REFERENCES

Aboseif, S., El-Sakka, A., Young, P., and Cunha, G. (1999). Mesenchymal reprogramming of adult human epithelial differentiation. **Differentiation**, **65**(2), 113-8.

Alpini, G., Kanno, N., Phinizy, J. L., Glaser, S., Francis, H., Taffetani, S., and LeSage, G. (2004). Tauroursodeoxycholate inhibits human cholangiocarcinoma growth via Ca2+-, PKC-, and MAPK-dependent pathways. **Am J Physiol Gastrointest Liver Physiol**, **286**(6), G973-82.

Alvaro, D. (2009). Serum and bile biomarkers for cholangiocarcinoma. **Curr Opin Gastroenterol**, **25**(3), 279-84.

Aycock, R. L., Bradshaw, A. C., Sage, E. H., and Starcher, B. (2004). Development of UV-induced squamous cell carcinomas is suppressed in the absence of SPARC. **J Invest Dermatol**, **123**(3), 592-9.

Baker, S. D., Diasio, R. B., O'Reilly, S., Lucas, V. S., Khor, S. P., Sartorius, S. E., Donehower, R. C., Grochow, L. B., Spector, T., Hohneker, J. A., and Rowinsky, E. K. (2000). Phase I and pharmacologic study of oral fluorouracil on a chronic daily schedule in combination with the dihydropyrimidine dehydrogenase inactivator eniluracil. **J Clin Oncol**, **18**(4), 915-26.

Bao, S., Ouyang, G., Bai, X., Huang, Z., Ma, C., Liu, M., Shao, R., Anderson, R. M., Rich, J. N., and Wang, X. F. (2004). Periostin potently promotes metastatic growth of colon cancer by augmenting cell survival via the Akt/PKB pathway. **Cancer Cell**, **5**(4), 329-39.

Barcellos-Hoff, M. H., and Ravani, S. A. (2000). Irradiated mammary gland stroma promotes the expression of tumorigenic potential by unirradiated epithelial cells. **Cancer Res**, **60**(5), 1254-60.

Baril, P., Gangeswaran, R., Mahon, P. C., Caulee, K., Kocher, H. M., Harada, T., Zhu, M., Kalthoff, H., Crnogorac-Jurcevic, T., and Lemoine, N. R. (2007). Periostin promotes invasiveness and resistance of pancreatic cancer cells to hypoxia-induced cell death: role of the beta4 integrin and the PI3k pathway. **Oncogene**, 26(14), 2082-94.

Barsky, S. H., Rao, C. N., Grotendorst, G. R., and Liotta, L. A. (1982). Increased content of Type V Collagen in desmoplasia of human breast carcinoma. **Am J Pathol, 108**(3), 276-83.

Baskin, L. S. (2001). Plasticity of the urothelial phenotype: effects of gastrointestinal mesenchyme/stroma and implications for urinary tract reconstruction. **Urology, 57**(6 Suppl 1), 104.

Benlimame, N., He, Q., Jie, S., Xiao, D., Xu, Y. J., Loignon, M., Schlaepfer, D. D., and Alaoui-Jamali, M. A. (2005). FAK signaling is critical for ErbB-2/ErbB-3 receptor cooperation for oncogenic transformation and invasion. **J Cell Biol, 171**(3), 505-16.

Bhamarapravati, N., Thammavit, W., and Vajrasthira, S. (1978). Liver changes in hamsters infected with a liver fluke of man, *Opisthorchis viverrini*. **Am J Trop Med Hyg, 27**(4), 787-94.

Bhowmick, N. A., Chytil, A., Plieth, D., Gorska, A. E., Dumont, N., Shappell, S., Washington, M. K., Neilson, E. G., and Moses, H. L. (2004). TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. **Science, 303**(5659), 848-51.

Bhowmick, N. A., Neilson, E. G., and Moses, H. L. (2004). Stromal fibroblasts in cancer initiation and progression. **Nature, 432**(7015), 332-7.

Bhudhisawasdi, V. (1997). Place of surgery in opisthorchiasis associated cholangiocarcinoma. **Southeast Asian J Trop Med Public Health**, 28 Suppl 1, 85-90.

Billingham, R. E., Orr, J. W., and Woodhouse, D. L. (1951). Transplantation of skin components during chemical carcinogenesis with 20-methylcholanthrene. **Br J Cancer, 5**(4), 417-32.

Bonfoco, E., Chen, W., Paul, R., Cheresh, D. A., and Cooper, N. R. (2000). beta1 integrin antagonism on adherent, differentiated human neuroblastoma cells triggers an apoptotic signaling pathway. **Neuroscience, 101**(4), 1145-52.

Brauchle, M., Angermeyer, K., Hubner, G., and Werner, S. (1994). Large induction of keratinocyte growth factor expression by serum growth factors and pro-inflammatory cytokines in cultured fibroblasts. **Oncogene, 9**(11), 3199-204.

Brigstock, D. R. (1999). The connective tissue growth factor/cysteine-rich 61/nephroblastoma overexpressed (CCN) family. **Endocr. Rev**, **20**, 189-206.

Brooks, P. C., Stromblad, S., Klemke, R., Visscher, D., Sarkar, F. H., and Cheresh, D. A. (1995). Antiintegrin alpha v beta 3 blocks human breast cancer growth and angiogenesis in human skin. **J Clin Invest**, **96**(4), 1815-22.

Broome, U., Olsson, R., Loof, L., Bodemar, G., Hultcrantz, R., Danielsson, A., Prytz, H., Sandberg-Gertzen, H., Wallerstedt, S., and Lindberg, G. (1996). Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. **Gut**, **38**(4), 610-5.

Brown, P. D., and Giavazzi, R. (1995). Matrix metalloproteinase inhibition: a review of anti-tumour activity. **Ann Oncol**, **6**(10), 967-74.

Burgess, H. A., and Reiner, O. (2000). Doublecortin-like kinase is associated with microtubules in neuronal growth cones. **Mol Cell Neurosci**, **16**(5), 529-41.

Camps, J. L., Chang, S. M., Hsu, T. C., Freeman, M. R., Hong, S. J., Zhau, H. E., von Eschenbach, A. C., and Chung, L. W. (1990). Fibroblast-mediated acceleration of human epithelial tumor growth *in vivo*. **Proc Natl Acad Sci U S A**, **87**(1), 75-9.

Carrano, A. C., and Pagano, M. (2001). Role of the F-box protein Skp2 in adhesion-dependent cell cycle progression. **J Cell Biol**, **153**(7), 1381-90.

Cary, L. A., and Guan, J. L. (1999). Focal adhesion kinase in integrin-mediated signaling. **Front Biosci**, **4**, D102-13.

Caswell, P. T., Chan, M., Lindsay, A. J., McCaffrey, M. W., Boettiger, D., and Norman, J. C. (2008). Rab-coupling protein coordinates recycling of alpha5beta1 integrin and EGFR1 to promote cell migration in 3D microenvironments. **J Cell Biol**, **183**(1), 143-55.

Chen, C. Y., Lin, X. Z., Tsao, H. C., and Shiesh, S. C. (2003). The value of biliary fibronectin for diagnosis of cholangiocarcinoma. **Hepatogastroenterology**, **50**(52), 924-7.

Chen, M. F. (1999). Peripheral cholangiocarcinoma (cholangiocellular carcinoma): clinical features, diagnosis and treatment. **J Gastroenterol Hepatol**, **14**(12), 1144-9.

Chiquet-Ehrismann, R., Mackie, E. J., Pearson, C. A., and Sakakura, T. (1986). Tenascin: an extracellular matrix protein involved in tissue interactions during fetal development and oncogenesis. **Cell**, **47**(1), 131-9.

Choi, D., Lim, J. H., Lee, K. T., Lee, J. K., Choi, S. H., Heo, J. S., Jang, K. T., Lee, N. Y., Kim, S., and Hong, S. T. (2006). Cholangiocarcinoma and *Clonorchis sinensis* infection: a case-control study in Korea. **J Hepatol**, **44**(6), 1066-73.

Chu, P. Y., Li, T. K., Ding, S. T., Lai, I. R., and Shen, T. L. (2010). EGF-induced Grb7 recruits and promotes Ras activity essential for the tumorigenicity of Sk-Br3 breast cancer cells. **J Biol Chem**, (in press).

Chuaysri, C., Thuwajit, P., Paupairoj, A., Chau-In, S., Suthiphongchai, T., and Thuwajit, C. (2009). Alpha-smooth muscle actin-positive fibroblasts promote biliary cell proliferation and correlate with poor survival in cholangiocarcinoma. **Oncol Rep**, **21**(4), 957-69.

Crawford, Y., Kasman, I., Yu, L., Zhong, C., Wu, X., Modrusan, Z., Kaminker, J., and Ferrara, N. (2009). PDGF-C mediates the angiogenic and tumorigenic properties of fibroblasts associated with tumors refractory to anti-VEGF treatment. **Cancer Cell**, **15**(1), 21-34.

Croucher, D. R., Saunders, D. N., Lobov, S., and Ranson, M. (2008). Revisiting the biological roles of PAI2 (SERPINB2) in cancer. **Nat Rev Cancer**, **8**(7), 535-45.

De Wever, O., Demetter, P., Mareel, M., and Bracke, M. (2008). Stromal myofibroblasts are drivers of invasive cancer growth. **Int J Cancer**, **123**(10), 2229-38.

De Wever, O., and Mareel, M. (2003). Role of tissue stroma in cancer cell invasion. **J Pathol**, **200**(4), 429-47.

Devosse, T., Guillabert, A., D'Haene, N., Berton, A., De Nadai, P., Noel, S., Brait, M., Franssen, J. D., Sozzani, S., Salmon, I., and Parmentier, M. (2009). Formyl peptide receptor-like 2 is expressed and functional in plasmacytoid dendritic cells, tissue-specific macrophage subpopulations, and eosinophils. **J Immunol**, **182**(8), 4974-84.

Egeblad, M., and Werb, Z. (2002). New functions for the matrix metalloproteinases in cancer progression. **Nat Rev Cancer**, **2**(3), 161-74.

Elkins, D. B., Haswell-Elkins, M. R., Mairiang, E., Mairiang, P., Sithithaworn, P., Kaewkes, S., Bhudhisawasdi, V., and Uttaravichien, T. (1990). A high frequency of hepatobiliary disease and suspected cholangiocarcinoma associated with heavy *Opisthorchis viverrini* infection in a small community in north-east Thailand. **Trans R Soc Trop Med Hyg, 84**(5), 715-9.

Erkan, M., Kleeff, J., Gorbachevski, A., Reiser, C., Mitkus, T., Esposito, I., Giese, T., Buchler, M. W., Giese, N. A., and Friess, H. (2007). Periostin creates a tumor-supportive microenvironment in the pancreas by sustaining fibrogenic stellate cell activity. **Gastroenterology, 132**(4), 1447-64.

Fang, X., Gaudette, D., Furui, T., Mao, M., Estrella, V., Eder, A., Pustilnik, T., Sasagawa, T., Lapushin, R., Yu, S., Jaffe, R. B., Wiener, J. R., Erickson, J. R., and Mills, G. B. (2000). Lysophospholipid growth factors in the initiation, progression, metastases, and management of ovarian cancer. **Ann N Y Acad Sci, 905**, 188-208.

Flavell, D. J., and Flavell, S. U. (1986). *Opisthorchis viverrini*: pathogenesis of infection in immunodeprived hamsters. **Parasite Immunol, 8**(5), 455-66.

Fournier, A. K., Campbell, L. E., Castagnino, P., Liu, W. F., Chung, B. M., Weaver, V. M., Chen, C. S., and Assoian, R. K. (2008). Rac-dependent cyclin D1 gene expression regulated by cadherin- and integrin-mediated adhesion. **J Cell Sci, 121**(Pt 2), 226-33.

Friedman, S. L., Maher, J. J., and Bissell, D. M. (2000). Mechanisms and therapy of hepatic fibrosis: report of the AASLD Single Topic Basic Research Conference. **Hepatology, 32**(6), 1403-8.

Fromigue, O., Louis, K., Dayem, M., Milanini, J., Pages, G., Tartare-Deckert, S., Ponzio, G., Hofman, P., Barbry, P., Auberger, P., and Mari, B. (2003). Gene expression profiling of normal human pulmonary fibroblasts following co-culture with non-small-cell lung cancer cells reveals alterations related to matrix degradation, angiogenesis, cell growth and survival. **Oncogene, 22**(52), 8487-97.

Fukushima, N., Kikuchi, Y., Nishiyama, T., Kudo, A., and Fukayama, M. (2008). Periostin deposition in the stroma of invasive and intraductal neoplasms of the pancreas. **Mod Pathol, 21**(8), 1044-53.

Gabbiani, G., Ryan, G. B., and Majne, G. (1971). Presence of modified fibroblasts in granulation tissue and their possible role in wound contraction. **Experientia**, **27**(5), 549-50.

Gahmberg, C. G., Fagerholm, S. C., Nurmi, S. M., Chavakis, T., Marchesan, S., and Gronholm, M. (2009). Regulation of integrin activity and signalling. **Biochim Biophys Acta**, **1790**(6), 431-44.

Gatto, M., Bragazzi, M. C., Semeraro, R., Napoli, C., Gentile, R., Torrice, A., Gaudio, E., and Alvaro, D. (2010). Cholangiocarcinoma: update and future perspectives. **Dig Liver Dis**, **42**(4), 253-60.

Giancotti, F. G., and Tarone, G. (2003). Positional control of cell fate through joint integrin/receptor protein kinase signaling. **Annu Rev Cell Dev Biol**, **19**, 173-206.

Gilcrease, M. Z. (2007). Integrin signaling in epithelial cells. **Cancer Lett**, **247**(1), 1-25.

Gillan, L., Matei, D., Fishman, D. A., Gerbin, C. S., Karlan, B. Y., and Chang, D. D. (2002). Periostin secreted by epithelial ovarian carcinoma is a ligand for alpha(V)beta(3) and alpha(V)beta(5) integrins and promotes cell motility. **Cancer Res**, **62**(18), 5358-64.

