

Madsen and Bugge, <http://www.jcb.org/cgi/content/full/jcb.201501034/DC1>**Studies of protease localization in human breast cancer**

- Al-Raawi, D., H. Abu-El-Zahab, M. El-Shinawi, and M.M. Mohamed. 2011. Membrane type-1 matrix metalloproteinase (MT1-MMP) correlates with the expression and activation of matrix metalloproteinase-2 (MMP-2) in inflammatory breast cancer. *Int. J. Clin. Exp. Med.* 4:265–275.
- Atik, E., B. Akansu, S. Bakaris, and N. Aban. 2010. Expression of cyclooxygenase-2 and its relation to histological grade, inducible nitric oxide synthase, matrix metalloproteinase-2, CD-34, Caspase-3, and CD8 in invasive ductal carcinoma of the breast. *Saudi Med. J.* 31:130–134.
- Bachmeier, B.E., H. Rohrbach, J. De Waal, M. Jochum, and A.G. Nerlich. 2005. Enhanced expression and activation of major matrix metalloproteinases in distinct topographic areas of invasive breast carcinomas. *Int. J. Oncol.* 26:1203–1207.
- Bagnoli, F., V.M. Oliveira, M.A. Silva, G.C. Taromaru, J.F. Rinaldi, and T. Aoki. 2010. The interaction between aromatase, metalloproteinase 2,9 and CD44 in breast cancer. *Rev. Assoc. Med. Bras.* 56:472–477. <http://dx.doi.org/10.1590/S0104-42302010000400023>
- Baker, E.A., T.J. Stephenson, M.W. Reed, and N.J. Brown. 2002. Expression of proteinases and inhibitors in human breast cancer progression and survival. *Mol. Pathol.* 55:300–304. <http://dx.doi.org/10.1136/mp.55.5.300>
- Behrens, P., M. Rothe, A. Wellmann, J. Krischler, and N. Wernert. 2001. The Ets-1 transcription factor is up-regulated together with MMP 1 and MMP 9 in the stroma of pre-invasive breast cancer. *J. Pathol.* 194:43–50. <http://dx.doi.org/10.1002/path.844>
- Bisson, C., S. Blacher, M. Polette, J.F. Blanc, F. Kebers, J. Desreux, B. Tetu, J. Rosenbaum, J.M. Foidart, P. Birembaut, and A. Noel. 2003. Restricted expression of membrane type 1-matrix metalloproteinase by myofibroblasts adjacent to human breast cancer cells. *Int. J. Cancer.* 105:7–13. <http://dx.doi.org/10.1002/ijc.11012>
- Boström, P., M. Söderström, T. Vahlberg, K.O. Söderström, P.J. Roberts, O. Carpén, and P. Hirsimäki. 2011. MMP-1 expression has an independent prognostic value in breast cancer. *BMC Cancer.* 11:348. <http://dx.doi.org/10.1186/1471-2407-11-348>
- Brunner, O., S. Athar, L. Riethdorf, T. Löning, and H. Herbst. 1999. Matrix-metalloproteinases 1, 2, and 3 and their tissue inhibitors 1 and 2 in benign and malignant breast lesions: an in situ hybridization study. *Virchows Arch.* 435:566–573. <http://dx.doi.org/10.1007/s004280050442>
- Carriero, M.V., P. Franco, S. Del Vecchio, O. Massa, G. Botti, G. D' Aiuto, M.P. Stoppelli, and M. Salvatore. 1994. Tissue distribution of soluble and receptor-bound urokinase in human breast cancer using a panel of monoclonal antibodies. *Cancer Res.* 54:5445–5454.
- Castelló, R., J.M. Landete, F. España, C. Vázquez, C. Fuster, S.M. Almenar, L.A. Ramón, K.P. Radtke, and A. Estellés. 2007. Expression of plasminogen activator inhibitors type 1 and type 3 and urokinase plasminogen activator protein and mRNA in breast cancer. *Thromb. Res.* 120:753–762. <http://dx.doi.org/10.1016/j.thromres.2006.12.016>
- Caudroy, S., M. Polette, J.M. Tournier, H. Burlet, B. Toole, S. Zucker, and P. Birembaut. 1999. Expression of the extracellular matrix metalloproteinase inducer (EMMPRIN) and the matrix metalloproteinase-2 in bronchopulmonary and breast lesions. *J. Histochem. Cytochem.* 47:1575–1580. <http://dx.doi.org/10.1177/002215549904701209>
- Chang, H.J., M.J. Yang, Y.H. Yang, M.F. Hou, E.J. Hsueh, and S.R. Lin. 2009. MMP13 is potentially a new tumor marker for breast cancer diagnosis. *Oncol. Rep.* 22:1119–1127.
- Chazaud, B., R. Ricoux, C. Christov, A. Plonquet, R.K. Gherardi, and G. Barlovatz-Meimon. 2002. Promigratory effect of plasminogen activator inhibitor-1 on invasive breast cancer cell populations. *Am. J. Pathol.* 160:237–246. [http://dx.doi.org/10.1016/S0002-9440\(10\)64367-2](http://dx.doi.org/10.1016/S0002-9440(10)64367-2)
- Chenard, M.P., Y. Lutz, A. Mechine-Neuville, I. Stoll, J.P. Bellocq, M.C. Rio, and P. Basset. 1999. Presence of high levels of MT1-MMP protein in fibroblastic cells of human invasive carcinomas. *Int. J. Cancer.* 82:208–212. [http://dx.doi.org/10.1002/\(SICI\)1097-0215\(19990719\)82:2<208::AID-IJC10>3.0.CO;2-9](http://dx.doi.org/10.1002/(SICI)1097-0215(19990719)82:2<208::AID-IJC10>3.0.CO;2-9)
- Christensen, L., A.C. Wiborg Simonsen, C.W. Heegaard, S.K. Moestrup, J.A. Andersen, and P.A. Andreasen. 1996. Immunohistochemical localization of urokinase-type plasminogen activator, type-1 plasminogen-activator inhibitor, urokinase receptor and alpha(2)-macroglobulin receptor in human breast carcinomas. *Int. J. Cancer.* 66:441–452. [http://dx.doi.org/10.1002/\(SICI\)1097-0215\(19960516\)66:4<441::AID-IJC6>3.0.CO;2-W](http://dx.doi.org/10.1002/(SICI)1097-0215(19960516)66:4<441::AID-IJC6>3.0.CO;2-W)
- Cierna, Z., M. Mego, P. Janega, M. Karaba, G. Minarik, J. Benca, T. Sedláčková, S. Cingelova, P. Grunesova, D. Manasova, et al. 2014. Matrix metalloproteinase 1 and circulating tumor cells in early breast cancer. *BMC Cancer.* 14:472. <http://dx.doi.org/10.1186/1471-2407-14-472>
- Clavel, C., G. Chavanel, and P. Birembaut. 1986. Detection of the plasmin system in human mammary pathology using immunofluorescence. *Cancer Res.* 46:5743–5747.
- Clavel, C., M. Polette, M. Doco, I. Binninger, and P. Birembaut. 1992. Immunolocalization of matrix metallo-proteinases and their tissue inhibitor in human mammary pathology. *Bull. Cancer.* 79:261–270.
- Costantini, V., A. Sidoni, R. Devegilia, O.A. Cazzato, G. Bellezza, I. Ferri, E. Bucciarelli, and G.G. Nenci. 1996. Combined overexpression of urokinase, urokinase receptor, and plasminogen activator inhibitor-1 is associated with breast cancer progression: an immunohistochemical comparison of normal, benign, and malignant breast tissues. *Cancer.* 77:1079–1088. [http://dx.doi.org/10.1002/\(SICI\)1097-0142\(19960315\)77:6<1079::AID-CNCR12>3.0.CO;2-Z](http://dx.doi.org/10.1002/(SICI)1097-0142(19960315)77:6<1079::AID-CNCR12>3.0.CO;2-Z)
- Costantini, V., L.R. Zacharski, V.A. Memoli, B.J. Kudryk, S.M. Rousseau, and D.C. Stump. 1991. Occurrence of components of fibrinolysis pathways in situ in neoplastic and nonneoplastic human breast tissue. *Cancer Res.* 51:354–358.
- D'Andrea, M.R., M.R. Limiti, M. Bari, P. Zambenedetti, A. Montagutti, F. Ricci, G.L. Pappagallo, D. Sartori, O. Vinante, and P.L. Mingazzini. 2007. Correlation between genetic and biological aspects in primary non-metastatic breast cancers and corresponding synchronous axillary lymph node metastasis. *Breast Cancer Res. Treat.* 101:279–284. <http://dx.doi.org/10.1007/s10549-006-9300-2>
- Dacic, S., S. Kounelis, E. Kouri, and M.W. Jones. 2002. Immunohistochemical profile of cystosarcoma phyllodes of the breast: a study of 23 cases. *Breast J.* 8:376–381. <http://dx.doi.org/10.1046/j.1524-4741.2002.08608.x>
- Dalberg, K., E. Eriksson, U. Enberg, M. Kjellman, and M. Bäckdahl. 2000. Gelatinase A, membrane type 1 matrix metalloproteinase, and extracellular matrix metalloproteinase inducer mRNA expression: correlation with invasive growth of breast cancer. *World J. Surg.* 24:334–340. <http://dx.doi.org/10.1007/S002689910053>
- Damjanovich, L., C. Turzó, and R. Adány. 1994. Factors involved in the plasminogen activation system in human breast tumours. *Thromb. Haemost.* 71:684–691.
