, Y. and Kume, S. (1997) Sphingosine 1-phosphate, a bioactive sphingolipid abundantly stored in platelets, is a normal constituent of human plasma and serum. *J Biochem (Tokyo)*, **121**, 969-973.
- Yatomi, Y., Ruan, F., Hakomori, S. and Igarashi, Y. (1995) Sphingosine-1-phosphate: a platelet-activating sphingolipid released from agonist-stimulated human platelets. *Blood*, **86**, 193-202.
- Yokomizo, T., Izumi, T., Chang, K., Takuwa, Y. and Shimizu, T. (1997) A G-protein-coupled receptor for leukotriene B4 that mediates chemotaxis. *Nature*, **387**, 620-624.
- Yoshida, K., Matsuzaki, K., Mori, S., Tahashi, Y., Yamagata, H., Furukawa, F., Seki, T., Nishizawa, M., Fujisawa, J. and Okazaki, K. (2005) Transforming growth factor-beta and platelet-derived growth factor signal via c-Jun N-terminal kinase-dependent Smad2/3 phosphorylation in rat hepatic stellate cells after acute liver injury. *Am J Pathol*, **166**, 1029-1039.
- Young, N. and Van Brocklyn, J.R. (2006) Signal transduction of sphingosine-1-phosphate G protein-coupled receptors. *ScientificWorldJournal*, **6**, 946-966.
- Zhang, G., Contos, J.J., Weiner, J.A., Fukushima, N. and Chun, J. (1999) Comparative analysis of three murine G-protein coupled receptors activated by sphingosine-1-phosphate. *Gene*, **227**, 89-99.
- Zhang, Y. and Deryck, R. (1999) Regulation of Smad signalling by protein associations and signalling crosstalk. *Trends Cell Biol*, **9**, 274-279.
- Zhao, J. and Buick, R.N. (1995) Regulation of transforming growth factor beta receptors in H-ras oncogene-transformed rat intestinal epithelial cells. *Cancer Res*, **55**, 6181-6188.
- Zhou, Y., Scolavino, S., Funderburk, S.F., Ficociello, L.F., Zhang, X. and Klibanski, A. (2004) Receptor internalization-independent activation of Smad2 in activin signaling. *Mol Endocrinol*, **18**, 1818-1826.
- Zigmond, S.H. (2004) Formin-induced nucleation of actin filaments. *Curr Opin Cell Biol*, **16**, 99-105.