Golubovskaya, V. M., Finch, R., and Cance, W. G. (2005). Direct interaction of the N-terminal domain of focal adhesion kinase with the N-terminal transactivation domain of p53. **J Biol Chem**, **280**(26), 25008-21.

Goydos, J. S., Brumfield, A. M., Frezza, E., Booth, A., Lotze, M. T., and Carty, S. E. (1998). Marked elevation of serum interleukin-6 in patients with cholangiocarcinoma: validation of utility as a clinical marker. **Ann Surg**, **227**(3), 398-404.

Grey, A. M., Schor, A. M., Rushton, G., Ellis, I., and Schor, S. L. (1989). Purification of the migration stimulating factor produced by fetal and breast cancer patient fibroblasts. **Proc Natl Acad Sci U S A**, **86**(7), 2438-42.

Guo, W., and Giancotti, F. G. (2004). Integrin signalling during tumour progression. **Nat Rev Mol Cell Biol**, **5**(10), 816-26.

Gutheil, J. C., Campbell, T. N., Pierce, P. R., Watkins, J. D., Huse, W. D., Bodkin, D. J., and Cheresh, D. A. (2000). Targeted antiangiogenic therapy for cancer using Vitaxin: a humanized monoclonal antibody to the integrin alphavbeta3. **Clin Cancer Res**, **6**(8), 3056-61.

Hagihara, K., Watanabe, K., Chun, J., and Yamaguchi, Y. (2000). Glypican-4 is an FGF2-binding heparan sulfate proteoglycan expressed in neural precursor cells. **Dev Dyn**, **219**(3), 353-67.

Han, S., Ritzenthaler, J. D., Sitaraman, S. V., and Roman, J. (2006). Fibronectin increases matrix metalloproteinase 9 expression through activation of c-Fos via extracellular-regulated kinase and phosphatidylinositol 3-kinase pathways in human lung carcinoma cells. **J Biol Chem**, **281**(40), 29614-24.

Hannigan, G., Troussard, A. A., and Dedhar, S. (2005). Integrin-linked kinase: a cancer therapeutic target unique among its ILK. **Nat Rev Cancer**, **5**(1), 51-63.

Haswell-Elkins, M. R., Satarug, S., Tsuda, M., Mairiang, E., Esumi, H., Sithithaworn, P., Mairiang, P., Saitoh, M., Yongvanit, P., and Elkins, D. B. (1994). Liver fluke infection and cholangiocarcinoma: model of endogenous nitric oxide and extragastric nitrosation in human carcinogenesis. **Mutat Res**, **305**(2), 241-52.

Heffelfinger, S. C., Miller, M. A., Yassin, R., and Gear, R. (1999). Angiogenic growth factors in preinvasive breast disease. **Clin Cancer Res**, **5**(10), 2867-76.

Hirohata, S., Wang, L. W., Miyagi, M., Yan, L., Seldin, M. F., Keene, D. R., Crabb, J. W., and Apte, S. S. (2002). Punctin, a novel ADAMTS-like molecule, ADAMTSL-1, in extracellular matrix. **J Biol Chem**, **277**(14), 12182-9.

Hodges, G. M., Hicks, R. M., and Spacey, G. D. (1977). Epithelial-stromal interactions in normal and chemical carcinogen-treated adult bladder. **Cancer Res**, **37**(10), 3720-30.

Hong, L., Sun, H., Lv, X., Yang, D., Zhang, J., and Shi, Y. (2009). Expression of periostin in the serum of NSCLC and its function on proliferation and migration of human lung adenocarcinoma cell line (A549) *in vitro*. **Mol Biol Rep**, **37**(5), 2285-93.

Hong, W. K., and Sporn, M. B. (1997). Recent advances in chemoprevention of cancer. **Science**, **278**(5340), 1073-7.

Honjo, S., Srivatanakul, P., Sriplung, H., Kikukawa, H., Hanai, S., Uchida, K., Todoroki, T., Jedpiyawongse, A., Kittiwatanachot, P., Sripa, B., Deerasamee, S., and Miwa, M. (2005). Genetic and environmental determinants of risk for cholangiocarcinoma via *Opisthorchis viverrini* in a densely infested area in Nakhon Phanom, northeast Thailand. **Int J Cancer**, **117**(5), 854-60.

Horiuchi, K., Amizuka, N., Takeshita, S., Takamatsu, H., Katsuura, M., Ozawa, H., Toyama, Y., Bonewald, L. F., and Kudo, A. (1999). Identification and characterization of a novel protein, periostin, with restricted expression to periosteum and periodontal ligament and increased expression by transforming growth factor beta. **J Bone Miner Res**, **14**(7), 1239-49.

Howell, O. W., Scharfman, H. E., Herzog, H., Sundstrom, L. E., Beck-Sickinger, A., and Gray, W. P. (2003). Neuropeptide Y is neuroproliferative for post-natal hippocampal precursor cells. **J Neurochem**, **86**(3), 646-59.

Hynes, R. O. (1987). Integrins: a family of cell surface receptors. Cell 48(4), 549-54.

Hynes, R. O. (2002). Integrins: bidirectional, allosteric signaling machines. **Cell**, **110**(6), 673-87.

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**(6549), 539-44.

Isono, T., Kim, C. J., Ando, Y., Sakurai, H., Okada, Y., and Inoue, H. (2009). Suppression of cell invasiveness by periostin via TAB1/TAK1. **Int J Oncol**, **35**(2), 425-32.

Itatsu, K., Zen, Y., Yamaguchi, J., Ohira, S., Ishikawa, A., Ikeda, H., Sato, Y., Harada, K., Sasaki, M., Sakamoto, H., Nagino, M., Nimura, Y., Ohta, T., and Nakanuma, Y. (2008). Expression of matrix metalloproteinase 7 is an unfavorable postoperative prognostic factor in cholangiocarcinoma of the perihilar, hilar, and extrahepatic bile ducts. **Hum Pathol**, **39**(5), 710-9.

Itoh, T., Tanioka, M., Yoshida, H., Yoshioka, T., Nishimoto, H., and Itohara, S. (1998). Reduced angiogenesis and tumor progression in gelatinase A-deficient mice. **Cancer Res**, **58**(5), 1048-51.

Iyer, S. N., Gurujeyalakshmi, G., and Giri, S. N. (1999). Effects of pirfenidone on transforming growth factor-beta gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. **J Pharmacol Exp Ther**, **291**(1), 367-73.

Kalluri, R., and Zeisberg, M. (2006). Fibroblasts in cancer. **Nat Rev Cancer**, **6**(5), 392-401.

Kanno, A., Satoh, K., Masamune, A., Hirota, M., Kimura, K., Umino, J., Hamada, S., Satoh, A., Egawa, S., Motoi, F., Unno, M., and Shimosegawa, T. (2008). Periostin, secreted from stromal cells, has biphasic effect on cell migration and correlates with the epithelial to mesenchymal transition of human pancreatic cancer cells. **Int J Cancer**, **122**(12), 2707-18.

Khan, S. A., Toledano, M. B., and Taylor-Robinson, S. D. (2008). Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. **HPB (Oxford)**, **10**(2), 77-82.

Kikuchi, Y., Kashima, T. G., Nishiyama, T., Shimazu, K., Morishita, Y., Shimazaki, M., Kii, I., Horie, H., Nagai, H., Kudo, A., and Fukayama, M. (2008). Periostin is expressed in pericryptal fibroblasts and cancer-associated fibroblasts in the colon. **J Histochem Cytochem**, **56**(8), 753-64.

Kim, C. J., Isono, T., Tambe, Y., Chano, T., Okabe, H., Okada, Y., and Inoue, H. (2008a). Role of alternative splicing of periostin in human bladder carcinogenesis. **Int J Oncol**, **32**(1), 161-9.

Kim, C. J., Yoshioka, N., Tambe, Y., Kushima, R., Okada, Y., and Inoue, H. (2005). Periostin is down-regulated in high grade human bladder cancers and suppresses in vitro cell invasiveness and *in vivo* metastasis of cancer cells. **Int J Cancer**, **117**(1), 51-8.

Kim, E. M., Kim, J. S., Choi, M. H., Hong, S. T., and Bae, Y. M. (2008b). Effects of excretory/secretory products from *Clonorchis sinensis* and the carcinogen dimethylnitrosamine on the proliferation and cell cycle modulation of human epithelial HEK293T cells. **Korean J Parasitol**, **46**(3), 127-32.

Kim, Y. I. (1984). Liver carcinoma and liver fluke infection. **Arzneimittelforschung**, **34**(9B), 1121-6.

Kirchmair R, H.-A. R., Gutierrez J, (1993). Secretoneurin-aneuropeptide generated in brain, adrenal medulla and other endocrine tissues by proteolytic processing of secretogranin II (chromogranin C). **Neuroscience**, **53**, 359-365.

Kohl, N. E. (1999). Farnesyltransferase inhibitors. Preclinical development. **Ann N Y Acad Sci**, **886**, 91-102.

Kohn, E. C., Alessandro, R., Spoonster, J., Wersto, R. P., and Liotta, L. A. (1995). Angiogenesis: role of calcium-mediated signal transduction. **Proc Natl Acad Sci U S A**, **92**(5), 1307-11.

Kren, A., Baeriswyl, V., Lehembre, F., Wunderlin, C., Strittmatter, K., Antoniadis, H., Fassler, R., Cavallaro, U., and Christofori, G. (2007). Increased tumor cell dissemination and cellular senescence in the absence of beta1-integrin function. **EMBO J, 26**(12), 2832-42.

Kruzynska-Frejtag, A., Wang, J., Maeda, M., Rogers, R., Krug, E., Hoffman, S., Markwald, R. R., and Conway, S. J. (2004). Periostin is expressed within the developing teeth at the sites of epithelial-mesenchymal interaction. **Dev Dyn, 229**(4), 857-68.

Kudo, Y., Ogawa, I., Kitajima, S., Kitagawa, M., Kawai, H., Gaffney, P. M., Miyauchi, M., and Takata, T. (2006). Periostin promotes invasion and anchorage-independent growth in the metastatic process of head and neck cancer. **Cancer Res, 66**(14), 6928-35.

Kudo, Y., Siriwardena, B. S., Hatano, H., Ogawa, I., and Takata, T. (2007). Periostin: novel diagnostic and therapeutic target for cancer. **Histol Histopathol, 22**(10), 1167-74.

Kuhn, B., del Monte, F., Hajjar, R. J., Chang, Y. S., Lebeche, D., Arab, S., and Keating, M. T. (2007). Periostin induces proliferation of differentiated cardiomyocytes and promotes cardiac repair. **Nat Med, 13**(8), 962-9.

Lazard, D., Sastre, X., Frid, M. G., Glukhova, M. A., Thiery, J. P., and Koteliansky, V. E. (1993). Expression of smooth muscle-specific proteins in myoepithelium and stromal myofibroblasts of normal and malignant human breast tissue. **Proc Natl Acad Sci U S A, 90**(3), 999-1003.

Lee, J. H., Rim, H. J., and Bak, U. B. (1993). Effect of *Clonorchis sinensis* infection and dimethylnitrosamine administration on the induction of cholangiocarcinoma in Syrian golden hamsters. **Korean J Parasitol, 31**(1), 21-30.

Li, J. S., Sun, G. W., Wei, X. Y., and Tang, W. H. (2007). Expression of periostin and its clinicopathological relevance in gastric cancer. **World J Gastroenterol, 13**(39), 5261-6.

Lim, M. K., Ju, Y. H., Franceschi, S., Oh, J. K., Kong, H. J., Hwang, S. S., Park, S. K., Cho, S. I., Sohn, W. M., Kim, D. I., Yoo, K. Y., Hong, S. T., and Shin, H. R. (2006). *Clonorchis sinensis* infection and increasing risk of cholangiocarcinoma in the Republic of Korea. **Am J Trop Med Hyg, 75**(1), 93-6.

Lin, J. T., Chen, M. K., Yeh, K. T., Chang, C. S., Chang, T. H., Lin, C. Y., Wu, Y. C., Su, B. W., Lee, K. D., and Chang, P. J. (2010). Association of High Levels of Jagged-1 and Notch-1 Expression with Poor Prognosis in Head and Neck Cancer. **Ann Surg Oncol**, (in press).

Lindner, V., Wang, Q., Conley, B. A., Friesel, R. E., and Vary, C. P. (2005). Vascular injury induces expression of periostin: implications for vascular cell differentiation and migration. **Arterioscler Thromb Vasc Biol, 25**(1), 77-83.

Lindvall, C., Hou, M., Komurasaki, T., Zheng, C., Henriksson, M., Sedivy, J. M., Bjorkholm, M., Teh, B. T., Nordenskjold, M., and Xu, D. (2003). Molecular characterization of human telomerase reverse transcriptase-immortalized human fibroblasts by gene expression profiling: activation of the epiregulin gene. **Cancer Res, 63**(8), 1743-7.

Liotta, L. A., and Kohn, E. C. (2001). The microenvironment of the tumour-host interface. **Nature, 411**(6835), 375-9.

Lipsett, P. A., Pitt, H. A., Colombani, P. M., Boitnott, J. K., and Cameron, J. L. (1994). Choledochal cyst disease. A changing pattern of presentation. **Ann Surg, 220**(5), 644-52.

Litvin, J., Zhu, S., Norris, R., and Markwald, R. (2005). Periostin family of proteins: therapeutic targets for heart disease. **Anat Rec A Discov Mol Cell Evol Biol, 287**(2), 1205-12.

Liu, B. Y., Soloviev, I., Chang, P., Lee, J., Huang, X., Zhong, C., Ferrara, N., Polakis, P., and Sakanaka, C. (2010). Stromal cell-derived factor-1/CXCL12 contributes to MMTV-Wnt1 tumor growth involving Gr1+CD11b+ cells. **PLoS One, 5**(1), e8611.

Liu, S., Calderwood, D. A., and Ginsberg, M. H. (2000). Integrin cytoplasmic domain-binding proteins. **J Cell Sci, 113**(Pt 20), 3563-71.