- Davidson, B., S. Konstantinovskiy, S. Nielsen, H.P. Dong, A. Berner, M. Vyberg, and R. Reich. 2004. Altered expression of metastasis-associated and regulatory molecules in effusions from breast cancer patients: a novel model for tumor progression. *Clin. Cancer Res.* 10:7335–7346. <http://dx.doi.org/10.1158/1078-0432.CCR-04-0183>
- Davies, B., D.W. Miles, L.C. Happerfield, M.S. Naylor, L.G. Bobrow, R.D. Rubens, and F.R. Balkwill. 1993. Activity of type IV collagenases in benign and malignant breast disease. *Br. J. Cancer.* 67:1126–1131. <http://dx.doi.org/10.1038/bjc.1993.207>
- del Casar, J.M., G. Carreño, L.O. González, S. Junquera, S. González-Reyes, J.M. González, M. Bongera, A.M. Merino, and F.J. Vizoso. 2010a. Expression of metalloproteinases and their inhibitors in primary tumors and in local recurrences after mastectomy for breast cancer. *J. Cancer Res. Clin. Oncol.* 136:1049–1058. <http://dx.doi.org/10.1007/s00432-009-0750-x>
- Del Casar, J.M., L.O. González, E. Alvarez, S. Junquera, L. Marín, L. González, M. Bongera, J. Vázquez, and F.J. Vizoso. 2009. Comparative analysis and clinical value of the expression of metalloproteinases and their inhibitors by intratumor stromal fibroblasts and those at the invasive front of breast carcinomas. *Breast Cancer Res. Treat.* 116:39–52. <http://dx.doi.org/10.1007/s10549-009-0351-z>

- Del Casar, J.M., S. González-Reyes, L.O. González, J.M. González, S. Junquera, M. Bongera, M.F. García, A. Andicoechea, C. Serra, and F.J. Vizoso. 2010b. Expression of metalloproteases and their inhibitors in different histological types of breast cancer. *J. Cancer Res. Clin. Oncol.* 136:811–819. <http://dx.doi.org/10.1007/s00432-009-0721-2>
- Djonov, V., N. Cresto, D.M. Aebersold, P.H. Burri, H.J. Altermatt, M. Hristic, G. Berclaz, A. Ziemiecki, and A.C. Andres. 2002. Tumor cell specific expression of MMP-2 correlates with tumor vascularisation in breast cancer. *Int. J. Oncol.* 21:25–30.
- Dublin, E., A. Hanby, N.K. Patel, R. Liebman, and D. Barnes. 2000. Immunohistochemical expression of uPA, uPAR, and PAI-1 in breast carcinoma. Fibroblastic expression has strong associations with tumor pathology. *Am. J. Pathol.* 157:1219–1227. [http://dx.doi.org/10.1016/S0002-9440\(10\)64637-8](http://dx.doi.org/10.1016/S0002-9440(10)64637-8)
- Eiró, N., I. Pidal, B. Fernandez-García, S. Junquera, M.L. Lamelas, J.M. del Casar, L.O. González, A. López-Muñiz, and F.J. Vizoso. 2012. Impact of CD68/(CD3+CD20) ratio at the invasive front of primary tumors on distant metastasis development in breast cancer. *PLoS ONE.* 7:e52796. <http://dx.doi.org/10.1371/journal.pone.0052796>
- Escot, C., Y. Zhao, C. Puech, and H. Rochefort. 1996. Cellular localisation by in situ hybridisation of cathepsin D, stromelysin 3, and urokinase plasminogen activator RNAs in breast cancer. *Breast Cancer Res. Treat.* 38:217–226. <http://dx.doi.org/10.1007/BF01806676>
- Fernández-Guinea, O., A. Álvarez-Cofiño, N. Eiró, L.O. González, J.M. del Casar, B. Fernandez-García, M.L. Lamelas, A. Andicoechea, and F.J. Vizoso. 2013. Low microvascular density at the tumor center is related to the expression of metalloproteases and their inhibitors and with the occurrence of distant metastasis in breast carcinomas. *Int. J. Clin. Oncol.* 18:629–640. <http://dx.doi.org/10.1007/s10147-012-0428-2>
- Ferrier, C.M., H.H. de Witte, H. Straatman, D.H. van Tienoven, W.L. van Geloof, F.J. Rietveld, C.G. Sweep, D.J. Ruiter, and G.N. van Muijen. 1999. Comparison of immunohistochemistry with immunoassay (ELISA) for the detection of components of the plasminogen activation system in human tumour tissue. *Br. J. Cancer.* 79:1534–1541. <http://dx.doi.org/10.1038/sj.bjc.6690245>
- Fisher, J.L., C.L. Field, H. Zhou, T.L. Harris, M.A. Henderson, and P.F. Choong. 2000. Urokinase plasminogen activator system gene expression is increased in human breast carcinoma and its bone metastases—a comparison of normal breast tissue, non-invasive and invasive carcinoma and osseous metastases. *Breast Cancer Res. Treat.* 61:1–12. <http://dx.doi.org/10.1023/A:1006445129195>
- Folgueira, M.A., S. Maistro, M.L. Katayama, R.A. Roela, F.G. Mundim, S. Nanogaki, G.H. de Bock, and M.M. Brentani. 2013. Markers of breast cancer stromal fibroblasts in the primary tumour site associated with lymph node metastasis: a systematic review including our case series. *Biosci. Rep.* 33:e00085. <http://dx.doi.org/10.1042/BSR20130060>
- Fujiwara, A., E. Shibata, H. Terashima, A. Shishido, J. Nishiki, K. Yoshida, K. Miyauchi, A. Madachi, and N. Matsuura. 2006. Evaluation of matrix metalloproteinase-2 (MMP-2) activity with film in situ zymography for improved cytological diagnosis of breast tumors. *Breast Cancer.* 13:272–278. <http://dx.doi.org/10.2325/jbcs.13.272>
- García, M.F., S. González-Reyes, L.O. González, S. Junquera, N. Berdize, J.M. Del Casar, M. Medina, and F.J. Vizoso. 2010. Comparative study of the expression of metalloproteases and their inhibitors in different localizations within primary tumours and in metastatic lymph nodes of breast cancer. *Int. J. Exp. Pathol.* 91:324–334. <http://dx.doi.org/10.1111/j.1365-2613.2010.00709.x>
- Giannelli, G., E. Fransvea, F. Marinocci, C. Bergamini, A. Daniele, S. Colucci, A. Paradiso, M. Quaranta, and S. Antonaci. 2002. Gelatinase levels in male and female breast cancer. *Biochem. Biophys. Res. Commun.* 292:161–166. <http://dx.doi.org/10.1006/bbrc.2002.6599>
- Göhring, U.J., A. Scharl, U. Thelen, A. Ahr, and G. Crombach. 1996. Comparative prognostic value of Cathepsin D and urokinase plasminogen activator, detected by immunohistochemistry, in primary breast carcinoma. *Anticancer Res.* 16:1011–1018.
- Gonzalez, L.O., M.D. Corte, J. Vazquez, S. Junquera, R. Sanchez, A.C. Alvarez, J.C. Rodriguez, M.L. Lamelas, and F.J. Vizoso. 2008a. Androgen receptor expression in breast cancer: relationship with clinicopathological characteristics of the tumors, prognosis, and expression of metalloproteases and their inhibitors. *BMC Cancer.* 8:149. <http://dx.doi.org/10.1186/1471-2407-8-149>
- Gonzalez, L.O., M.D. Corte, J. Vazquez, S. Junquera, R. Sanchez, A. Viña, J.C. Rodriguez, M.L. Lamelas, and F. Vizoso. 2008b. Study of matrix metalloproteinases and their tissue inhibitors in ductal in situ carcinomas of the breast. *Histopathology.* 53:403–415. <http://dx.doi.org/10.1111/j.1365-2559.2008.03136.x>
- González, L.O., S. González-Reyes, S. Junquera, L. Marín, L. González, J.M. Del Casar, J.M. González, and F. Vizoso. 2010. Expression of metalloproteases and their inhibitors by tumor and stromal cells in ductal carcinoma in situ of the breast and their relationship with microinvasive events. *J. Cancer Res. Clin. Oncol.* 136:1313–1321. <http://dx.doi.org/10.1007/s00432-010-0782-2>
- González, L.O., I. Pidal, S. Junquera, M.D. Corte, J. Vázquez, J.C. Rodríguez, M.L. Lamelas, A.M. Merino, J.L. García-Muñiz, and F.J. Vizoso. 2007. Overexpression of matrix metalloproteinases and their inhibitors in mononuclear inflammatory cells in breast cancer correlates with metastasis-relapse. *Br. J. Cancer.* 97:957–963.
- Haas, S., T.W. Park, J.C. Hahne, and H.P. Fischer. 2008. Influence of preoperative core biopsies on uPA/PAI-1 expression in breast cancer tissue. *Virchows Arch.* 452:277–283. <http://dx.doi.org/10.1007/s00428-007-0563-8>
- Harvey, S., S. Kohga, S.N. Sait, G. Markus, T.C. Hurd, M. Martinick, J. Geradts, R. Saxena, and J.F. Gibbs. 2009. Co-expression of urokinase with haptoglobin in human carcinomas. *J. Surg. Res.* 152:189–197. <http://dx.doi.org/10.1016/j.jss.2008.06.016>
- Haupt, L.M., R.E. Irving, S.R. Weinstein, M.G. Irving, and L.R. Griffiths. 2008. Matrix metalloproteinase localisation by in situ-RT-PCR in archival human breast biopsy material. *Mol. Cell. Probes.* 22:83–89. <http://dx.doi.org/10.1016/j.mcp.2007.06.009>
- Heppner, K.J., L.M. Matrisian, R.A. Jensen, and W.H. Rodgers. 1996. Expression of most matrix metalloproteinase family members in breast cancer represents a tumor-induced host response. *Am. J. Pathol.* 149:273–282.
- Hildenbrand, R., and A. Schaaf. 2009. The urokinase-system in tumor tissue stroma of the breast and breast cancer cell invasion. *Int. J. Oncol.* 34:15–23.
- Hildenbrand, R., A. Schaaf, A. Dorn-Beineke, H. Allgayer, M. Sütterlin, A. Marx, and P. Stroebel. 2009. Tumor stroma is the predominant uPA-, uPAR-, PAI-1-expressing tissue in human breast cancer: prognostic impact. *Histol. Histopathol.* 24:869–877.
- Hirvonen, R., A. Talvensaaari-Mattila, P. Pääkkö, and T. Turpeenniemi-Hujanen. 2003. Matrix metalloproteinase-2 (MMP-2) in T(1-2)N0 breast carcinoma. *Breast Cancer Res. Treat.* 77:85–91. <http://dx.doi.org/10.1023/A:1021152910976>
- Höyhty, M., R. Fridman, D. Komarek, K. Porter-Jordan, W.G. Stetler-Stevenson, L.A. Liotta, and C.M. Liang. 1994. Immunohistochemical localization of matrix metalloproteinase 2 and its specific inhibitor TIMP-2 in neoplastic tissues with monoclonal antibodies. *Int. J. Cancer.* 56:500–505. <http://dx.doi.org/10.1002/ijc.2910560408>
- Hubbard, A.L., J. Lauder, R.A. Hawkins, and T.J. Anderson. 1995. Disregulation of urokinase plasminogen activator gene in breast cancer. *Eur. J. Cancer.* 31:103–107. [http://dx.doi.org/10.1016/0959-8049\(94\)00430-D](http://dx.doi.org/10.1016/0959-8049(94)00430-D)
- Hurd, T.C., S. Sait, S. Kohga, J. Winston, M. Martinick, R. Saxena, H. Lankes, G. Markus, S. Harvey, and J.F. Gibbs. 2007. Plasminogen activator system localization in 60 cases of ductal carcinoma in situ. *Ann. Surg. Oncol.* 14:3117–3124. <http://dx.doi.org/10.1245/s10434-007-9529-y>
- Ioannidis, I., B. Dimo, A. Karameris, G. Vilaras, H. Gakiopoulou, E. Patsouris, and A.C. Lazaris. 2010. Comparative study of the immunohistochemical expression of metalloproteinases 2, 7 and 9 between clearly invasive carcinomas and “in situ” trophoblast invasion. *Neoplasma.* 57:20–28. [http://dx.doi.org/10.4149/neo\\_2010\\_01\\_020](http://dx.doi.org/10.4149/neo_2010_01_020)
- Ishigaki, S., M. Toi, T. Ueno, H. Matsumoto, M. Muta, M. Koike, and M. Seiki. 1999. Significance of membrane type 1 matrix metalloproteinase expression in breast cancer. *Jpn. J. Cancer Res.* 90:516–522. <http://dx.doi.org/10.1111/j.1349-7006.1999.tb00778.x>
- Ito, Y., T. Kobayashi, T. Takeda, E. Wakasugi, Y. Tamaki, Y. Nakano, N. Matsuura, and M. Monden. 1996. Immunolocalization of the components of the plasminogen activating system in breast carcinoma tissue. *Oncol. Rep.* 3:1021–1027.
- Iwata, H., S. Kobayashi, H. Iwase, A. Masaoka, N. Fujimoto, and Y. Okada. 1996. Production of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human breast carcinomas. *Jpn. J. Cancer Res.* 87:602–611. <http://dx.doi.org/10.1111/j.1349-7006.1996.tb00266.x>

- Izbicka, E., R.T. Streeper, I.T. Yeh, O. Pressley, M. Grant, J.V. Andrews, J. Kuhn, and J. O'Shaughnessy. 2010. Effects of alpha-difluoromethylornithine on markers of proliferation, invasion, and apoptosis in breast cancer. *Anticancer Res.* 30:2263–2269.
- Jahkola, T., T. Toivonen, K. von Smitten, I. Virtanen, V.M. Wasenius, and C. Blomqvist. 1999. Cathepsin-D, urokinase plasminogen activator and type-1 plasminogen activator inhibitor in early breast cancer: an immunohistochemical study of prognostic value and relations to tenascin-C and other factors. *Br. J. Cancer.* 80:167–174. <http://dx.doi.org/10.1038/sj.bjc.6690336>
- Jänicke, F., M. Schmitt, and H. Graeff. 1991. Clinical relevance of the urokinase-type and tissue-type plasminogen activators and of their type 1 inhibitor in breast cancer. *Semin. Thromb. Hemost.* 17:303–312. <http://dx.doi.org/10.1055/s-2007-1002624>
- Jankun, J., H.W. Merrick, and P.J. Goldblatt. 1993. Expression and localization of elements of the plasminogen activation system in benign breast disease and breast cancers. *J. Cell. Biochem.* 53:135–144. <http://dx.doi.org/10.1002/jcb.240530206>
- Jones, J.L., P. Glynn, and R.A. Walker. 1999. Expression of MMP-2 and MMP-9, their inhibitors, and the activator MT1-MMP in primary breast carcinomas. *J. Pathol.* 189:161–168. [http://dx.doi.org/10.1002/\(SICI\)1096-9896\(199910\)189:2<161::AID-PATH406>3.0.CO;2-2](http://dx.doi.org/10.1002/(SICI)1096-9896(199910)189:2<161::AID-PATH406>3.0.CO;2-2)
- Kennedy, S., M.J. Duffy, C. Duggan, C. Barnes, R. Rafferty, and M.D. Kramer. 1998. Semi-quantitation of urokinase plasminogen activator and its receptor in breast carcinomas by immunocytochemistry. *Br. J. Cancer.* 77:1638–1641. <http://dx.doi.org/10.1038/bjc.1998.268>
- Kim, G.E., J.H. Kim, K.H. Lee, Y.D. Choi, J.S. Lee, J.H. Lee, J.H. Nam, C. Choi, M.H. Park, and J.H. Yoon. 2012. Stromal matrix metalloproteinase-14 expression correlates with the grade and biological behavior of mammary phyllodes tumors. *Appl. Immunohistochem. Mol. Morphol.* 20:298–303. <http://dx.doi.org/10.1097/PAI.0b013e318235a132>
- Kim, H.J., C.I. Park, B.W. Park, H.D. Lee, and W.H. Jung. 2006. Expression of MT-1 MMP, MMP2, MMP9 and TIMP2 mRNAs in ductal carcinoma in situ and invasive ductal carcinoma of the breast. *Yonsei Med. J.* 47:333–342. <http://dx.doi.org/10.3349/ymj.2006.47.3.333>
- Köhrmann, A., U. Kammerer, M. Kapp, J. Dietl, and J. Anacker. 2009. Expression of matrix metalloproteinases (MMPs) in primary human breast cancer and breast cancer cell lines: New findings and review of the literature. *BMC Cancer.* 9:188. <http://dx.doi.org/10.1186/1471-2407-9-188>
- Lang, D.S., U. Heilenkötter, W. Schumm, O. Behrens, R. Simon, E. Vollmer, and T. Goldmann. 2013. Optimized immunohistochemistry in combination with image analysis: a reliable alternative to quantitative ELISA determination of uPA and PAI-1 for routine risk group discrimination in breast cancer. *Breast.* 22:736–743. <http://dx.doi.org/10.1016/j.breast.2012.12.011>
- Lebeau, A., C. Müller-Aufdemkamp, C. Allmacher, U. Sauer, A. Nerlich, R. Lichtinghagen, and U. Löhrs. 2004. Cellular protein and mRNA expression patterns of matrix metalloproteinases-2, -3 and -9 in human breast cancer: correlation with tumour growth. *J. Mol. Histol.* 35:443–455. <http://dx.doi.org/10.1023/B:HJO.0000045943.26251.24>
- Lebeau, A., A.G. Nerlich, U. Sauer, R. Lichtinghagen, and U. Löhrs. 1999. Tissue distribution of major matrix metalloproteinases and their transcripts in human breast carcinomas. *Anticancer Res.* 19(5B):4257–4264.
- Lhoták, S., L.J. Elavathil, S. Vukmirović-Popović, W.C. Duivenvoorden, R.G. Tozer, and G. Singh. 2000. Immunolocalization of matrix metalloproteinases and their inhibitors in clinical specimens of bone metastasis from breast carcinoma. *Clin. Exp. Metastasis.* 18:463–470. <http://dx.doi.org/10.1023/A:1011800919981>
- Li, H.C., D.C. Cao, Y. Liu, Y.F. Hou, J. Wu, J.S. Lu, G.H. Di, G. Liu, F.M. Li, Z.L. Ou, et al. 2004. Prognostic value of matrix metalloproteinases (MMP-2 and MMP-9) in patients with lymph node-negative breast carcinoma. *Breast Cancer Res. Treat.* 88:75–85. <http://dx.doi.org/10.1007/s10549-004-1200-8>
- Li, X., X. Kong, Y. Wang, and Q. Yang. 2013. 53BP1 is a novel regulator of angiogenesis in breast cancer. *Cancer Sci.* 104:1420–1426. <http://dx.doi.org/10.1111/cas.12247>
- Liapis, G., E. Mylona, P. Alexandrou, I. Giannopoulou, I. Nikolaou, S. Markaki, A. Keramopoulos, and L. Nakopoulou. 2007. Effect of the different phosphorylated Smad2 protein localizations on the invasive breast carcinoma phenotype. *APMIS.* 115:104–114. [http://dx.doi.org/10.1111/j.1600-0463.2007.apm\\_517.x](http://dx.doi.org/10.1111/j.1600-0463.2007.apm_517.x)
- Lindsay, C.K., U.P. Thorgeirsson, H. Tsuda, and S. Hirohashi. 1997. Expression of tissue inhibitor of metalloproteinase-1 and type IV collagenase/gelatinase messenger RNAs in human breast cancer. *Hum. Pathol.* 28:359–366. [http://dx.doi.org/10.1016/S0046-8177\(97\)90136-2](http://dx.doi.org/10.1016/S0046-8177(97)90136-2)
- Lu, J., H. Li, D. Cao, G. Di, J. Wu, K. Sheng, Q. Han, Z. Shen, and Z. Shao. 2007. Clinical significance of aromatase protein expression in axillary node negative breast cancer. *J. Cancer Res. Clin. Oncol.* 133:401–409. <http://dx.doi.org/10.1007/s00432-006-0186-5>
- Magkou, C., L. Nakopoulou, C. Zoubouli, K. Karali, I. Theohari, P. Bakarakos, and I. Giannopoulou. 2008. Expression of the epidermal growth factor receptor (EGFR) and the phosphorylated EGFR in invasive breast carcinomas. *Breast Cancer Res.* 10:R49. <http://dx.doi.org/10.1186/bcr2103>
- Meteoglu, I., E. Dikicioglu, M. Erkus, N. Culhaci, F. Kacar, E. Ozkara, and M. Uyar. 2005. Breast carcinogenesis. Transition from hyperplasia to invasive lesions. *Saudi Med. J.* 26:1889–1896.