Lode, H. N., Moehler, T., Xiang, R., Jonczyk, A., Gillies, S. D., Cheresh, D. A., and Reisfeld, R. A. (1999). Synergy between an antiangiogenic integrin alphav antagonist and an antibody-cytokine fusion protein eradicates spontaneous tumor metastases. **Proc Natl Acad Sci U S A**, **96**(4), 1591-6.

Lu, W., Luo, Y., Kan, M., and McKeehan, W. L. (1999). Fibroblast growth factor-10. A second candidate stromal to epithelial cell andromedin in prostate. **J Biol Chem**, **274**(18), 12827-34.

Luque, A., Carpizo, D. R., and Iruela-Arispe, M. L. (2003). ADAMTS1/METH1 inhibits endothelial cell proliferation by direct binding and sequestration of VEGF165. **J Biol Chem**, **278**(26), 23656-65.

Lynch, C. C., and Matrisian, L. M. (2002). Matrix metalloproteinases in tumor-host cell communication. **Differentiation**, **70**(9-10), 561-73.

Mairiang, E., Elkins, D. B., Mairiang, P., Chaiyakum, J., Chamadol, N., Loapaiboon, V., Posri, S., Sithithaworn, P., and Haswell-Elkins, M. (1992). Relationship between intensity of *Opisthorchis viverrini* infection and hepatobiliary disease detected by ultrasonography. **J Gastroenterol Hepatol**, **7**(1), 17-21.

Maruyama, M., Kobayashi, N., Westerman, K. A., Sakaguchi, M., Allain, J. E., Totsugawa, T., Okitsu, T., Fukazawa, T., Weber, A., Stolz, D. B., Leboulch, P., and Tanaka, N. (2004). Establishment of a highly differentiated immortalized human cholangiocyte cell line with SV40T and hTERT. **Transplantation**, **77**(3), 446-51.

Masiero, L., Lapidos, K. A., Ambudkar, I., and Kohn, E. C. (1999). Regulation of the RhoA pathway in human endothelial cell spreading on type IV collagen: role of calcium influx. **J Cell Sci**, **112**(Pt 19), 3205-13.

Matsumoto, E., Yoshida, T., Kawarada, Y., and Sakakura, T. (1999). Expression of fibronectin isoforms in human breast tissue: production of extra domain A+/extra domain B+ by cancer cells and extra domain A+ by stromal cells. **Jpn J Cancer Res**, **90**(3), 320-5.

McIntyre, E., Blackburn, E., Brown, P. J., Johnson, C. G., and Gullick, W. J. (2010). The complete family of epidermal growth factor receptors and their ligands are co-ordinately expressed in breast cancer. **Breast Cancer Res Treat**, **122**(1), 105-10.

Menakongka, A., and Suthiphongchai, T. (2010). Involvement of PI3K and ERK1/2 pathways in hepatocyte growth factor-induced cholangiocarcinoma cell invasion. **World J Gastroenterol**, **16**(6), 713-22.

Mercier, I., Casimiro, M. C., Wang, C., Rosenberg, A. L., Quong, J., Minkeu, A., Allen, K. G., Danilo, C., Sotgia, F., Bonuccelli, G., Jasmin, J. F., Xu, H., Bosco, E., Aronow, B., Witkiewicz, A., Pestell, R. G., Knudsen, E. S., and Lisanti, M. P. (2008). Human breast cancer-associated fibroblasts (CAFs) show caveolin-1 downregulation and RB tumor suppressor functional inactivation: Implications for the response to hormonal therapy. **Cancer Biol Ther**, **7**(8), 1212-25.

Mercurio, A. M., and Rabinovitz, I. (2001). Towards a mechanistic understanding of tumor invasion-lessons from the alpha6beta 4 integrin. **Semin Cancer Biol**, **11**(2), 129-41.

Micke, P., Kappert, K., Ohshima, M., Sundquist, C., Scheidl, S., Lindahl, P., Heldin, C. H., Botling, J., Ponten, F., and Ostman, A. (2007). In situ identification of genes regulated specifically in fibroblasts of human basal cell carcinoma. **J Invest Dermatol**, **127**(6), 1516-23.

Micke, P., and Ostman, A. (2005). Exploring the tumour environment: cancer-associated fibroblasts as targets in cancer therapy. **Expert Opin Ther Targets**, **9**(6), 1217-33.

Mitra, S. K., and Schlaepfer, D. D. (2006). Integrin-regulated FAK-Src signaling in normal and cancer cells. **Curr Opin Cell Biol**, **18**(5), 516-23.

Miwa, S., Miyagawa, S., Soeda, J., and Kawasaki, S. (2002). Matrix metalloproteinase-7 expression and biologic aggressiveness of cholangiocellular carcinoma. **Cancer**, **94**(2), 428-34.

Mizushima, H., Hirosaki, T., Miyata, S., Takamura, H., Miyagi, Y., and Miyazaki, K. (2002). Expression of laminin-5 enhances tumorigenicity of human fibrosarcoma cells in nude mice. **Jpn J Cancer Res**, **93**(6), 652-9.

Mueller, M. M., and Fusenig, N. E. (2004). Friends or foes - bipolar effects of the tumour stroma in cancer. **Nat Rev Cancer**, **4**(11), 839-49.

Murakami, N., Koufuji, K., and Shirouzu, K. (2001). Influence of hepatocyte growth factor secreted from fibroblasts on the growth and invasion of scirrhous gastric cancer. **Int Surg**, **86**(3), 151-7.

Nakagawa, H., Liyanarachchi, S., Davuluri, R. V., Auer, H., Martin, E. W., Jr., de la Chapelle, A., and Frankel, W. L. (2004). Role of cancer-associated stromal fibroblasts in metastatic colon cancer to the liver and their expression profiles. **Oncogene**, **23**(44), 7366-77.

Nakajima, T., Kondo, Y., Miyazaki, M., and Okui, K. (1988). A histopathologic study of 102 cases of intrahepatic cholangiocarcinoma: histologic classification and modes of spreading. **Hum Pathol**, **19**(10), 1228-34.

Nakamura, T., Matsumoto, K., Kiritoshi, A., Tano, Y., and Nakamura, T. (1997). Induction of hepatocyte growth factor in fibroblasts by tumor-derived factors affects invasive growth of tumor cells: *in vitro* analysis of tumor-stromal interactions. **Cancer Res**, **57**(15), 3305-13.

Nakanuma, H., Terada, Ed. (1997). Clinical and pathologic features of cholangiocarcinoma. **New York: Churchill Livingstone**, 125-128.

Nakanuma, Y., Harada, K., Ishikawa, A., Zen, Y., and Sasaki, M. (2003). Anatomic and molecular pathology of intrahepatic cholangiocarcinoma. **J Hepatobiliary Pancreat Surg**, **10**(4), 265-81.

Nehls, O., Gregor, M., and Klump, B. (2004). Serum and bile markers for cholangiocarcinoma. **Semin Liver Dis**, **24**(2), 139-54.

Noel, A., and Foidart, J. M. (1998). The role of stroma in breast carcinoma growth in vivo. **J Mammary Gland Biol Neoplasia**, **3**(2), 215-25.

Ohira, S., Itatsu, K., Sasaki, M., Harada, K., Sato, Y., Zen, Y., Ishikawa, A., Oda, K., Nagasaka, T., Nimura, Y., and Nakanuma, Y. (2006). Local balance of transforming growth factor-beta1 secreted from cholangiocarcinoma cells and stromal-derived factor-1 secreted from stromal fibroblasts is a factor involved in invasion of cholangiocarcinoma. **Pathol Int**, **56**(7), 381-9.

Okamura, N., Yoshida, M., Shibuya, A., Sugiura, H., Okayasu, I., and Ohbu, M. (2005). Cellular and stromal characteristics in the scirrhous hepatocellular carcinoma: comparison with hepatocellular carcinomas and intrahepatic cholangiocarcinomas. **Pathol Int**, **55**(11), 724-31.

Olumi, A. F., Grossfeld, G. D., Hayward, S. W., Carroll, P. R., Tlsty, T. D., and Cunha, G. R. (1999). Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. **Cancer Res**, **59**(19), 5002-11.

Osmak, M., Babic, D., Abramic, M., Milicic, D., Vrhovec, I., and Skrk, J. (2001). Plasminogen activator inhibitor type 2: potential prognostic factor for endometrial carcinomas. **Neoplasma**, **48**(6), 462-7.

Ouyang, G., Liu, M., Ruan, K., Song, G., Mao, Y., and Bao, S. (2009). Up-regulated expression of periostin by hypoxia in non-small-cell lung cancer cells promotes cell survival via the Akt/PKB pathway. **Cancer Lett**, **281**(2), 213-9.

Parkin DM, W. S., Ferlay J, Teppo L, Thomas DBE, Ed. (2002). Cancer incidence in five continents. Vol. VIII. **Lyon: International Agency for Research on Cancer**, 1-781.

Parsons, J. T., and Parsons, S. J. (1997). Src family protein tyrosine kinases: cooperating with growth factor and adhesion signaling pathways. **Curr Opin Cell Biol**, **9**(2), 187-92.

Patsenker, E., Wilkens, L., Banz, V., Osterreicher, C. H., Weimann, R., Eisele, S., Keogh, A., Stroka, D., Zimmermann, A., and Stickel, F. (2010). The alphavbeta6 integrin is a highly specific immunohistochemical marker for cholangiocarcinoma. **J Hepatol**, **52**(3), 362-9.

Perbal, B. (2001). The expression of chicken NOV, a member of the CCN gene family, in early stage development. Mol. **Pathol**, **54**, 57-79.

Perrotte, P., Matsumoto, T., Inoue, K., Kuniyasu, H., Eve, B. Y., Hicklin, D. J., Radinsky, R., and Dinney, C. P. (1999). Anti-epidermal growth factor receptor antibody C225 inhibits angiogenesis in human transitional cell carcinoma growing orthotopically in nude mice. **Clin Cancer Res**, **5**(2), 257-65.

Picard, O., Rolland, Y., and Poupon, M. F. (1986). Fibroblast-dependent tumorigenicity of cells in nude mice: implication for implantation of metastases. **Cancer Res**, **46**(7), 3290-4.

Powell, D. W., Mifflin, R. C., Valentich, J. D., Crowe, S. E., Saada, J. I., and West, A. B. (1999). Myofibroblasts. I. Paracrine cells important in health and disease. **Am J Physiol**, **277**(1 Pt 1), C1-9.

Probst, M. R., Beer, M., Beer, D., Jeno, P., Meyer, U. A., and Gasser, R. (1994). Human liver arylacetamide deacetylase. Molecular cloning of a novel esterase involved in the metabolic activation of arylamine carcinogens with high sequence similarity to hormone-sensitive lipase. **J Biol Chem**, **269**(34), 21650-6.

Puglisi, F., Puppin, C., Pegolo, E., Andreetta, C., Pascoletti, G., D'Aurizio, F., Pandolfi, M., Fasola, G., Piga, A., Damante, G., and Di Loreto, C. (2008). Expression of periostin in human breast cancer. **J Clin Pathol**, **61**(4), 494-8.

Puppin, C., Fabbro, D., Dima, M., Di Loreto, C., Puxeddu, E., Filetti, S., Russo, D., and Damante, G. (2008). High periostin expression correlates with aggressiveness in papillary thyroid carcinomas. **J Endocrinol**, **197**(2), 401-8.

Ramage, J. K., Donaghy, A., Farrant, J. M., Iorns, R., and Williams, R. (1995). Serum tumor markers for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. **Gastroenterology**, **108**(3), 865-9.

Regales, L., Gong, Y., Shen, R., de Stanchina, E., Vivanco, I., Goel, A., Koutcher, J. A., Spassova, M., Ouerfelli, O., Mellinghoff, I. K., Zakowski, M. F., Politi, K. A., and Pao, W. (2009). Dual targeting of EGFR can overcome a major drug resistance mutation in mouse models of EGFR mutant lung cancer. **J Clin Invest**, **119**(10), 3000-10.

Riener, M. O., Fritzsche, F. R., Soll, C., Pestalozzi, B. C., Probst-Hensch, N., Clavien, P. A., Jochum, W., Soltermann, A., Moch, H., and Kristiansen, G. (2009). Expression of the extracellular matrix protein periostin in liver tumours and bile duct carcinomas. **Histopathology**, **56**(5), 600-6.

Rinehart, C. A., and Torti, V. R. (1997). Aging and cancer: the role of stromal interactions with epithelial cells. **Mol Carcinog**, **18**(4), 187-92.

Robinson, E. E., Zazzali, K. M., Corbett, S. A., and Foty, R. A. (2003). Alpha5beta1 integrin mediates strong tissue cohesion. **J Cell Sci**, **116**(Pt 2), 377-86.

Rodemann, H. P., and Muller, G. A. (1991). Characterization of human renal fibroblasts in health and disease: II. *In vitro* growth, differentiation, and collagen synthesis of fibroblasts from kidneys with interstitial fibrosis. **Am J Kidney Dis**, **17**(6), 684-6.

Ronnov-Jessen, L., Petersen, O. W., and Bissell, M. J. (1996). Cellular changes involved in conversion of normal to malignant breast: importance of the stromal reaction. **Physiol Rev**, **76**(1), 69-125.

Rosenthal, E. L., McCrory, A., Talbert, M., Carroll, W., Magnuson, J. S., and Peters, G. E. (2004). Expression of proteolytic enzymes in head and neck cancer-associated fibroblasts. **Arch Otolaryngol Head Neck Surg**, **130**(8), 943-7.

Ruan, K., Bao, S., and Ouyang, G. (2009). The multifaceted role of periostin in tumorigenesis. **Cell Mol Life Sci**, **66**(14), 2219-30.

Ruoslahti, E., and Pierschbacher, M. D. (1987). New perspectives in cell adhesion: RGD and integrins. **Science**, **238**(4826), 491-7.

Russell, P. J., Bennett, S., and Stricker, P. (1998). Growth factor involvement in progression of prostate cancer. **Clin Chem**, **44**(4), 705-23.