- Min, K.W., D.H. Kim, S.I. Do, K. Kim, H.J. Lee, S.W. Chae, J.H. Sohn, J.S. Pyo, Y.H. Oh, W.S. Kim, et al. 2014. Expression patterns of stromal MMP-2 and tumoural MMP-2 and -9 are significant prognostic factors in invasive ductal carcinoma of the breast. *APMIS.* 122:1196–1206. <http://dx.doi.org/10.1111/apm.12285>
- Minisini, A.M., D. Fabbro, C. Di Loreto, M. Pestrin, S. Russo, G.G. Cardellino, C. Andreetta, G. Damante, and F. Puglisi. 2007. Markers of the uPA system and common prognostic factors in breast cancer. *Am. J. Clin. Pathol.* 128:112–117. <http://dx.doi.org/10.1309/M0GXVXA89BVLJ5C9>
- Monteagudo, C., M.J. Merino, J. San-Juan, L.A. Liotta, and W.G. Stetler-Stevenson. 1990. Immunohistochemical distribution of type IV collagenase in normal, benign, and malignant breast tissue. *Am. J. Pathol.* 136:585–592.
- Mylona, E., A. Nomikos, C. Magkou, M. Kamberou, I. Papassideri, A. Keramopoulos, and L. Nakopoulou. 2007. The clinicopathological and prognostic significance of membrane type 1 matrix metalloproteinase (MT1-MMP) and MMP-9 according to their localization in invasive breast carcinoma. *Histopathology.* 50:338–347. <http://dx.doi.org/10.1111/j.1365-2559.2007.02615.x>
- Nakopoulou, L., I. Giannopoulou, H. Gakiopoulou, H. Liapis, A. Tzonou, and P.S. Davaris. 1999. Matrix metalloproteinase-1 and -3 in breast cancer: correlation with progesterone receptors and other clinicopathologic features. *Hum. Pathol.* 30:436–442. [http://dx.doi.org/10.1016/S0046-8177\(99\)90120-X](http://dx.doi.org/10.1016/S0046-8177(99)90120-X)
- Nakopoulou, L., I. Tsirmpa, P. Alexandrou, A. Louvrou, C. Ampela, S. Markaki, and P.S. Davaris. 2003. MMP-2 protein in invasive breast cancer and the impact of MMP-2/TIMP-2 phenotype on overall survival. *Breast Cancer Res. Treat.* 77:145–155. <http://dx.doi.org/10.1023/A:1021371028777>
- Nam, E., S.N. Lee, S.A. Im, D.Y. Kim, K.E. Lee, and S.H. Sung. 2005. Expression of cyclooxygenase-2 in human breast cancer: relationship with HER-2/neu and other clinicopathological prognostic factors. *Cancer Res. Treat.* 37:165–170. <http://dx.doi.org/10.4143/crt.2005.37.3.165>
- Nielsen, B.S., F. Rank, M. Illemann, L.R. Lund, and K. Danø. 2007. Stromal cells associated with early invasive foci in human mammary ductal carcinoma in situ coexpress urokinase and urokinase receptor. *Int. J. Cancer.* 120:2086–2095. <http://dx.doi.org/10.1002/ijc.22340>
- Nielsen, B.S., F. Rank, J.M. López, M. Balbin, F. Vizoso, L.R. Lund, K. Danø, and C. López-Otín. 2001a. Collagenase-3 expression in breast myofibroblasts as a molecular marker of transition of ductal carcinoma in situ lesions to invasive ductal carcinomas. *Cancer Res.* 61:7091–7100.
- Nielsen, B.S., M. Sehested, S. Duun, F. Rank, S. Timshel, J. Rygaard, M. Johnsen, and K. Danø. 2001b. Urokinase plasminogen activator is localized in stromal cells in ductal breast cancer. *Lab. Invest.* 81:1485–1501. <http://dx.doi.org/10.1038/labinvest.3780363>
- Nielsen, B.S., M. Sehested, S. Timshel, C. Pyke, and K. Danø. 1996. Messenger RNA for urokinase plasminogen activator is expressed in myofibroblasts adjacent to cancer cells in human breast cancer. *Lab. Invest.* 74:168–177.
- Nielsen, T.O., H.N. Andrews, M. Cheang, J.E. Kucab, F.D. Hsu, J. Ragaz, C.B. Gilks, N. Makretsov, C.D. Bajdik, C. Brookes, et al. 2004. Expression of the insulin-like growth factor I receptor and urokinase plasminogen activator in breast cancer is associated with poor survival: potential for intervention with 17-allylamino geldanamycin. *Cancer Res.* 64:286–291. <http://dx.doi.org/10.1158/0008-5472.CAN.03-1242>
- Niemiec, J., A. Adamczyk, K. Małeck, A. Ambicka, and J. Ry. 2013. Tumor grade and matrix metalloproteinase 2 expression in stromal fibroblasts help to stratify the high-risk group of patients with early breast cancer identified on the basis of St Gallen recommendations. *Clin. Breast Cancer.* 13:119–128. <http://dx.doi.org/10.1016/j.clbc.2012.12.005>

- Niemiec, J.A., A. Adamczyk, K. Malecki, K. Majchrzyk, and J. Ryś. 2012. Relationships between immunophenotype, Ki-67 index, microvascular density, Ep-CAM/P-cadherin, and MMP-2 expression in early-stage invasive ductal breast cancer. *Appl. Immunohistochem. Mol. Morphol.* 20:550–560. <http://dx.doi.org/10.1097/PAI.0b013e31824f21af>
- Okada, A., J.P. Bellocq, N. Rouyer, M.P. Chenard, M.C. Rio, P. Chambon, and P. Basset. 1995. Membrane-type matrix metalloproteinase (MT-MMP) gene is expressed in stromal cells of human colon, breast, and head and neck carcinomas. *Proc. Natl. Acad. Sci. USA.* 92:2730–2734. <http://dx.doi.org/10.1073/pnas.92.7.2730>
- Okada, Y. 2000. Tumor cell-matrix interaction; pericellular matrix degradation and metastasis. *Verh. Dtsch. Ges. Pathol.* 84:33–42.
- Pacheco, M.M., M. Mourão, E.B. Mantovani, I.N. Nishimoto, and M.M. Brentani. 1998. Expression of gelatinases A and B, stromelysin-3 and matrilysin genes in breast carcinomas: clinico-pathological correlations. *Clin. Exp. Metastasis.* 16:577–585. <http://dx.doi.org/10.1023/A:1006580415796>
- Peihong, S., and F. Perry. 2007. Expression of nm23, MMP-2, TIMP-2 in breast neoplasm in Zhengzhou Center Hospital, China. *Ethiop. Med. J.* 45:79–83.
- Pellikainen, J.M., K.M. Ropponen, V.V. Kataja, J.K. Kellokoski, M.J. Eskelinen, and V.M. Kosma. 2004. Expression of matrix metalloproteinase (MMP)-2 and MMP-9 in breast cancer with a special reference to activator protein-2, HER2, and prognosis. *Clin. Cancer Res.* 10:7621–7628. <http://dx.doi.org/10.1158/1078-0432.CCR-04-1061>
- Polette, M., C. Clavel, M. Cockett, S. Girod de Bentzmann, G. Murphy, and P. Birembaut. 1993. Detection and localization of mRNAs encoding matrix metalloproteinases and their tissue inhibitor in human breast pathology. *Invasion Metastasis.* 13:31–37.
- Polette, M., N. Gilbert, I. Stas, B. Nawrocki, A. Noël, A. Remacle, W.G. Stetler-Stevenson, P. Birembaut, and M. Foidart. 1994. Gelatinase A expression and localization in human breast cancers. An in situ hybridization study and immunohistochemical detection using confocal microscopy. *Virchows Arch.* 424:641–645. <http://dx.doi.org/10.1007/BF01069745>
- Polette, M., B. Nawrocki, C. Gilles, H. Sato, M. Seiki, J.M. Tournier, and P. Birembaut. 1996. MT-MMP expression and localisation in human lung and breast cancers. *Virchows Arch.* 428:29–35. <http://dx.doi.org/10.1007/BF00192924>
- Poulsom, R., A.M. Hanby, M. Pignatelli, R.E. Jeffery, J.M. Longcroft, L. Rogers, and G.W. Stamp. 1993. Expression of gelatinase A and TIMP-2 mRNAs in desmoplastic fibroblasts in both mammary carcinomas and basal cell carcinomas of the skin. *J. Clin. Pathol.* 46:429–436. <http://dx.doi.org/10.1136/jcp.46.5.429>
- Rakha, E.A., M. Tun, E. Junainah, I.O. Ellis, and A. Green. 2012. Encapsulated papillary carcinoma of the breast: a study of invasion associated markers. *J. Clin. Pathol.* 65:710–714. <http://dx.doi.org/10.1136/jclinpath-2012-200710>
- Ranogajec, I., J. Jaki -Razumovi , V. Puzovi , and J. Gabrilovac. 2012. Prognostic value of matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9) and aminopeptidase N/CD13 in breast cancer patients. *Med. Oncol.* 29:561–569. <http://dx.doi.org/10.1007/s12032-011-9984-y>
- Ribeiro-Silva, A., H. Becker de Moura, F. Ribeiro do Vale, and S. Zucoloto. 2005. The differential regulation of human telomerase reverse transcriptase and vascular endothelial growth factor may contribute to the clinically more aggressive behavior of p63-positive breast carcinomas. *Int. J. Biol. Markers.* 20:227–234.
- Ribeiro-Silva, A., F. Ribeiro do Vale, and S. Zucoloto. 2006. Vascular endothelial growth factor expression in the basal subtype of breast carcinoma. *Am. J. Clin. Pathol.* 125:512–518. <http://dx.doi.org/10.1309/D744C4NM15J3B00D>
- Shah, M., D. Huang, T. Blick, A. Connor, L.A. Reiter, J.R. Hardink, C.C. Lynch, M. Waltham, and E.W. Thompson. 2012. An MMP13-selective inhibitor delays primary tumor growth and the onset of tumor-associated osteolytic lesions in experimental models of breast cancer. *PLoS ONE.* 7:e29615.
- Sivula, A., A. Talvensaaari-Mattila, J. Lundin, H. Joensuu, C. Haglund, A. Ristimäki, and T. Turpeenniemi-Hujanen. 2005. Association of cyclooxygenase-2 and matrix metalloproteinase-2 expression in human breast cancer. *Breast Cancer Res. Treat.* 89:215–220. <http://dx.doi.org/10.1007/s10549-004-0714-4>
- Soini, Y., T. Hurskainen, M. Höyhty, A. Oikarinen, and H. Autio-Harmaninen. 1994. 72 KD and 92 KD type IV collagenase, type IV collagen, and laminin mRNAs in breast cancer: a study by in situ hybridization. *J. Histochem. Cytochem.* 42:945–951. <http://dx.doi.org/10.1177/42.7.8014478>
- Sullu, Y., G.G. Demirag, A. Yildirim, F. Karagoz, and B. Kandemir. 2011. Matrix metalloproteinase-2 (MMP-2) and MMP-9 expression in invasive ductal carcinoma of the breast. *Pathol. Res. Pract.* 207:747–753. <http://dx.doi.org/10.1016/j.prp.2011.09.010>
- Surowiak, P., D. Murawa, V. Materna, A. Maciejczyk, M. Pudelko, S. Ciesla, J. Breborowicz, P. Murawa, M. Zabel, M. Dietel, and H. Lage. 2007. Occurrence of stromal myofibroblasts in the invasive ductal breast cancer tissue is an unfavourable prognostic factor. *Anticancer Res.* 27(4C):2917–2924.
- Talvensaaari-Mattila, A., P. Pääkkö, G. Blanco-Sequeiros, and T. Turpeenniemi-Hujanen. 2001. Matrix metalloproteinase-2 (MMP-2) is associated with the risk for a relapse in postmenopausal patients with node-positive breast carcinoma treated with antiestrogen adjuvant therapy. *Breast Cancer Res. Treat.* 65:55–61. <http://dx.doi.org/10.1023/A:1006458601568>
- Talvensaaari-Mattila, A., P. Pääkkö, M. Höyhty, G. Blanco-Sequeiros, and T. Turpeenniemi-Hujanen. 1998. Matrix metalloproteinase-2 immunoreactive protein: a marker of aggressiveness in breast carcinoma. *Cancer.* 83:1153–1162. [http://dx.doi.org/10.1002/\(SICI\)1097-0142\(19980915\)83:6<1153::AID-CNCR14>3.0.CO;2-4](http://dx.doi.org/10.1002/(SICI)1097-0142(19980915)83:6<1153::AID-CNCR14>3.0.CO;2-4)
- Talvensaaari-Mattila, A., P. Pääkkö, and T. Turpeenniemi-Hujanen. 2003. Matrix metalloproteinase-2 (MMP-2) is associated with survival in breast carcinoma. *Br. J. Cancer.* 89:1270–1275. <http://dx.doi.org/10.1038/sj.bjc.6601238>
- Têtu, B., J. Brisson, H. Lapointe, and P. Bernard. 1998. Prognostic significance of stromelysin 3, gelatinase A, and urokinase expression in breast cancer. *Hum. Pathol.* 29:979–985. [http://dx.doi.org/10.1016/S0046-8177\(98\)90204-0](http://dx.doi.org/10.1016/S0046-8177(98)90204-0)
- Têtu, B., J. Brisson, C.S. Wang, H. Lapointe, G. Beaudry, and C. Blanchette. 2001. Expression of cathepsin D, stromelysin-3, and urokinase by reactive stromal cells on breast carcinoma prognosis. *Cancer.* 92:2957–2964. [http://dx.doi.org/10.1002/1097-0142\(20011201\)92:11<2957::AID-CNCR10112>3.0.CO;2-6](http://dx.doi.org/10.1002/1097-0142(20011201)92:11<2957::AID-CNCR10112>3.0.CO;2-6)
- Têtu, B., J. Brisson, C.S. Wang, H. Lapointe, G. Beaudry, C. Blanchette, and D. Trudel. 2006. The influence of MMP-14, TIMP-2 and MMP-2 expression on breast cancer prognosis. *Breast Cancer Res.* 8:R28. <http://dx.doi.org/10.1186/bcr1503>
- Ueno, H., H. Nakamura, M. Inoue, K. Imai, M. Noguchi, H. Sato, M. Seiki, and Y. Okada. 1997. Expression and tissue localization of membrane-types 1, 2, and 3 matrix metalloproteinases in human invasive breast carcinomas. *Cancer Res.* 57:2055–2060.
- Umeda, T., Y. Eguchi, K. Okino, M. Kodama, and T. Hattori. 1997. Cellular localization of urokinase-type plasminogen activator, its inhibitors, and their mRNAs in breast cancer tissues. *J. Pathol.* 183:388–397. [http://dx.doi.org/10.1002/\(SICI\)1096-9896\(199712\)183:4<388::AID-PATH943>3.0.CO;2-1](http://dx.doi.org/10.1002/(SICI)1096-9896(199712)183:4<388::AID-PATH943>3.0.CO;2-1)
- Uría, J.A., M. Stähle-Bäckdahl, M. Seiki, A. Fueyo, and C. López-Otrín. 1997. Regulation of collagenase-3 expression in human breast carcinomas is mediated by stromal-epithelial cell interactions. *Cancer Res.* 57:4882–4888.
- Visscher, D.W., M. Höyhty, S.K. Ottosen, C.M. Liang, F.H. Sarkar, J.D. Crissman, and R. Fridman. 1994. Enhanced expression of tissue inhibitor of metalloproteinase-2 (TIMP-2) in the stroma of breast carcinomas correlates with tumor recurrence. *Int. J. Cancer.* 59:339–344. <http://dx.doi.org/10.1002/ijc.2910590308>
- Vizoso, F.J., L.O. González, M.D. Corte, J.C. Rodríguez, J. Vázquez, M.L. Lamelas, S. Junquera, A.M. Merino, and J.L. García-Muñiz. 2007. Study of matrix metalloproteinases and their inhibitors in breast cancer. *Br. J. Cancer.* 96:903–911. <http://dx.doi.org/10.1038/sj.bjc.6603666>
- Wadowska-Jaszczynska, K., R. Jach, K. Stangel-Wóciakiewicz, M. Kabzi ska-Turek, P. Przybylska, A. Basta, H. Huras, G. Dyduch, M. Rado -Pokracka, and O. Dziadek. 2011. Results in treatment of early breast cancers and the level of selected metalloproteinases. *Neuroendocrinol. Lett.* 32:821–830.
- Wang, H.X., C. Qin, F.Y. Han, X.H. Wang, and N. Li. 2014. HIF-2 $\alpha$  as a prognostic marker for breast cancer progression and patient survival. *Genet. Mol. Res.* 13:2817–2826. <http://dx.doi.org/10.4238/2014.January.22.6>
- Wolf, C., N. Rouyer, Y. Lutz, C. Adida, M. Lorient, J.P. Bellocq, P. Chambon, and P. Basset. 1993. Stromelysin 3 belongs to a subgroup of proteinases expressed in breast carcinoma fibroblastic cells and possibly implicated in tumor progression. *Proc. Natl. Acad. Sci. USA.* 90:1843–1847. <http://dx.doi.org/10.1073/pnas.90.5.1843>
- Xu, N., Z. Lei, X.L. Li, J. Zhang, C. Li, G.Q. Feng, D.N. Li, J.Y. Liu, Q. Wei, T.T. Bian, and T.Y. Zou. 2013. Clinical study of tumor angiogenesis and perfusion imaging using multi-slice spiral computed tomography for breast cancer. *Asian Pac. J. Cancer Prev.* 14:429–433. <http://dx.doi.org/10.7314/APJCP.2013.14.1.429>

- Yao, G., P. He, L. Chen, X. Hu, F. Gu, and C. Ye. 2013. MT1-MMP in breast cancer: induction of VEGF-C correlates with metastasis and poor prognosis. *Cancer Cell Int.* 13:98. <http://dx.doi.org/10.1186/1475-2867-13-98>
- Zhang, B., X. Cao, Y. Liu, W. Cao, F. Zhang, S. Zhang, H. Li, L. Ning, L. Fu, Y. Niu, et al. 2008. Tumor-derived matrix metalloproteinase-13 (MMP-13) correlates with poor prognoses of invasive breast cancer. *BMC Cancer.* 8:83. <http://dx.doi.org/10.1186/1471-2407-8-83>
- Zhang, Y.G., J. Du, X.X. Tian, Y.F. Zhong, and W.G. Fang. 2007. Expression of E-cadherin, beta-catenin, cathepsin D, gelatinases and their inhibitors in invasive ductal breast carcinomas. *Chin. Med. J. (Engl.)*. 120:1597–1605.