Saigusa, K., Imoto, I., Tanikawa, C., Aoyagi, M., Ohno, K., Nakamura, Y., and Inazawa, J. (2007). RGC32, a novel p53-inducible gene, is located on centrosomes during mitosis and results in G2/M arrest. **Oncogene**, **26**(8), 1110-21.

Sasaki, H., Dai, M., Auclair, D., Fukai, I., Kiriyama, M., Yamakawa, Y., Fujii, Y., and Chen, L. B. (2001a). Serum level of the periostin, a homologue of an insect cell adhesion molecule, as a prognostic marker in nonsmall cell lung carcinomas. **Cancer**, **92**(4), 843-8.

Sasaki, H., Lo, K. M., Chen, L. B., Auclair, D., Nakashima, Y., Moriyama, S., Fukai, I., Tam, C., Loda, M., and Fujii, Y. (2001b). Expression of Periostin, homologous with an insect cell adhesion molecule, as a prognostic marker in non-small cell lung cancers. **Jpn J Cancer Res**, **92**(8), 869-73.

Sasaki, H., Yu, C. Y., Dai, M., Tam, C., Loda, M., Auclair, D., Chen, L. B., and Elias, A. (2003). Elevated serum periostin levels in patients with bone metastases from breast but not lung cancer. **Breast Cancer Res Treat**, **77**(3), 245-52.

Schaller, M. D., Otey, C. A., Hildebrand, J. D., and Parsons, J. T. (1995). Focal adhesion kinase and paxillin bind to peptides mimicking beta integrin cytoplasmic domains. **J Cell Biol**, **130**(5), 1181-7.

Schlaepfer, D. D., and Mitra, S. K. (2004). Multiple connections link FAK to cell motility and invasion. **Curr Opin Genet Dev**, **14**(1), 92-101.

Schmidt-Hansen, B., Klingelhofer, J., Grum-Schwensen, B., Christensen, A., Andresen, S., Kruse, C., Hansen, T., Ambartsumian, N., Lukanidin, E., and Grigorian, M. (2004). Functional significance of metastasis-inducing S100A4(Mts1) in tumor-stroma interplay. **J Biol Chem**, **279**(23), 24498-504.

Schneller, M., Vuori, K., and Ruoslahti, E. (1997). Alphavbeta3 integrin associates with activated insulin and PDGF beta receptors and potentiates the biological activity of PDGF. **EMBO J**, **16**(18), 5600-7.

Scott, J., Shousha, S., Thomas, H. C., and Sherlock, S. (1980). Bile duct carcinoma: a late complication of congenital hepatic fibrosis. Case report and review of literature. **Am J Gastroenterol**, **73**(2), 113-9.

Shao, R., Bao, S., Bai, X., Blanchette, C., Anderson, R. M., Dang, T., Gishizky, M. L., Marks, J. R., and Wang, X. F. (2004). Acquired expression of periostin by human breast cancers promotes tumor angiogenesis through up-regulation of vascular endothelial growth factor receptor 2 expression. **Mol Cell Biol**, **24**(9), 3992-4003.

Shayesteh, L., Lu, Y., Kuo, W. L., Baldocchi, R., Godfrey, T., Collins, C., Pinkel, D., Powell, B., Mills, G. B., and Gray, J. W. (1999). PIK3CA is implicated as an oncogene in ovarian cancer. **Nat Genet**, **21**(1), 99-102.

Sherr, C. J., and McCormick, F. (2002). The RB and p53 pathways in cancer. **Cancer Cell**, **2**(2), 103-12.

Shimazaki, M., and Kudo, A. (2008). Impaired capsule formation of tumors in periostin-null mice. **Biochem Biophys Res Commun**, **367**(4), 736-42.

Shimonishi, T., Miyazaki, K., Kono, N., Sabit, H., Tuneyama, K., Harada, K., Hirabayashi, J., Kasai, K., and Nakanuma, Y. (2001). Expression of endogenous galectin-1 and galectin-3 in intrahepatic cholangiocarcinoma. **Hum Pathol**, **32**(3), 302-10.

Shin, H. R., Oh, J. K., Masuyer, E., Curado, M. P., Bouvard, V., Fang, Y. Y., Wiangnon, S., Sripa, B., and Hong, S. T. (2010). Epidemiology of cholangiocarcinoma: an update focusing on risk factors. **Cancer Sci**, **101**(3), 579-85.

Shirabe, K., Shimada, M., Kajiyama, K., Hasegawa, H., Gion, T., Ikeda, Y., Takenaka, K., and Sugimachi, K. (1999). Expression of matrix metalloproteinase-9 in surgically resected intrahepatic cholangiocarcinoma. **Surgery**, **126**(5), 842-6.

Shirakata, Y., Komurasaki, T., Toyoda, H., Hanakawa, Y., Yamasaki, K., Tokumaru, S., Sayama, K., and Hashimoto, K. (2000). Epiregulin, a novel member of the epidermal growth factor family, is an autocrine growth factor in normal human keratinocytes. **J Biol Chem, 275**(8), 5748-53.

Sills, A. K., Jr., Williams, J. I., Tyler, B. M., Epstein, D. S., Sipos, E. P., Davis, J. D., McLane, M. P., Pitchford, S., Cheshire, K., Gannon, F. H., Kinney, W. A., Chao, T. L., Donowitz, M., Laterra, J., Zasloff, M., and Brem, H. (1998). Squalamine inhibits angiogenesis and solid tumor growth *in vivo* and perturbs embryonic vasculature. **Cancer Res, 58**(13), 2784-92.

Singer, C., Rasmussen, A., Smith, H. S., Lippman, M. E., Lynch, H. T., and Cullen, K. J. (1995). Malignant breast epithelium selects for insulin-like growth factor II expression in breast stroma: evidence for paracrine function. **Cancer Res, 55**(11), 2448-54.

Singer, C. F., Gschwantler-Kaulich, D., Fink-Retter, A., Haas, C., Hudelist, G., Czerwenka, K., and Kubista, E. (2008). Differential gene expression profile in breast cancer-derived stromal fibroblasts. **Breast Cancer Res Treat, 110**(2), 273-81.

Sirica, A. E. (2005). Cholangiocarcinoma: molecular targeting strategies for chemoprevention and therapy. **Hepatology, 41**(1), 5-15.

Siriwardena, B. S., Kudo, Y., Ogawa, I., Kitagawa, M., Kitajima, S., Hatano, H., Tilakaratne, W. M., Miyauchi, M., and Takata, T. (2006). Periostin is frequently overexpressed and enhances invasion and angiogenesis in oral cancer. **Br J Cancer, 95**(10), 1396-403.

Smout, M. J., Laha, T., Mulvenna, J., Sripa, B., Suttiprapa, S., Jones, A., Brindley, P. J., and Loukas, A. (2009). A granulin-like growth factor secreted by the carcinogenic liver fluke, *Opisthorchis viverrini*, promotes proliferation of host cells. **PLoS Pathog, 5**(10), e1000611.

Sriamporn, S., Pisani, P., Pipitgool, V., Suwanrungruang, K., Kamsa-ard, S., and Parkin, D. M. (2004). Prevalence of *Opisthorchis viverrini* infection and incidence of cholangiocarcinoma in Khon Kaen, Northeast Thailand. **Trop Med Int Health, 9**(5), 588-94.

Sripa, B., and Kaewkes, S. (2000). Localisation of parasite antigens and inflammatory responses in experimental opisthorchiasis. **Int J Parasitol**, **30**(6), 735-40.

Sripa, B., Kaewkes, S., Sithithaworn, P., Mairiang, E., Laha, T., Smout, M., Pairojkul, C., Bhudhisawasdi, V., Tesana, S., Thinkamrop, B., Bethony, J. M., Loukas, A., and Brindley, P. J. (2007). Liver fluke induces cholangiocarcinoma. **PLoS Med**, **4**(7), e201.

Sripa, B., and Pairojkul, C. (2008). Cholangiocarcinoma: lessons from Thailand. **Curr Opin Gastroenterol**, **24**(3), 349-56.

Srivatanakul, P. (2001). Epidemiology of Liver Cancer in Thailand. **Asian Pac J Cancer Prev**, **2**(2), 117-121.

Steiglitz, B. M., Keene, D. R., and Greenspan, D. S. (2002). PCOLCE2 encodes a functional procollagen C-proteinase enhancer (PCPE2) that is a collagen-binding protein differing in distribution of expression and post-translational modification from the previously described PCPE1. **J Biol Chem**, **277**(51), 49820-30.

Tai, I. T., Dai, M., and Chen, L. B. (2005). Periostin induction in tumor cell line explants and inhibition of *in vitro* cell growth by anti-periostin antibodies. **Carcinogenesis**, **26**(5), 908-15.

Takanami, I., Abiko, T., and Koizumi, S. (2008). Expression of periostin in patients with non-small cell lung cancer: correlation with angiogenesis and lymphangiogenesis. **Int J Biol Markers**, **23**(3), 182-6.

Takeshita, S., Kikuno, R., Tezuka, K., and Amann, E. (1993). Osteoblast-specific factor 2: cloning of a putative bone adhesion protein with homology with the insect protein fasciclin I. **Biochem J**, **294**(Pt 1), 271-8.

Terada, T., Makimoto, K., Terayama, N., Suzuki, Y., and Nakanuma, Y. (1996). Alpha-smooth muscle actin-positive stromal cells in cholangiocarcinomas, hepatocellular carcinomas and metastatic liver carcinomas. **J Hepatol**, **24**(6), 706-12.

Thant, A. A., Nawa, A., Kikkawa, F., Ichigotani, Y., Zhang, Y., Sein, T. T., Amin, A. R., and Hamaguchi, M. (2000). Fibronectin activates matrix metalloproteinase-9 secretion via the MEK1-MAPK and the PI3K-Akt pathways in ovarian cancer cells. **Clin Exp Metastasis**, **18**(5), 423-8.

Thuwajit, C., Thuwajit, P., Kaewkes, S., Sripa, B., Uchida, K., Miwa, M., and Wongkham, S. (2004). Increased cell proliferation of mouse fibroblast NIH-3T3 *in vitro* induced by excretory/secretory product(s) from *Opisthorchis viverrini*. **Parasitology**, **129**(Pt 4), 455-64.

Thuwajit, C., Thuwajit, P., Uchida, K., Daorueang, D., Kaewkes, S., Wongkham, S., and Miwa, M. (2006). Gene expression profiling defined pathways correlated with fibroblast cell proliferation induced by *Opisthorchis viverrini* excretory/secretory product. **World J Gastroenterol**, **12**(22), 3585-92.

Tilman, G., Mattiussi, M., Brasseur, F., van Baren, N., and Decottignies, A. (2007). Human periostin gene expression in normal tissues, tumors and melanoma: evidences for periostin production by both stromal and melanoma cells. **Mol Cancer**, **6**, 80.

Tischler, V., Fritzsche, F. R., Wild, P. J., Stefan, C., Seifert, H. H., Riener, M. O., Hermanns, T., Mortezavi, A., Gerhardt, J., Schraml, P., Jung, K., Moch, H., Soltermann, A., and Kristiansen, G. (2010). Periostin is up-regulated in high grade and high stage prostate cancer. **BMC Cancer**, **10**(1), 273.

Tomari, K., Kumagai, T., Shimizu, T., and Takeda, K. (2005). Bone morphogenetic protein-2 induces hypophosphorylation of Rb protein and repression of E2F in androgen-treated LNCaP human prostate cancer cells. **Int J Mol Med**, **15**(2), 253-8.

Trojanowska, M. (2008). Role of PDGF in fibrotic diseases and systemic sclerosis. **Rheumatology**, **47**, v2-v4.

Trusolino, L., Bertotti, A., and Comoglio, P. M. (2001). A signaling adapter function for alpha6beta4 integrin in the control of HGF-dependent invasive growth. **Cell**, **107**(5), 643-54.

Tuomi, S., Mai, A., Nevo, J., Laine, J. O., Vilkki, V., Ohman, T. J., Gahmberg, C. G., Parker, P. J., and Ivaska, J. (2009). PKCepsilon regulation of an alpha5 integrin-ZO-1 complex controls lamellae formation in migrating cancer cells. **Sci Signal**, **2**(77), ra32.

Uchida, K., Samma, S., Momose, H., Kashihara, N., Rademaker, A., and Oyasu, R. (1990). Stimulation of urinary bladder tumorigenesis by carcinogen-exposed stroma. **J Urol**, **143**(3), 618-21.

Uttaravichien, T., Bhudhisawasdi, V., Pairojkul, C., and Pugkhem, A. (1999). Intrahepatic cholangiocarcinoma in Thailand. **J Hepatobiliary Pancreat Surg, 6**(2), 128-35.

Uttaravichien, T., Buddhisawasdi, V., Pairojkul, C. (1996). Bile duct cancer and the liver fluke: Pathology, presentation and surgical management. **Asian J Surg, 19**, 267-270.

van den Hooff, A. (1983). Connective tissue changes in cancer. **Int Rev Connect Tissue Res, 10**, 395-432.

Varley, C., Hill, G., Pellegrin, S., Shaw, N. J., Selby, P. J., Trejdosiewicz, L. K., and Southgate, J. (2005). Autocrine regulation of human urothelial cell proliferation and migration during regenerative responses *in vitro*. **Exp Cell Res, 306**(1), 216-29.

Vatanasapt, V., Uttaravichien, T., Mairiang, E. O., Pairojkul, C., Chartbanchachai, W., and Haswell-Elkins, M. (1990). Cholangiocarcinoma in north-east Thailand. **Lancet, 335**(8681), 116-7.

Vazquez, F., Hastings, G., Ortega, M. A., Lane, T. F., Oikemus, S., Lombardo, M., and Iruela-Arispe, M. L. (1999). METH-1, a human ortholog of ADAMTS-1, and METH-2 are members of a new family of proteins with angio-inhibitory activity. **J Biol Chem, 274**(33), 23349-57.

Volpes, R., van den Oord, J. J., and Desmet, V. J. (1993). Integrins as differential cell lineage markers of primary liver tumors. **Am J Pathol, 142**(5), 1483-92.