- Zhao, H., T. Morimoto, M. Sasa, T. Tanaka, and K. Izumi. 2002. Immunohistochemical expression of uPA, PAI-1, cathepsin D and apoptotic cells in ductal carcinoma in situ of the breast. *Breast Cancer.* 9:118–126. <http://dx.doi.org/10.1007/BF02967576>
- Zhao, M., H.G. Hu, J. Huang, Q. Zou, J. Wang, M.Q. Liu, Y. Zhao, G.Z. Li, S. Xue, and Z.S. Wu. 2013. Expression and correlation of Twist and gelatinases in breast cancer. *Exp Ther Med.* 6:97–100.

## Studies of protease localization in human colon cancer

- Ahmed, M.M., and S.H. Mohammed. 2011. Matrix metalloproteinases 2 and 9 in situ mRNA expression in colorectal tumors from Iraqi patients. *Indian J. Pathol. Microbiol.* 54:7–14. <http://dx.doi.org/10.4103/0377-4929.77316>
- Behrens, P., M. Mathiak, E. Mangold, S. Kirdorf, A. Wellmann, F. Fogt, M. Rothe, A. Florin, and N. Wernert. 2003. Stromal expression of invasion-promoting, matrix-degrading proteases MMP-1 and -9 and the Ets 1 transcription factor in HNPCC carcinomas and sporadic colorectal cancers. *Int. J. Cancer.* 107:183–188. <http://dx.doi.org/10.1002/ijc.11336>
- Bendardaf, R., A. Buhmeida, R. Ristamäki, K. Syrjänen, and S. Pyrhönen. 2007. MMP-1 (collagenase-1) expression in primary colorectal cancer and its metastases. *Scand. J. Gastroenterol.* 42:1473–1478. <http://dx.doi.org/10.1080/00365520701485449>
- Bendardaf, R., H. Lamum, P. Vihinen, R. Ristamäki, J. Laine, and S. Pyrhönen. 2003. Low collagenase-1 (MMP-1) and MT1-MMP expression levels are favourable survival markers in advanced colorectal carcinoma. *Oncology.* 65:337–346. <http://dx.doi.org/10.1159/000074647>
- Berney, C.R., R.J. Fisher, J. Yang, P.J. Russell, and P.J. Crowe. 1999. Protein markers in colorectal cancer: predictors of liver metastasis. *Ann. Surg.* 230:179–184. <http://dx.doi.org/10.1097/0000658-199908000-00007>
- Berney, C.R., J. Yang, R.J. Fisher, P.J. Russell, and P.J. Crowe. 1998a. Correlates of urokinase-type plasminogen activator in colorectal cancer: positive relationship with nm23 and c-erbB-2 protein expression. *Oncol. Res.* 10:47–54.
- Berney, C.R., J.L. Yang, R.J. Fisher, P.J. Russell, and P.J. Crowe. 1998b. Vascular endothelial growth factor expression is reduced in liver metastasis from colorectal cancer and correlates with urokinase-type plasminogen activator. *Anticancer Res.* 18(2A):973–977.
- Bodey, B., B. Bodey Jr., S.E. Siegel, and H.E. Kaiser. 2000. Prognostic significance of matrix metalloproteinase expression in colorectal carcinomas. *In Vivo.* 14:659–666.
- Buø, L., G.I. Meling, T.S. Karlsrud, H.T. Johansen, and A.O. Aasen. 1995. Antigen levels of urokinase plasminogen activator and its receptor at the tumor-host interface of colorectal adenocarcinomas are related to tumor aggressiveness. *Hum. Pathol.* 26:1133–1138. [http://dx.doi.org/10.1016/0046-8177\(95\)90276-7](http://dx.doi.org/10.1016/0046-8177(95)90276-7)
- Burtin, P., G. Chavanel, and J. Andre. 1985. The plasmin system in human colonic tumors: an immunofluorescence study. *Int. J. Cancer.* 35:307–314. <http://dx.doi.org/10.1002/ijc.2910350305>
- Burtin, P., G. Chavanel, J. André-Bougaran, and A. Gentile. 1987. The plasmin system in human adenocarcinomas and their metastases. A comparative immunofluorescence study. *Int. J. Cancer.* 39:170–178. <http://dx.doi.org/10.1002/ijc.2910390208>
- Cabibi, D., A. Calascibetta, F. Aragona, A. Martorana, M. Campione, and R. Sanguedolce. 2009. Differing expression of metalloprotease and of adhesion molecules in signet-ring cell and intestinal colorectal carcinoma. *Anticancer Res.* 29:4417–4422.
- Chan, C.C., M. Menges, H.D. Orzechowski, N. Orendain, G. Pistorius, G. Feifel, M. Zeitz, and A. Stallmach. 2001. Increased matrix metalloproteinase 2 concentration and transcript expression in advanced colorectal carcinomas. *Int. J. Colorectal Dis.* 16:133–140. <http://dx.doi.org/10.1007/s003840100287>
- Cho, Y.B., W.Y. Lee, S.Y. Song, H.J. Shin, S.H. Yun, and H.K. Chun. 2007. Matrix metalloproteinase-9 activity is associated with poor prognosis in T3-T4 node-negative colorectal cancer. *Hum. Pathol.* 38:1603–1610. <http://dx.doi.org/10.1016/j.humpath.2007.03.018>
- Collins, H.M., T.M. Morris, and S.A. Watson. 2001. Spectrum of matrix metalloproteinase expression in primary and metastatic colon cancer: relationship to the tissue inhibitors of metalloproteinases and membrane type-1-matrix metalloproteinase. *Br. J. Cancer.* 84:1664–1670. <http://dx.doi.org/10.1054/bjoc.2001.1831>
- Curran, S., S.R. Dundas, J. Buxton, M.F. Leeman, R. Ramsay, and G.I. Murray. 2004. Matrix metalloproteinase/tissue inhibitors of matrix metalloproteinase phenotype identifies poor prognosis colorectal cancers. *Clin. Cancer Res.* 10:8229–8234. <http://dx.doi.org/10.1158/1078-0432.CCR-04-0424>
- D'Errico, A., S. Garbisa, L.A. Liotta, V. Castronovo, W.G. Stetler-Stevenson, and W.F. Grigioni. 1991. Augmentation of type IV collagenase, laminin receptor, and Ki67 proliferation antigen associated with human colon, gastric, and breast carcinoma progression. *Mod. Pathol.* 4:239–246.
- Delbaldo, C., M. Cunningham, J.D. Vassalli, and A.P. Sappino. 1995. Plasmin-catalyzed proteolysis in colorectal neoplasia. *Cancer Res.* 55:4688–4695.
- Delektorskaya, V.V., A.G. Perevoshchikov, D.A. Golovkov, and N.E. Kushlinskii. 2007. Prognostic significance of expression of matrix metalloproteinase in colorectal adenocarcinomas and their metastases. *Bull. Exp. Biol. Med.* 143:455–458. <http://dx.doi.org/10.1007/s10517-007-0155-2>
- Ferrier, C.M., H.H. de Witte, H. Straatman, D.H. van Tienoven, W.L. van Geloof, F.J. Rietveld, C.G. Sweep, D.J. Ruiter, and G.N. van Muijen. 1999. Comparison of immunohistochemistry with immunoassay (ELISA) for the detection of components of the plasminogen activation system in human tumour tissue. *Br. J. Cancer.* 79:1534–1541. <http://dx.doi.org/10.1038/sj.bjc.6690245>
- Foda, A.A., A.K. El-Hawary, and A. Abdel-Aziz. 2013. Differential expression of matrix metalloproteinase-13 in mucinous and nonmucinous colorectal carcinomas. *Ann. Diagn. Pathol.* 17:347–351. <http://dx.doi.org/10.1016/j.anndiagpath.2013.04.003>
- Foda, A.A., A.K. El-Hawary, and A. Abdel-Aziz. 2014. Matrix metalloproteinase-13 expression in the progression of colorectal adenoma to carcinoma. *Tumour Biol.* 35:5653–5658. <http://dx.doi.org/10.1007/s13277-014-1748-9>
- Fujii, T., T. Obara, S. Tanno, H. Ura, and Y. Kohgo. 1999. Urokinase-type plasminogen activator and plasminogen activator inhibitor-1 as a prognostic factor in human colorectal carcinomas. *Hepatogastroenterology.* 46:2299–2308.
- Gallegos, N.C., C. Smales, F.J. Savage, R.M. Hembry, and P.B. Boulous. 1995. The distribution of matrix metalloproteinases and tissue inhibitor of metalloproteinases in colorectal cancer. *Surg. Oncol.* 4:21–29. [http://dx.doi.org/10.1016/S0960-7404\(10\)80027-1](http://dx.doi.org/10.1016/S0960-7404(10)80027-1)
- Gomes, E.G., M.J. Jucá, H.L. de Menezes, B.L. Nunes, H. Costa, F.O. Lima, and D. Matos. 2009. Correlation between the immunohistochemical expressions of MMP-1, MMP-7 and VEGF and prognostic factors in colorectal adenocarcinoma. *Acta Cir. Bras.* 24:303–310. <http://dx.doi.org/10.1590/S0102-86502009000400010>
- González, L., N. Eiró, L.O. González, A. Andicoechea, E. Barbón, J.L. García-Muñiz, and F.J. Vizoso. 2012. Effect of the expression of matrix metalloproteinases and their tissue inhibitors on survival of patients with resectable colorectal cancer. *Dig. Dis. Sci.* 57:2063–2071. <http://dx.doi.org/10.1007/s10620-012-2154-z>
- Gray, S.T., K. Yun, T. Motoori, and Y.M. Kuys. 1993. Interstitial collagenase gene expression in colonic neoplasia. *Am. J. Pathol.* 143:663–671.
- Grigioni, W.F., A. D'Errico, M. Fiorentino, P. Baccarini, M. Onisto, C. Caenazzo, W.G. Stetler-Stevenson, S. Garbisa, and A.M. Mancini. 1994. Gelatinase A (MMP-2) and its mRNA detected in both neoplastic and stromal cells of tumors with different invasive and metastatic properties. *Diagn. Mol. Pathol.* 3:163–169. <http://dx.doi.org/10.1097/00019606-199409000-00005>
- Groblewska, M., B. Mroczko, M. Gryko, A. Pryczynicz, K. Guzi ska-Ustymowicz, B. K. dra, A. Kemonia, and M. Szmikowski. 2014. Serum levels and tissue expression of matrix metalloproteinase 2 (MMP-2) and tissue inhibitor of metalloproteinases 2 (TIMP-2) in colorectal cancer patients. *Tumour Biol.* 35:3793–3802. <http://dx.doi.org/10.1007/s13277-013-1502-8>

- Grøndahl-Hansen, J., E. Raffkiaer, L.T. Kirkeby, P. Kristensen, L.R. Lund, and K. Danø. 1991. Localization of urokinase-type plasminogen activator in stromal cells in adenocarcinomas of the colon in humans. *Am. J. Pathol.* 138:111–117.
- Guo, H., A. Tatsuguchi, S. Shinji, S. Fujimori, S. Tanaka, K. Gudis, Y. Sugisaki, K. Furukawa, T. Tajiri, Y. Fukuda, et al. 2006. Cyclooxygenase-2 expression correlates with membrane-type-1 matrix metalloproteinase expression in colorectal cancer tissue. *Dis. Colon Rectum.* 49:1184–1192. <http://dx.doi.org/10.1007/s10350-006-0588-0>
- Harvey, S., S. Kohga, S.N. Sait, G. Markus, T.C. Hurd, M. Martinick, J. Geradts, R. Saxena, and J.F. Gibbs. 2009. Co-expression of urokinase with haptoglobin in human carcinomas. *J. Surg. Res.* 152:189–197. <http://dx.doi.org/10.1016/j.jss.2008.06.016>
- Harvey, S.R., S.N. Sait, Y. Xu, J.L. Bailey, R.M. Penetrante, and G. Markus. 1999. Demonstration of urokinase expression in cancer cells of colon adenocarcinomas by immunohistochemistry and in situ hybridization. *Am. J. Pathol.* 155:1115–1120. [http://dx.doi.org/10.1016/S0002-9440\(10\)65214-5](http://dx.doi.org/10.1016/S0002-9440(10)65214-5)
- Hiedlmeyer, E., S. Regus, S. Wassermann, F. Hlubek, A. Haynl, A. Dimmler, C. Koch, C. Knoll, M. van Beest, U. Reuning, et al. 2004. Beta-catenin up-regulates the expression of the urokinase plasminogen activator in human colorectal tumors. *Cancer Res.* 64:1209–1214. <http://dx.doi.org/10.1158/0008-5472.CAN-3627-2>
- Hilska, M., P.J. Roberts, Y.U. Collan, V.J. Laine, J. Kössi, P. Hirsimäki, O. Rahkonen, and M. Laato. 2007. Prognostic significance of matrix metalloproteinases-1, -2, -7 and -13 and tissue inhibitors of metalloproteinases-1, -2, -3 and -4 in colorectal cancer. *Int. J. Cancer.* 121:714–723. <http://dx.doi.org/10.1002/ijc.22747>
- Hong, S.W., Y.K. Kang, B. Lee, W.Y. Lee, Y.G. Jang, I.W. Paik, and H. Lee. 2011. Matrix metalloproteinase-2 and -7 expression in colorectal cancer. *J Korean Soc Coloproctol.* 27:133–139. <http://dx.doi.org/10.3393/jksc.2011.27.3.133>
- Huang, M.Y., H.J. Chang, F.Y. Chung, M.J. Yang, Y.H. Yang, J.Y. Wang, and S.R. Lin. 2010. MMP13 is a potential prognostic marker for colorectal cancer. *Oncol. Rep.* 24:1241–1247.
- Illemann, M., N. Bird, A. Majeed, O.D. Laerum, L.R. Lund, K. Danø, and B.S. Nielsen. 2009. Two distinct expression patterns of urokinase, urokinase receptor and plasminogen activator inhibitor-1 in colon cancer liver metastases. *Int. J. Cancer.* 124:1860–1870. <http://dx.doi.org/10.1002/ijc.24166>
- Inafuku, Y., T. Furuhashi, M. Tayama, K. Okita, T. Nishidate, T. Mizuguchi, Y. Kimura, and K. Hirata. 2009. Matrix metalloproteinase-2 expression in stromal tissues is a consistent prognostic factor in stage II colon cancer. *Cancer Sci.* 100:852–858. <http://dx.doi.org/10.1111/j.1349-7006.2009.01116.x>
- Inuzuka, K., Y. Ogata, H. Nagase, and K. Shirouzu. 2000. Significance of coexpression of urokinase-type plasminogen activator, and matrix metalloproteinase 3 (stromelysin) and 9 (gelatinase B) in colorectal carcinoma. *J. Surg. Res.* 93:211–218. <http://dx.doi.org/10.1006/jrsr.2000.5952>
- Jeffery, N., M.H. McLean, E.M. El-Omar, and G.I. Murray. 2009. The matrix metalloproteinase/tissue inhibitor of matrix metalloproteinase profile in colorectal polyp cancers. *Histopathology.* 54:820–828. <http://dx.doi.org/10.1111/j.1365-2559.2009.03301.x>
- Kang, J.C., J.S. Chen, C.H. Lee, J.J. Chang, and Y.S. Shieh. 2010. Intratumoral macrophage counts correlate with tumor progression in colorectal cancer. *J. Surg. Oncol.* 102:242–248. <http://dx.doi.org/10.1002/jso.21617>
- Kawanishi, H., K. Tanaka, S. Takai, H. Takada, M. Yamamura, K. Hioki, H. Nagura, and M. Yamamoto. 1991. Immunohistochemical analysis of plasminogen activator expression in human colorectal carcinomas: correlation with CEA distribution and tumor cell kinetics. *J. Surg. Oncol.* 46:246–256. <http://dx.doi.org/10.1002/jso.2930460408>
- Kikuchi, R., T. Noguchi, S. Takeno, N. Kubo, and Y. Uchida. 2000. Immunohistochemical detection of membrane-type-1-matrix metalloproteinase in colorectal carcinoma. *Br. J. Cancer.* 83:215–218.
- Kim, S.J., E. Shiba, F. Tsukamoto, M. Izukura, T. Taguchi, K. Yoneda, Y. Tanji, Y. Kimoto, and S.I. Takai. 1998. The expression of urokinase type plasminogen activator is a novel prognostic factor inukes B and C colorectal cancer. *Oncol. Rep.* 5:431–435.
- Kim, T.S., and Y.B. Kim. 1999. Correlation between expression of matrix metalloproteinase-2 (MMP-2), and matrix metalloproteinase-9 (MMP-9) and angiogenesis in colorectal adenocarcinoma. *J. Korean Med. Sci.* 14:263–270. <http://dx.doi.org/10.3346/jkms.1999.14.3.263>
- Kim, Y.W., Y.T. Ko, N.K. Kim, H.C. Chung, B.S. Min, K.Y. Lee, J.P. Park, and H. Kim. 2010. A comparative study of protein expression in primary colorectal cancer and synchronous hepatic metastases: the significance of matrix metalloproteinase-1 expression as a predictor of liver metastasis. *Scand. J. Gastroenterol.* 45:217–225. <http://dx.doi.org/10.3109/00365520903453158>
- Kitadai, Y., L.M. Ellis, Y. Takahashi, C.D. Bucana, H. Anzai, E. Tahara, and I.J. Fidler. 1995. Multiparametric in situ messenger RNA hybridization analysis to detect metastasis-related genes in surgical specimens of human colon carcinomas. *Clin. Cancer Res.* 1:1095–1102.
- Kitadai, Y., L.M. Ellis, S.L. Tucker, G.F. Greene, C.D. Bucana, K.R. Cleary, Y. Takahashi, E. Tahara, and I.J. Fidler. 1996. Multiparametric in situ mRNA hybridization analysis to predict disease recurrence in patients with colon carcinoma. *Am. J. Pathol.* 149:1541–1551.
- Klinge, U., R. Rosch, K. Junge, C.J. Krones, M. Stumpf, P. Lynen-Jansen, P.R. Mertens, and V. Schumpelick. 2007. Different matrix micro-environments in colon cancer and diverticular disease. *Int. J. Colorectal Dis.* 22:515–520. <http://dx.doi.org/10.1007/s00384-006-0199-1>
- Kohga, S., S.R. Harvey, R.M. Weaver, and G. Markus. 1985. Localization of plasminogen activators in human colon cancer by immunoperoxidase staining. *Cancer Res.* 45:1787–1796.
- Koretz, K., P. Möller, and R. Schwartz-Albiez. 1993. Plasminogen activators and plasminogen activator inhibitors in human colorectal carcinoma tissues are not expressed by the tumour cells. *Eur. J. Cancer.* 29A:1184–1189.
- Koskensalo, S., J. Hagström, N. Linder, M. Lundin, T. Sorsa, J. Louhimo, and C. Haglund. 2012. Lack of MMP-9 expression is a marker for poor prognosis in Dukes' B colorectal cancer. *BMC Clin. Pathol.* 12:24. <http://dx.doi.org/10.1186/1472-6890-12-24>
- Lee, S.W., Y.Y. Ahn, Y.S. Kim, S.B. Kang, S.W. Nam, D.S. Lee, H.Y. Jeong, and J.M. Kim. 2012. The Immunohistochemical Expression of STAT3, Bcl-xL, and MMP-2 Proteins in Colon Adenoma and Adenocarcinoma. *Gut Liver.* 6:45–51. <http://dx.doi.org/10.5009/gnl.2012.6.1.45>
- Leeman, M.F., J.A. McKay, and G.I. Murray. 2002. Matrix metalloproteinase 13 activity is associated with poor prognosis in colorectal cancer. *J. Clin. Pathol.* 55:758–762. <http://dx.doi.org/10.1136/jcp.55.10.758>
- Levy, A.T., V. Cioce, M.E. Sobel, S. Garbisa, W.F. Grigioni, L.A. Liotta, and W.G. Stetler-Stevenson. 1991. Increased expression of the Mr 72,000 type IV collagenase in human colonic adenocarcinoma. *Cancer Res.* 51:439–444.