Wang, J., Ying, G., Jung, Y., Lu, J., Zhu, J., Pienta, K. J., and Taichman, R. S. (2010a). Characterization of phosphoglycerate kinase-1 expression of stromal cells derived from tumor microenvironment in prostate cancer progression. **Cancer Res, 70**(2), 471-80.

Wang, Z., Li, Y., Banerjee, S., Kong, D., Ahmad, A., Nogueira, V., Hay, N., and Sarkar, F. H. (2010b). Down-regulation of Notch-1 and Jagged-1 inhibits prostate cancer cell growth, migration and invasion, and induces apoptosis via inactivation of Akt, mTOR, and NF-kappaB signaling pathways. **J Cell Biochem, 109**(4), 726-36.

Watanapa, P., and Watanapa, W. B. (2002). Liver fluke-associated cholangiocarcinoma. **Br J Surg, 89**(8), 962-70.

Wolgemuth, D. J. (2008). Function of cyclins in regulating the mitotic and meiotic cell cycles in male germ cells. **Cell Cycle**, **7**(22), 3509-13.

Wright, J. H., McDonnell, S., Portella, G., Bowden, G. T., Balmain, A., and Matrisian, L. M. (1994). A switch from stromal to tumor cell expression of stromelysin-1 mRNA associated with the conversion of squamous to spindle carcinomas during mouse skin tumor progression. **Mol Carcinog**, **10**(4), 207-15.

Wu, G. S., Zou, S. Q., Liu, Z. R., Tang, Z. H., and Wang, J. H. (2003). Celecoxib inhibits proliferation and induces apoptosis via prostaglandin E2 pathway in human cholangiocarcinoma cell lines. **World J Gastroenterol**, **9**(6), 1302-6.

Wu, L., Bernard-Trifilo, J. A., Lim, Y., Lim, S. T., Mitra, S. K., Uryu, S., Chen, M., Pallen, C. J., Cheung, N. K., Mikolon, D., Mielgo, A., Stupack, D. G., and Schlaepfer, D. D. (2008). Distinct FAK-Src activation events promote alpha5beta1 and alpha4beta1 integrin-stimulated neuroblastoma cell motility. **Oncogene**, **27**(10), 1439-48.

Xouri, G., and Christian, S. (2010). Origin and function of tumor stroma fibroblasts. **Semin Cell Dev Biol**, **21**(1), 40-6.

Yan, W., and Shao, R. (2006). Transduction of a mesenchyme-specific gene periostin into 293T cells induces cell invasive activity through epithelial-mesenchymal transformation. **J Biol Chem**, **281**(28), 19700-8.

Yang, S. F., Hsieh, Y. S., Lin, C. L., Hsu, N. Y., Chiou, H. L., Chou, F. P., and Chu, S. C. (2005). Increased plasma levels of urokinase plasminogen activator and matrix metalloproteinase-9 in non-small cell lung cancer patients. **Clin Chim Acta**, **354**(1-2), 91-9.

Yee, D., Rosen, N., Favoni, R. E., and Cullen, K. J. (1991). The insulin-like growth factors, their receptors, and their binding proteins in human breast cancer. **Cancer Treat Res**, **53**, 93-106.

Yoshioka, N., Fuji, S., Shimakage, M., Kodama, K., Hakura, A., Yutsudo, M., Inoue, H., and Nojima, H. (2002). Suppression of anchorage-independent growth of human cancer cell lines by the TRIF52/periostin/OSF-2 gene. **Exp Cell Res**, **279**(1), 91-9.

Yotsumoto, F., Fukami, T., Yagi, H., Funakoshi, A., Yoshizato, T., Kuroki, M., and Miyamoto, S. (2010). Amphiregulin regulates the activation of ERK and Akt through epidermal growth factor receptor and HER3 signals involved in the progression of pancreatic cancer. **Cancer Sci**, (in press).

Yuan, Z. Q., Sun, M., Feldman, R. I., Wang, G., Ma, X., Jiang, C., Coppola, D., Nicosia, S. V., and Cheng, J. Q. (2000). Frequent activation of AKT2 and induction of apoptosis by inhibition of phosphoinositide-3-OH kinase/Akt pathway in human ovarian cancer. **Oncogene**, **19**(19), 2324-30.

Zeng, Z. Z., Yao, H., Staszewski, E. D., Rockwood, K. F., Markwart, S. M., Fay, K. S., Spalding, A. C., and Livant, D. L. (2009). alpha(5)beta(1) Integrin Ligand PHSRN Induces Invasion and alpha(5) mRNA in Endothelial Cells to Stimulate Angiogenesis. **Transl Oncol**, **2**(1), 8-20.

Zhang, Z., Vuori, K., Reed, J. C., and Ruoslahti, E. (1995). The alpha 5 beta 1 integrin supports survival of cells on fibronectin and up-regulates Bcl-2 expression. **Proc Natl Acad Sci U S A**, **92**(13), 6161-5.

Zhao, F. L., and Guo, W. (2010). Expression of stromal derived factor-1 (SDF-1) and chemokine receptor (CXCR4) in bone metastasis of renal carcinoma. **Mol Biol Rep**, (in press).

Zheng, M., Bocangel, D., Ramesh, R., Ekmekcioglu, S., Poindexter, N., Grimm, E. A., and Chada, S. (2008). Interleukin-24 overcomes temozolomide resistance and enhances cell death by down-regulation of O6-methylguanine-DNA methyltransferase in human melanoma cells. **Mol Cancer Ther**, **7**(12), 3842-51.

Zou, J., Ren, J. H., Feng, D., Wang, H., and Xu, J. (2008). Compensatory function of bradykinin B1 receptor in the inhibitory effect of captopril on cardiomyocyte hypertrophy and cardiac fibroblast proliferation in neonatal rats. **Chin Med J (Engl)**, **121**(13), 1220-5.

APPENDICES

APPENDIX A
PRIMARY CULTURE FIBROBLASTS AND HUMAN BILIARY EPITHELIAL CELL LINES

A-1 Primary culture fibroblasts

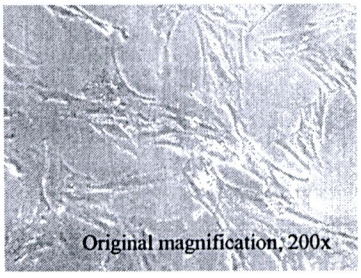
Cell Name	Cf1
Species	*Homo Sapiens*
Sex	Male
Age	56-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Papillary
Establisher	Chuaysri, C. et al. 2009
Medium	10% FBS containing DMEM with 20% epidermal growth factor
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C

Cell Name	Cf2
Species	*Homo Sapiens*
Sex	Male
Age	44-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Papillary
Establisher	Chuaysri, C. et al. 2009
Medium	10% FBS containing DMEM
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C

Cell Name	Lf1
Species	*Homo Sapiens*
Sex	Male
Age	56-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Papillary
Establisher	Chuaysri, C. et al. 2009
Medium	10% FBS containing DMEM with 20% epidermal growth factor
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C

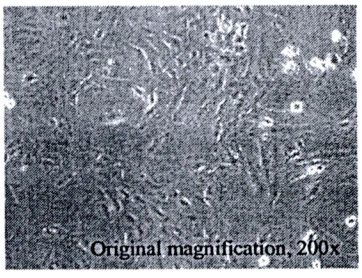
A-1 Primary culture fibroblasts (Cont.)

Cell Name	Lf2
Species	*Homo Sapiens*
Sex	Male
Age	44-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Papillary
Establisher	Chuaysri, C. et al. 2009
Medium	10% FBS containing DMEM
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C



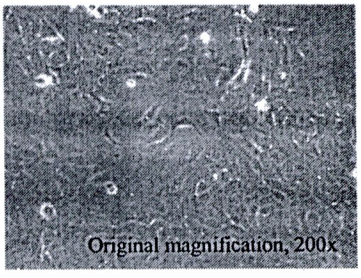
A-2 Non-tumorigenic biliary epithelial cells

Cell Name	MMNK1
Species	*Homo Sapiens*
Source	SV40T-transduced human liver OUMS-21cells
Establisher	Maruyama et al., 2004
Medium	10% FBS containing HAM F-12
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C



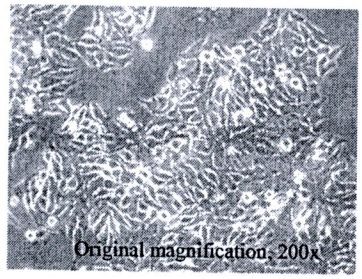
A-3 Tumorigenic biliary epithelial cells

Cell Name	KKU-M213
Species	*Homo Sapiens*
Sex	Male
Age	58-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Well-differentiated
Establisher	Sripa, B. et al.
Medium	10% FBS containing HAM F-12
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C



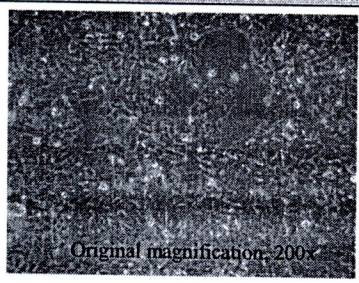
A-3 Tumorigenic biliary epithelial cells (Cont.)

Cell Name	KKU-OCA17
Species	*Homo Sapiens*
Sex	Male
Age	38-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Well-differentiated
Establisher	Sripa, B. et al.
Medium	10% FBS containing HAM F-12
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C



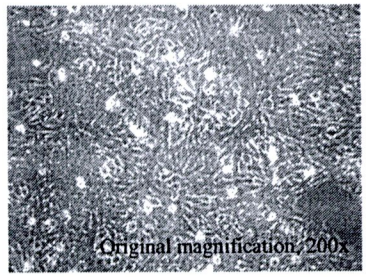
Cell Name	KKU-M214
Species	*Homo Sapiens*
Sex	Male
Age	52-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Well-differentiated
Establisher	Sripa, B. et al.
Medium	10% FBS containing HAM F-12
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C

Cell Name	KKU-M156
Species	*Homo Sapiens*
Sex	Male
Age	68-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Moderately-differentiated
Establisher	Sripa, B. et al.
Medium	10% FBS containing HAM F-12
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C

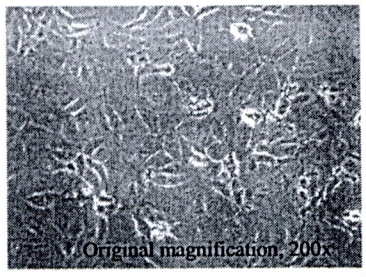


A-3 Tumorigenic biliary epithelial cells (Cont.)

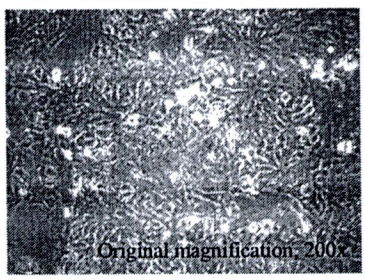
Cell Name	KKU-M055
Species	*Homo Sapiens*
Sex	Male
Age	56-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Moderately-differentiated
Establisher	Sripa, B. et al.
Medium	10% FBS containing HAM F-12
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C



Cell Name	KKU-M139
Species	*Homo Sapiens*
Sex	Female
Age	53-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Moderately-differentiated
Establisher	Sripa, B. et al.
Medium	10% FBS containing HAM F-12
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C



Cell Name	KKU-100
Species	*Homo Sapiens*
Sex	Female
Age	65-year-old
Diagnosis	Cholangiocarcinoma
Histological type	Poorly-differentiated
Establisher	Sripa, B. et al.
Medium	10% FBS containing HAM F-12
Passage Method	Cells treated with 0.25% Trypsin-EDTA for 5 min at 37°C



APPENDIX B

RAW DATA OF PN EXPRESSION IN CCA TISSUES

B-1 Raw data of PN expression in 52 CCA tissues

No.	Patient code	Age (yr)	Sex	Tumor size (cm)	Tumor staging	Histological type	Vascular invasion	Lymph node metastasis	Survival (d)	Status 4/10/07	Grading (IxA)	Level of PN expression*
1	M005	75	F	3	4	WD	Absence	Presence	277	Death	0	Low
2	M009	57	M	5	4B	MD	Absence	Absence	119	Death	6	High
3	M012	61	F	3	4	MD	Absence	Absence	118	Death	9	High
4	M014	70	M	2	3	WD	Absence	Absence	215	Death	4	Low
5	M030	37	F	12	3	Pap	Absence	Absence	245	Death	1	Low
6	M037	60	M	5	4B	Pap	Absence	Presence	429	Death	4	Low
7	M040	54	F	7	4	MD	Absence	Absence	425	Death	6	High
8	M043	50	M	9	4B	WD	Absence	Absence	191	Death	9	High
9	M055	56	M	7	4B	MD	Absence	Absence	34	Death	9	High
10	M057	61	M	10	4B	WD	Absence	Absence	211	Death	6	High
11	M068	54	M	5	4A	PD	Absence	Absence	395	Death	4	Low
12	M071	46	M	8	4B	WD	Absence	Presence	50	Death	6	High
13	M079	55	M	2	4A	WD	Absence	Absence	297	Death	6	High
14	M082	53	M	5	4A	Pap	Absence	Absence	637	Death	4	Low
15	M090	53	M	7	4A	Pap	Absence	Absence	294	Death	9	High
16	M097	58	M	2	2	WD	Absence	Absence	225	Death	0	Low
17	M101	64	M	9	4A	MD	Absence	Absence	51	Death	6	High
18	M102	56	M	7	4B	PD	Absence	Presence	35	Death	0	Low

B-1 Raw data of PN expression in 52 CCA tissues (Cont.)

No.	Patient code	Age (yr)	Sex	Tumor size (cm)	Tumor staging	Histological type	Vascular invasion	Lymph node metastasis	Survival (d)	Status 4/10/07	Grading (IxA)	Level of PN expression*
19	M114	61	M	3	4B	Pap	Absence	Absence	26	Death	9	High
20	M117	72	M	3.5	4B	PD	Absence	Absence	140	Death	9	High
21	M123	55	M	4	4B	WD	Absence	Absence	10	Death	6	High
22	M131	63	F	3	4B	Pap	Absence	Absence	1011	Death	0	Low
23	M136	49	F	5.5	3	WD	Absence	Absence	308	Death	9	High
24	M137	53	M	4	4	WD	Absence	Absence	3010	Death	4	Low
25	M139	53	F	5.5	4	MD	Presence	Presence	14	Death	6	High
26	M140	45	F	4.5	4B	WD	Absence	Presence	313	Death	9	High
27	M148	56	M	13	2	PD	Presence	Absence	214	Death	2	Low
28	M152	55	M	4.5	4B	MD	Presence	Absence	514	Death	0	Low
29	M155	52	M	8	4B	WD	Absence	Absence	358	Death	9	High
30	M157	72	F	8	4B	PD	Presence	Presence	139	Death	3	Low
31	M171	65	F	5	4B	WD	Absence	Presence	145	Death	6	High
32	M174	59	F	3	1	Pap	Absence	Absence	3146	Alive	0	Low
33	M189	67	M	7.5	3	Pap	Absence	Absence	2465	Death	2	Low
34	M209	61	F	5	4A	PD	Presence	Presence	157	Death	9	High
35	M213	58	M	8	4A	Pap	Presence	Presence	45	Death	9	High
36	M236	61	F	12	2	Pap	Absence	Absence	1277	Death	9	High

B-1 Raw data of PN expression in 52 CCA tissues (Cont.)

No.	Patient code	Age (yr)	Sex	Tumor size (cm)	Tumor staging	Histological type	Vascular invasion	Lymph node metastasis	Survival (d)	Status 4/10/07	Grading (IxA)	Level of PN expression*
37	M240	69	M	5	4B	WD	Absence	Presence	202	Death	1	Low
38	M250	66	M	8	4B	MD	Absence	Presence	76	Death	9	High
39	M259	63	M	4	3	WD	Absence	Absence	2505	Death	6	High
40	M266	62	M	7	4	Pap	Absence	Absence	179	Death	9	High
41	M270	55	M	5	4B	WD	Absence	Presence	149	Death	6	High
42	M273	60	F	6	4B	WD	Presence	Absence	60	Death	6	High
43	M274	47	F	5	4B	Pap	Absence	Absence	189	Death	6	High
44	M275	49	M	1.5	4B	WD	Absence	Absence	2935	Alive	6	High
45	M294	51	F	5	3	PD	Presence	Absence	2893	Alive	0	Low
46	M303	52	M	2	4B	WD	Absence	Absence	94	Death	4	Low
47	M311	41	M	3	4B	Pap	Absence	Presence	329	Death	6	High
48	M319	67	F	4.5	4B	PD	Absence	Absence	1743	Death	0	Low
49	N019	62	M	10	4B	Pap	Presence	Absence	2143	Death	9	High
50	P060	64	F	8	4B	Pap	Absence	Presence	1407	Death	1	Low
51	P078	59	F	4	4A	WD	Presence	Absence	124	Death	2	Low
52	QO66	51	F	8	4B	WD	Presence	Absence	1850	Alive	0	Low

M: Male, F: Female, WD; Well-differentiated adenocarcinoma, MD; Moderately-differentiated adenocarcinoma, PD; Poorly-differentiated adenocarcinoma and Pap; Papillary carcinoma. I: intensity, A: % positive area, * Low expression: grade 0-4; High expression: grade 5-9

B-2 Raw data of PN expression in benign and HCC tissues

No.	Patient code	Age (yr)	Sex	Diagnosis	Grading (IxA)	Level of PN expression*
1	Q067	44	F	Cavenous haemangioma	3	Low
2	R082	51	M	Chronic inflammation	2	Low
3	T075	32	F	Liver necrosis with fibrosis	3	Low
4	U115	59	M	Calcified necrotic tissue with granulomatous reaction possible dead parasite	1	Low
5	X070	60	F	Chronic cholecystitis.	0	Low
6	X086	39	F	No tumor is identified	0	Low
7	X128	66	M	Biliary cystadenoma	1	Low
8	X180	54	M	Cavenous haemangioma	4	Low
9	R140	49	M	HCC	1	Low
10	R141	33	M	HCC	2	Low
11	W001	55	M	HCC	4	Low
12	W088	47	M	HCC	0	Low

M: Male, F: Female, WD; Well-differentiated adenocarcinoma, MD; Moderately-differentiated adenocarcinoma, PD; Poorly-differentiated adenocarcinoma and Pap; Papillary carcinoma .I: intensity, A: % positive area, * Low expression: grade 0-4; High expression: grade 5-9

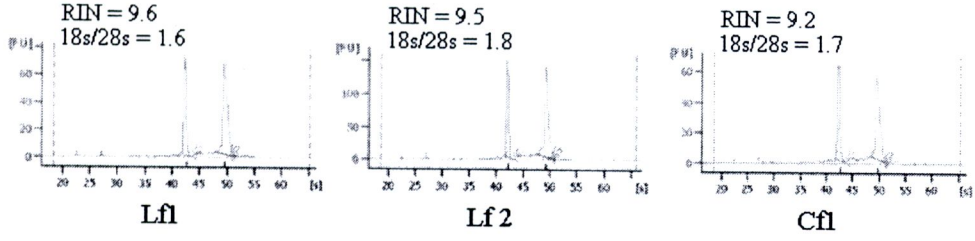
APPENDIX C

RNA EXTRAXTION AND MELTING CURVE ANALYSIS OF REAL TIME PCR

C-1 Quality analysis of RNA extracted from fibroblasts

Total RNA was extracted from 3-5 x 10^5 cells of Cf, Lf1 and Lf2, using RNeasy Micro Kit as the manufacturer's instruction. The quality of RNA was assessed by an Agilent RNA 6000 Nano Kit. RNA integrity number (RIN) of all 3 samples showed more than 9.0 (9.6 for Lf1, 9.5 for Lf2 and 9.2 for Cf1) (Fig C-1A) and 18S/28S ratio of ribosomal RNA showed nearly to 1.8 (1.6 for Lf1, 1.8 for Lf2 and 1.7 for Cf1). Herein, these RNA samples were accepted for the good quality of RNA to perform gene expression analysis.

A



B

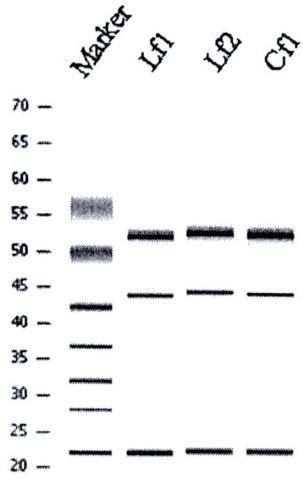
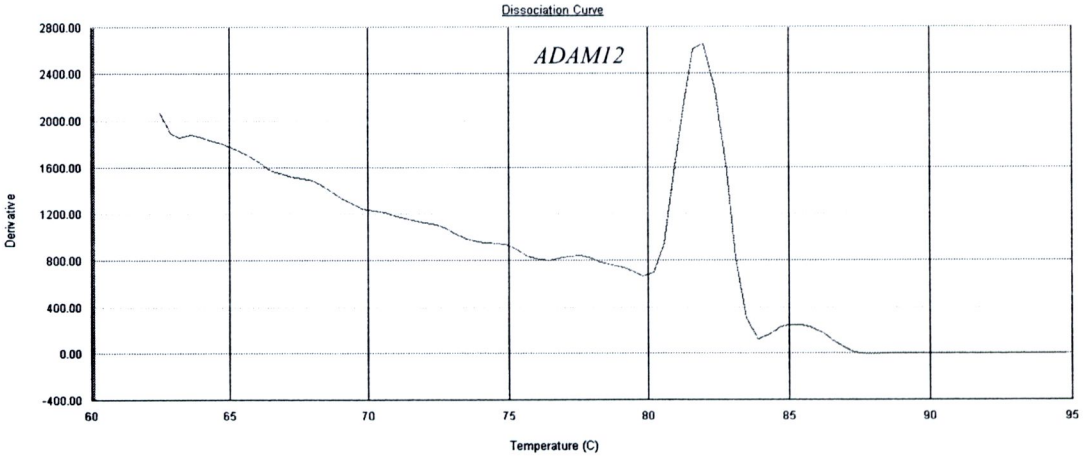
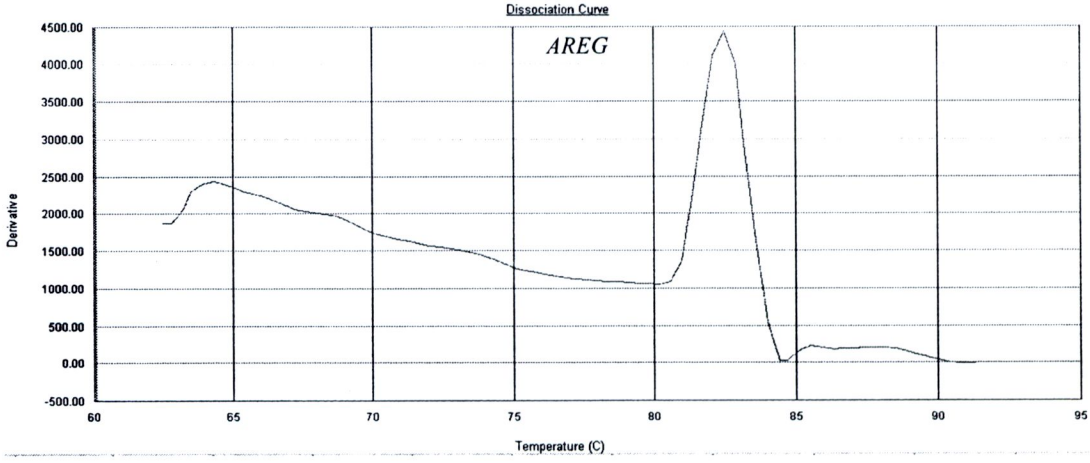
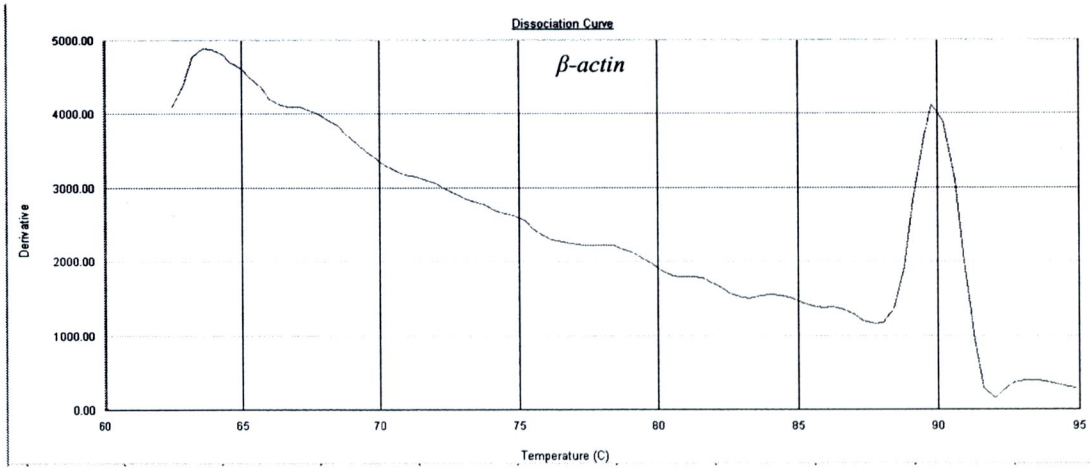


Figure C-1 Quality analysis of RNA extracted from fibroblasts. The RIN value and 18S:28S ratio of all 3 samples are shown (A). Gel electrophoresis shows bands of 18S and 28S ribosomal RNA compared to marker (B).

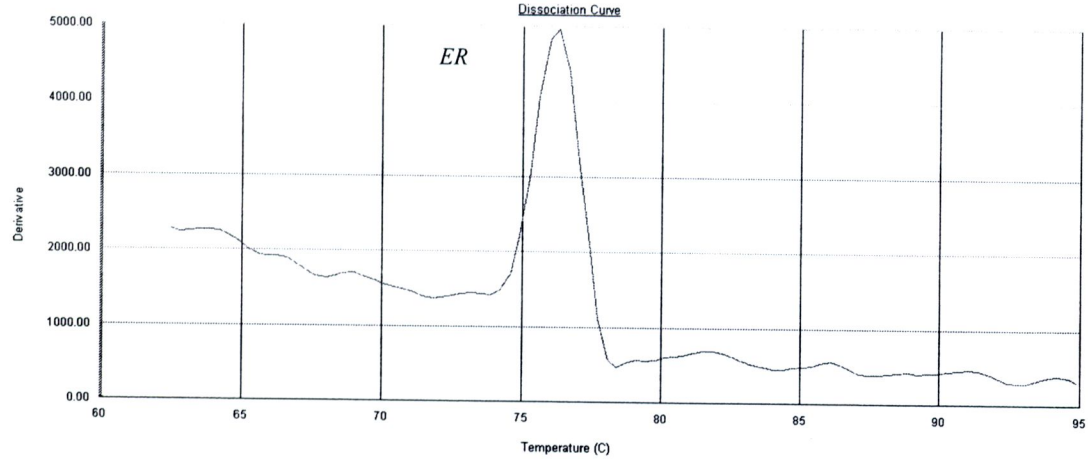
C-2 Melting curve analysis by ABI 7500 machine

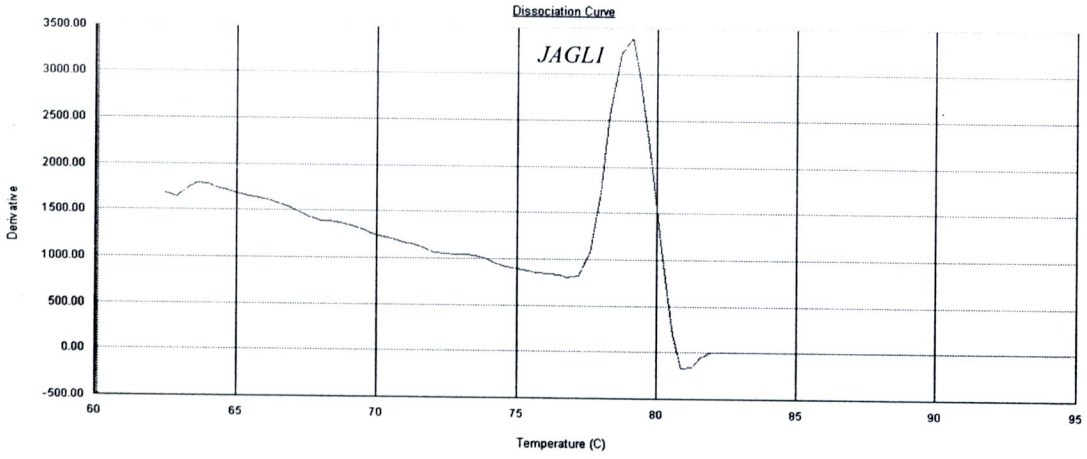


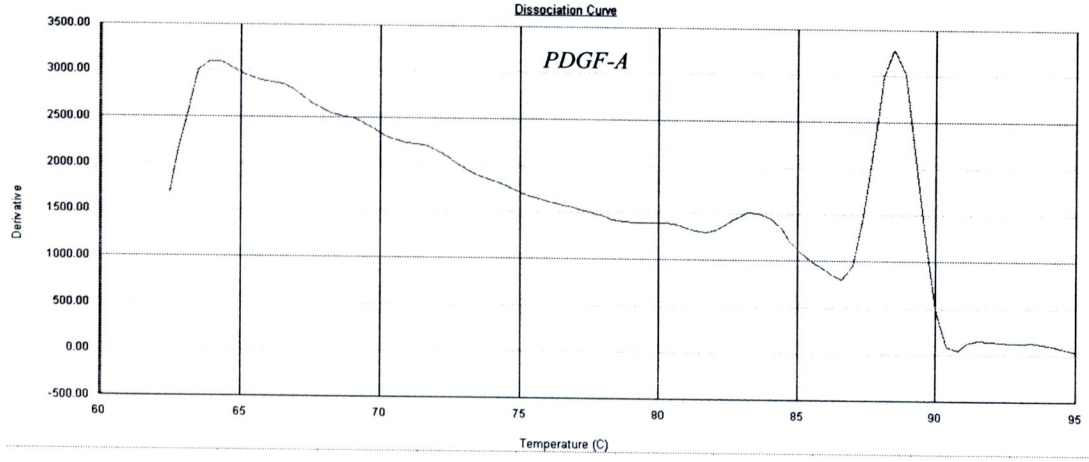




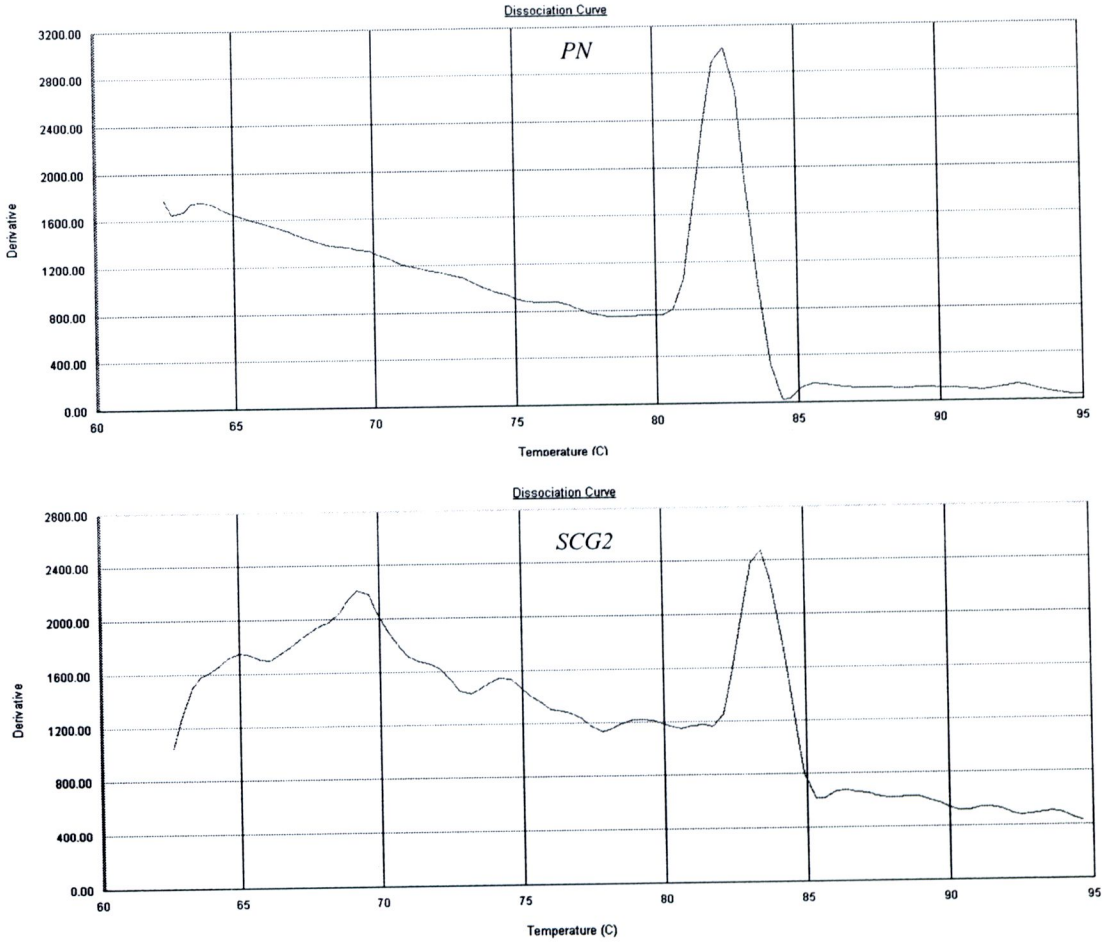
C-2 Melting curve analysis by ABI 7500 machine (Cont.)



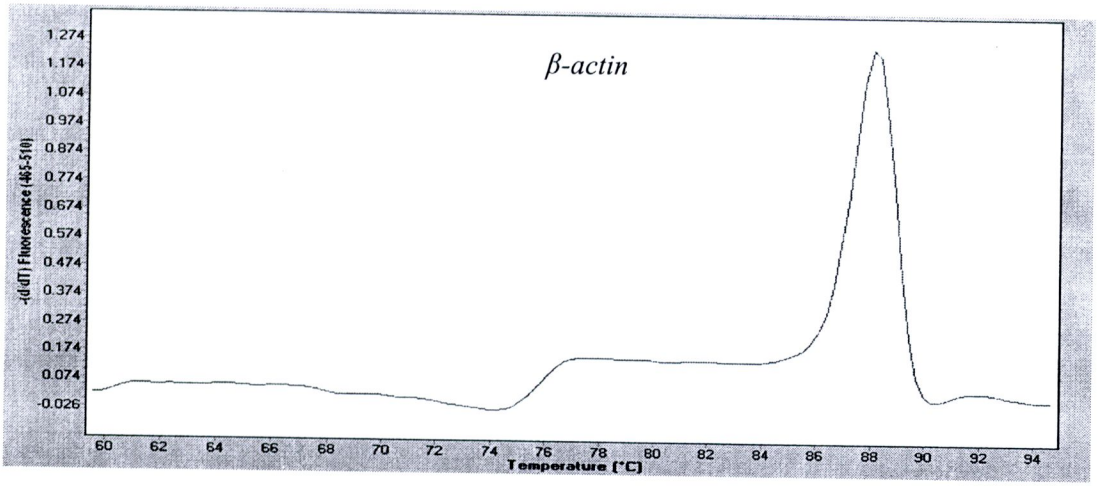


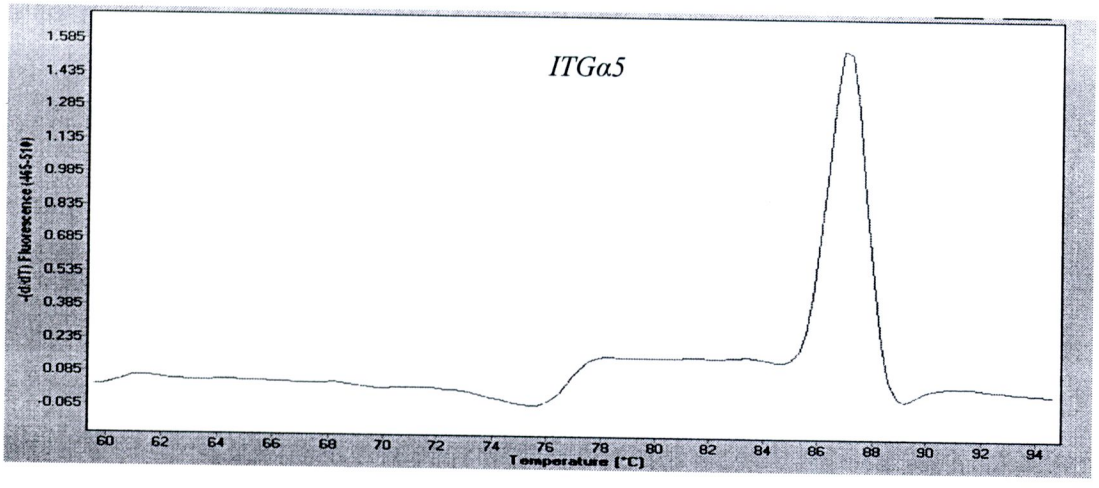


C-2 Melting curve analysis by ABI 7500 machine (Cont.)



C-3 Melting curve analysis by LightCycler® 480 system

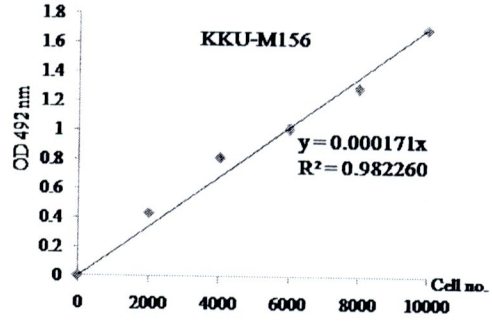


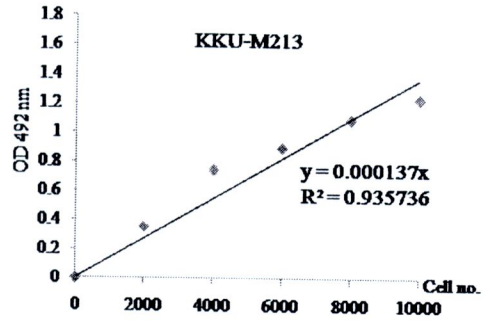


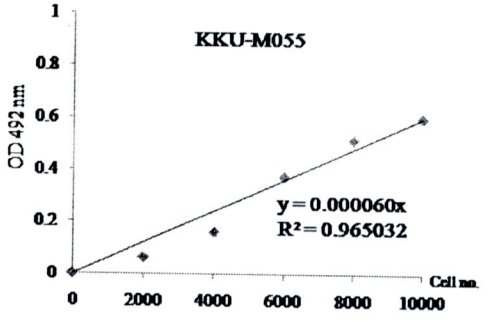
APPENDIX D

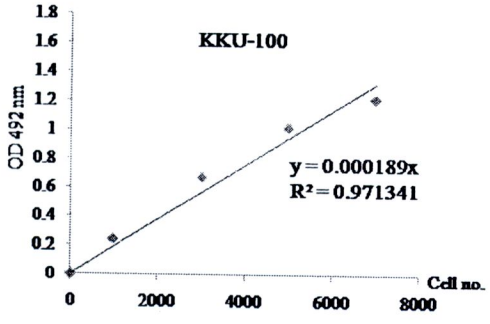
STANDARD CURVE OF CELL PROLIFERATION ASSAY

D-1 Standard curve of CCA cell lines measured by MTS assay





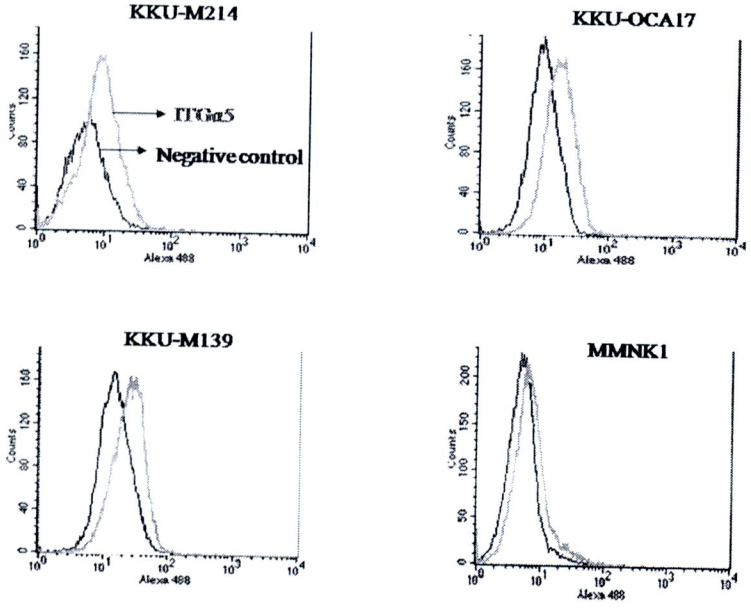




APPENDIX E

RAW DATA OF ITGα5 DETECTION ON BILIARY EPITHELIAL CELLS USING FLOW CYTOMETRY

E-1 Histogram plots of cell numbers in channel FL-1 (Alexa 488)



E-2 Raw data of MFI measured for ITGα5 signal

Biliary epithelial cell lines	Relative MFI (Normalized by negative control)
KKU-M213	2.0 ± 0.57
KKU-M156	1.4 ± 0.09
KKU-M055	1.6 ± 0.26
KKU-100	1.5 ± 0.21
KKU-M214	1.7 ± 0.22
KKU-OCA17	1.5 ± 0.24
KKU-M139	1.3 ± 0.42
MMNK1	1.5 ± 0.23

APPENDIX F
SECRETOME ANALYSIS OF CCA-ASSOCIATED FIBROBLASTS

Introduction

In addition to whole gene expression analysis of CCA-associated fibroblasts, the proteomic analysis of the substances released from these fibroblasts were performed in order to understand the possible effect that fibroblasts act paracrinely on the neighboring cancer cells or even autocrinely on themselves.

Material and methods

Cf2 and Lf2 were cultured in DMEM supplemented with 10% FBS until reach 80-90% confluence and then switched to 1% FBS containing DMEM for 48 h. The 48-h conditioned media (CM) was collected and centrifuged to get rid of cell debris.

The 1.4 mg Cf-CM and Lf-CM were subjected to RayBio® Biotin Label-based Human Antibody Array I (RayBiotech, Inc, Norcross, GA, USA) containing 507 human proteins followed the company's instruction. The signal was scanned using Axon GenePix scanner (RayBiotech, Inc, Norcross, GA, USA) and the data was analyzed by GeneSpring G.X. 7.3 (Agilent Technologies, Waldbronn, Germany).

Results

Among 507 proteins, 123 proteins were up-regulated for 2-fold or more in the Cf-CM compared to those of Lfs. These proteins were categorized into several biological functions including cytokine (63.4%), receptor (17.1%), growth factor (16.3%), matrix metalloproteinases (1.6%) and phosphorylated protein (1.6%) (Table F-1). Whereas 70 secreted proteins were down-regulated with less than 1-fold in Cf-CM compared to that of Lf-CM (Table E-2).

Table F-1 List of up-regulated proteins in Cf-CM

No	Biological function	No. of protein (%)	List of protein	Fold change (Cf/Lf)
1	**Cytokine**	**63.4**	- Endoglin / CD105	8.4
			- Lymphotactin/ XCL1	6.2
			- CXCL14 / BRAK	3.8
			- VEGF	3.7
			- Cripto-1	3.6
			- Pentraxin3 / TSG-14	3.3
			- WIF-1	3.1
			- Orexin A	3.0
			- TRAIL R4 / TNFRSF10D	3.0
			- GREMLIN	2.9
			- DcR3 / TNFRSF6B	2.9
			- MIF	2.9
			- Tarc	2.8
			- NeuroD1	2.8
			- Siglec-5 (CD170)	2.8
			- ENA-78	2.8
			- TRAIL/ TNFSF10	2.7
			- Activin A	2.7
			- ICAM-1	2.6
			- 6Ckine	2.6
			- uPAR	2.6
			- P-selectin	2.6
			- SMDF / NRG1Isoform	2.6
			- Activin RIB / ALK-4	2.5
			- Osteoactivin / GPNMB	2.5
			- FAM3B	2.4
			- RANK / TNFRSF11A	2.4
			- ALCAM	2.4
			- Thymopoietin	2.4
			- Thrombospondin-4	2.4
			- IL-31	2.4
			- MCP-2	2.4
			- MIP-3 beta	2.3
			- IL-16	2.3

Table F-1 List of up-regulated proteins in Cf-CM (Cont.)

No	Biological function	No. of protein (%)	List of protein	Fold change (Cf/Lf)
1	Cytokine (Cont.)	63.4	- Dkk-4	2.3
			- GRO-a	2.3
			- Galectin-3	2.3
			- VCAM-1 (CD106)	2.3
			- WISP-1 / CCN4	2.3
			- LECT2	2.3
			- Prolactin	2.2
			- IL-1 ra	2.2
			- Inhibin A	2.2
			- Sonic Hedgehog (Shh N- terminal)	2.2
			- PECAM-1 (CD31)	2.2
			- MDC	2.2
			- MIG	2.2
			- TACI / TNFRSF13B	2.2
			- IL-1 sRI	2.1
			- VEGF-B	2.1
			- Insulin	2.1
			- SDF-1 / CXCL12	2.1
			- IL-31 RA	2.1
			- Endostatin	2.1
			- IL-22 BP	2.1
			- L-Selectin (CD62L)	2.1
			- PDGF-C	2.1
			- FGF R5	2.1
			- MPIF-1 / CCL23	2.1
			- TSLP	2.1
			- Cerberus 1	2.1
			- IGFBP-1	2.1
			- BCMA / TNFRSF17	2.1
			- sgp130	2.1
			- Dkk-3	2.1
			- Kremen-1	2.1
			- ICAM-2	2.1

Table F-1 List of up-regulated proteins in Cf-CM (Cont.)

No	Biological function	No. of protein (%)	List of protein	Fold change (Cf/Lf)
1	Cytokine (Cont.)	63.4	- IL-6	2.0
			- CTLA-4 (CD152)	2.0
			- Latent TGF-beta bp1	2.0
			- sFRP-3	2.0
			- Soggy-1	2.0
			- TRAIL R3 / TNFRSF10C	2.0
			- M-CSF	2.0
			- CRIM 1	2.0
			- TRAIL R1 / DR4 /	2.0
			- TNFRSF10A	2.0
			- TMEFF1 / Tomoregulin-1	2.0
			- NT-3	2.0
2	Receptor	17.1	- VEGF R2(KDR)	3.1
			- SIGIRR	2.9
			- IL-13 R alpha 2	2.9
			- CCR6	2.8
			- IL-22 R	2.6
			- FGF R3	2.5
			- TMEFF2	2.4
			- TLR3	2.4
			- IL-1 R6 / IL-1 Rrp2	2.3
			- IL-2 R beta(CD122)	2.3
			- Frizzled-3	2.3
			- FGF R4	2.2
			- IL-1 R8	2.2
			- IL-17R	2.2
			- EGF R / ErbB1	2.2
			- Frizzled-7	2.2
			- 17 IFN-alpha / beta R2	2.1
			- Spinesin	2.1
			- TCCR / WSX-1	2.1
			- LFA-1 alpha	2.0
			- IL-1 R9	2.0

Table F-1 List of up-regulated proteins in Cf-CM (Cont.)

No	Biological function	No. of protein (%)	List of protein	Fold change (Cf/Lf)
3	**Growth factor**	**16.3**	- NRG1 Isoform GGF2	4.1
			- NRG3	3.3
			- GDF5	3.2
			- HRG-alpha	3.2
			- GDF9	3.2
			- GDF3	2.9
			- GDF8	2.7
			- GDF1	2.6
			- FGF-2 (b FGF)	2.6
			- HRG-beta1	2.6
			- TGF-alpha	2.6
			- NOV / CCN3	2.5
			- GDF11	2.4
			- EDG-1	2.4
			- NRG1-alpha / HRG1-alpha	2.3
			- GFR alpha-4	2.2
			- TGF-beta 1	2.1
			- FGF-21	2.0
			- TGF-beta 5	2.0
			- FGF-21	2.0
4	**Matrix metallo-proteinase**	**1.6**	- MMP-1	5.2
			- MMP-12	2.1
5	**Phosphorylated protein**	**1.6**	- TGF-beta RI / ALK-5	2.5
			- Smad 8	2.4

Table F-2 List of 70 down-regulated proteins in Cf-CM

Rank	Protein	Fold change (Cf/Lf)
1	Smad 4	0.9
2	Frizzled-6	0.9
3	FGF-16	0.9
4	FGF-10 / KGF-2	0.9
5	Activin RIA / ALK-2	0.9
6	CNTF R alpha	0.9
7	Axl	0.9
8	OSM	0.9
9	Hepassocin	0.9
10	Thrombospondin-1	0.9
11	Dkk-1	0.9
12	MMP-24 / MT5-MMP	0.9
13	IL-24	0.8
14	Glypican 3	0.8
15	Angiopoietin-like Factor	0.8
16	CCL14 / HCC-1 / HCC-3	0.8
17	IGFBP-rp1 / IGFBP-7	0.8
18	Pref-1	0.8
19	CXCR6	0.8
20	Smad 7	0.8
21	NCAM-1 / CD56	0.8
22	CCR2	0.8
23	CD40 / TNFRSF5	0.8
24	NRG1-beta1 / HRG1-beta1	0.8
25	IL-1 F6 / FIL1 epsilon	0.8
26	RELT / TNFRSF19L	0.8
27	CLC	0.8
28	BMP-7	0.8
29	LIF R alpha	0.8

Table F-2 List of 70 down-regulated proteins in Cf-CM (Cont.)

Rank	Protein	Fold change (Cf/Lf)
30	B7-1 (CD80)	0.8
31	TRANCE	0.8
32	Heregulin	0.7
33	MSPbeta-chain	0.7
34	BMP-5	0.7
35	CCR3	0.7
36	IL-3 R alpha	0.7
37	IL-4 R	0.7
38	MMP-8	0.7
39	MMP-10	0.7
40	Thrombospondin (TSP)	0.7
41	IL-19	0.7
42	TIMP-2	0.7
43	Progranulin	0.7
44	Dtk	0.7
45	Luciferase	0.7
46	Artemin	0.6
47	Neurturin	0.6
48	sFRP-4	0.6
49	BTC	0.6
50	Angiopoietin-1	0.6
51	IGFBP-6	0.6
52	E-Selectin	0.6
53	CV-2 / Crossveinless-2	0.6
54	BMP-3b / GDF-10	0.6
55	FGF-18	0.6
56	BD-1	0.6
57	CCR9	0.6
58	Osteoprotegerin / TNFRSF11B	0.5

Table F-2 List of 70 down-regulated proteins in Cf-CM (Cont.)

Rank	Protein	Fold change (Cf/Lf)
59	Siglec-9	0.5
60	Angiostatin	0.5
61	MMP-7	0.4
62	SCF	0.4
63	APRIL	0.4
64	BMP-15	0.4
65	Angiopoietin-like 1	0.4
66	Angiopoietin-like 2	0.3
67	GDF-15	0.3
68	ErbB3	0.3
69	HGF	0.1
70	uPA	0.1

APPENDIX G

O. VIVERRINI EXCRETORY/SECRETORY PRODUCT INDUCED *PN* EXPRESSION IN NON-TUMORIGENIC LIVER FIBROBLAST

Introduction

PN has been proposed as a TGF-β inducible gene. Recently, our group has reported the induction effect of *O. viverrini* excretory/secretory product (ESP) on cell proliferation of fibroblasts possibly through TGF-β signaling pathway (Thuwajit et al., 2006). It is of great interest to explore whether *O. viverrini* ESP when reach fibroblasts underlying the bile duct epithelium can activate PN expression.

Material and method

To investigate the capability of *O. viverrini* ESP to induce *PN* expression in non-tumorigenic liver fibroblast, Lf was subjected to treat with the parasitic product containing serum-free medium for 48 h and *PN* expression was measured using real time PCR. Lf cultured in serum-free medium was used as the negative control whereas Cf was served as positive control.

Results

The result showed that *PN* expression was markedly increased with statistical significance in Lf exposed to *O. viverrini* ESP compared the control cells without *O. viverrini* ESP treatment (Fig G-1). Though the level of PN expression in parasitic product-induced Lf was not as high as that observed in Cf, the result suggested that *O. viverrini* ESP could activate Lf to produce PN. With our study confirmed that CCA-associated fibroblasts produced PN, it may suggest *O. viverrini* infection induced CCA may, in part, activate fibroblasts to produced tumorigenic substance(s). This observation, though needs further experiment before conclusion, it supports the roles of *O. viverrini* in induction CCA through the parasitic substances.

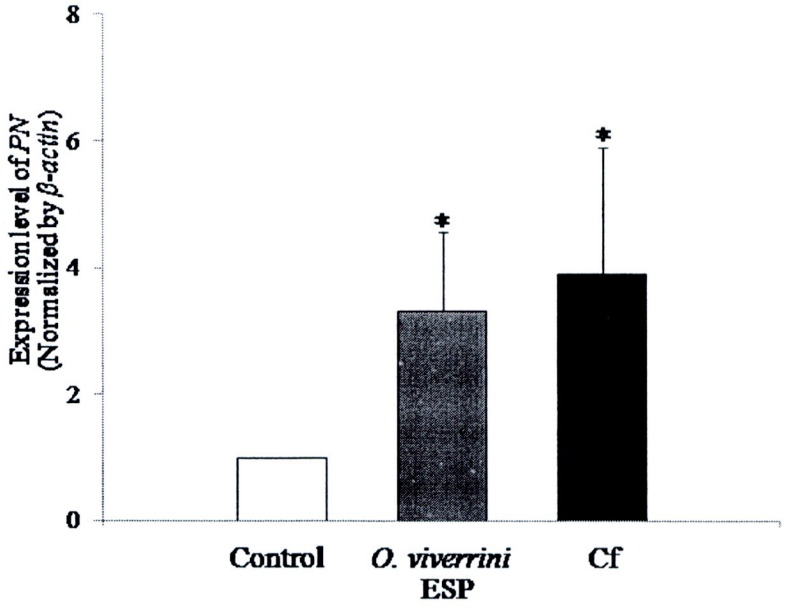


Figure G-1 *O. viverrini* ESP-induced *PN* expression in Lf. Expression level of PN in each condition was shown after normalized with *β-actin* level and assumed the level in the control condition to be 1. Bar represents mean ± SD of duplicate independent experiment. The * represents $P < 0.05$ compared with negative control.

VITAE

Name: Miss Kusumawadee Utispan

Date of birth: March 7, 1983

Place of birth: Khon Kaen, Thailand

Educations:

2001-2004 Bachelor Degree of Science (Medical Technology) (second class honours), Faculty of Associated Medical Science, Khon Kaen University

2004-2010 Student of the Doctor of Philosophy in Medical Biochemistry Program, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

Scholarship:

2007-2010 PhD Thailand Program Strategic Scholarships Fellowships Frontier Research Networks Commission on Higher Education, Thailand (CHE-PhD-THA)

Fellowship:

2007 Grant of University of Mobility in Asia and the Pacific (UMAP), Commission on Higher Education

Research training:

2007 Gene expression profile of cholangiocarcinoma-associated fibroblast using microarray technique under supervision of Professor Yoshimitsu Abiko, Department of Biochemistry and Molecular Biology, Nihon University School of Dentistry at Matsudo, Chiba, Japan