- Li, B.H., P. Zhao, S.Z. Liu, Y.M. Yu, M. Han, and J.K. Wen. 2005a. Matrix metalloproteinase-2 and tissue inhibitor of metallo-proteinase-2 in colorectal carcinoma invasion and metastasis. *World J. Gastroenterol.* 11:3046–3050. <http://dx.doi.org/10.3748/wjg.v11.i20.3046>
- Li, L., Y.H. Huang, Y. Li, F.Q. Wang, B.Y. Shang, and Y.S. Zhen. 2005b. Antitumor activity of anti-type IV collagenase monoclonal antibody and its lidamycin conjugate against colon carcinoma. *World J. Gastroenterol.* 11:4478–4483.
- Li, M., J.Y. Li, A.L. Zhao, and J. Gu. 2007a. Colorectal cancer or colon and rectal cancer? Clinicopathological comparison between colonic and rectal carcinomas. *Oncology.* 73:52–57. <http://dx.doi.org/10.1159/000120628>
- Li, M., J.Y. Li, A.L. Zhao, and J. Gu. 2011. Do young patients with colorectal cancer have a poorer prognosis than old patients? *J. Surg. Res.* 167:231–236. <http://dx.doi.org/10.1016/j.jss.2010.10.040>
- Li, M., J.Y. Li, A.L. Zhao, J.S. He, L.X. Zhou, Y.A. Li, and J. Gu. 2007b. Survival stratification panel of colorectal carcinoma with combined expression of carcinoembryonic antigen, matrix metalloproteinases-2, and p27 kip1. *Dis. Colon Rectum.* 50:1887–1898. <http://dx.doi.org/10.1007/s10350-007-9053-y>
- Lustosa, S.A., L.S. Viana, R.J. Affonso Jr., S.R. Silva, M.V. Denadai, S.R. de Toledo, I.D. Oliveira, and D. Matos. 2014. Expression profiling using a cDNA array and immunohistochemistry for the extracellular matrix genes FN-1, ITGA-3, ITGB-5, MMP-2, and MMP-9 in colorectal carcinoma progression and dissemination. *ScientificWorldJournal.* 2014:102541. <http://dx.doi.org/10.1155/2014/102541>
- Lyall, M.S., S.R. Dundas, S. Curran, and G.I. Murray. 2006. Profiling markers of prognosis in colorectal cancer. *Clin. Cancer Res.* 12:1184–1191. <http://dx.doi.org/10.1158/1078-0432.CCR-05-1864>

- Masaki, T., M. Sugiyama, H. Matsuoka, N. Abe, Y. Izumisato, A. Sakamoto, and Y. Atomi. 2003. Matrix metalloproteinases may contribute compensationally to tumor invasion in T1 colorectal carcinomas. *Anticancer Res.* 23(5b):4169–4173.
- Masaki, T., M. Sugiyama, H. Matsuoka, N. Abe, Y. Izumisato, A. Sakamoto, and Y. Atomi. 2003. Matrix metalloproteinases may contribute compensationally to tumor invasion in T1 colorectal carcinomas. *Anticancer Res.* 23(5b):4169–4173.
- Minoo, P., K. Baker, D. Baumhoer, L. Terracciano, A. Lugli, and I. Zlobec. 2010. Urokinase-type plasminogen activator is a marker of aggressive phenotype and an independent prognostic factor in mismatch repair-proficient colorectal cancer. *Hum. Pathol.* 41:70–78. <http://dx.doi.org/10.1016/j.humpath.2009.05.013>
- Mori, D., Y. Nakafusa, K. Miyazaki, and O. Tokunaga. 2005. Differential expression of Janus kinase 3 (JAK3), matrix metalloproteinase 13 (MMP13), heat shock protein 60 (HSP60), and mouse double minute 2 (MDM2) in human colorectal cancer progression using human cancer cDNA microarrays. *Pathol. Res. Pract.* 201:777–789. <http://dx.doi.org/10.1016/j.prp.2005.06.005>
- Mukai, M., S. Sadahiro, N. Tokunaga, K. Ishizu, I. Ito, T. Kameya, K. Ishikawa, H. Iwase, T. Suzuki, H. Ishida, et al. 1999. The expression of MMP-2 and TIMP-2 in patients with primary colorectal adenocarcinoma: correlation with liver metastasis. *Oncol. Rep.* 6:969–973.
- Mukai, M., S. Sadahiro, N. Tokunaga, K. Ishizu, I. Ito, T. Kameya, K. Ishikawa, H. Iwase, T. Suzuki, T. Kimura, et al. 1998. The expression of MMP-2 and TIMP-2 in patients with colorectal adenocarcinoma invaded to the submucosal and proper muscle layer. *Oncol. Rep.* 5:335–340.
- Mulcahy, H.E., M.J. Duffy, D. Gibbons, P. McCarthy, N.A. Parfrey, D.P. O'Donoghue, and K. Sheahan. 1994. Urokinase-type plasminogen activator and outcome in Dukes' B colorectal cancer. *Lancet.* 344:583–584. [http://dx.doi.org/10.1016/S0140-6736\(94\)91968-2](http://dx.doi.org/10.1016/S0140-6736(94)91968-2)
- Murai, S., T. Umemiya, M. Seiki, and K. Harigaya. 2004. Expression and localization of membrane-type-1 matrix metalloproteinase, CD 44, and laminin-5 $\gamma$ 2 chain during colorectal carcinoma tumor progression. *Virchows Arch.* 445:271–278. <http://dx.doi.org/10.1007/s00428-004-1029-x>
- Murray, G.I., M.E. Duncan, P. O'Neil, W.T. Melvin, and J.E. Fothergill. 1996. Matrix metalloproteinase-1 is associated with poor prognosis in colorectal cancer. *Nat. Med.* 2:461–462. <http://dx.doi.org/10.1038/nm0496-461>
- Naitoh, H., Y. Eguchi, H. Ueyama, M. Kodama, and T. Hattori. 1995. Localization of urokinase-type plasminogen activator, plasminogen activator inhibitor-1, 2 and plasminogen in colon cancer. *Jpn. J. Cancer Res.* 86:48–56. <http://dx.doi.org/10.1111/j.1349-7006.1995.tb02987.x>
- Newell, K.J., J.P. Witty, W.H. Rodgers, and L.M. Matrisian. 1994. Expression and localization of matrix-degrading metalloproteinases during colorectal tumorigenesis. *Mol. Carcinog.* 10:199–206. <http://dx.doi.org/10.1002/mc.2940100404>
- Ngan, C.Y., H. Yamamoto, I. Seshimo, K. Ezumi, M. Terayama, H. Hemmi, I. Takemasa, M. Ikeda, M. Sekimoto, and M. Monden. 2007. A multivariate analysis of adhesion molecules expression in assessment of colorectal cancer. *J. Surg. Oncol.* 95:652–662. <http://dx.doi.org/10.1002/jso.20638>
- Nunes, B.L., M.J. Jucá, E.G. Gomes, H.L. Menezes, H.O. Costa, D. Matos, and S.S. Saad. 2009. Metalloproteinase-1, metalloproteinase-7, and p53 immunoeexpression and their correlation with clinicopathological prognostic factors in colorectal adenocarcinoma. *Int. J. Biol. Markers.* 24:156–164.
- Obermeyer, K., S. Krueger, B. Peters, B. Falkenberg, A. Roessner, and C. Röcken. 2007. The expression of low density lipoprotein receptor-related protein in colorectal carcinoma. *Oncol. Rep.* 17:361–367.
- Ogura, E., H. Senzaki, Y. Kiyozuka, H. Takada, K. Hioki, and A. Tsubura. 1997. Expression and localization of matrix metalloproteinases and tissue inhibitors of metalloproteinases as a prognostic factor in advanced colorectal carcinomas. *Oncol. Rep.* 4:701–705.
- Ohtani, H., H. Motohashi, H. Sato, M. Seiki, and H. Nagura. 1996. Dual over-expression pattern of membrane-type metalloproteinase-1 in cancer and stromal cells in human gastrointestinal carcinoma revealed by in situ hybridization and immunoelectron microscopy. *Int. J. Cancer.* 68:565–570. [http://dx.doi.org/10.1002/\(SICI\)1097-0215\(19961127\)68:5<565::AID-IJC2>3.0.CO;2-X](http://dx.doi.org/10.1002/(SICI)1097-0215(19961127)68:5<565::AID-IJC2>3.0.CO;2-X)
- Ohtani, H., T. Nagai, and H. Nagura. 1995. Similarities of in situ mRNA expression between gelatinase A (MMP-2) and type I procollagen in human gastrointestinal carcinoma: comparison with granulation tissue reaction. *Jpn. J. Cancer Res.* 86:833–839. <http://dx.doi.org/10.1111/j.1349-7006.1995.tb03093.x>
- Okada, A., J.P. Bellocq, N. Rouyer, M.P. Chenard, M.C. Rio, P. Chambon, and P. Basset. 1995. Membrane-type matrix metalloproteinase (MT-MMP) gene is expressed in stromal cells of human colon, breast, and head and neck carcinomas. *Proc. Natl. Acad. Sci. USA.* 92:2730–2734. <http://dx.doi.org/10.1073/pnas.92.7.2730>
- Omran, O.M., and M. Thabet. 2012. Gelatinases A and B expression in human colorectal cancer in upper Egypt: a clinicopathological study. *Ultrastruct. Pathol.* 36:108–116. <http://dx.doi.org/10.3109/01913123.2011.641671>
- Otani, Y., I. Okazaki, M. Arai, K. Kameyama, N. Wada, K. Maruyama, K. Yoshino, M. Kitajima, Y. Hosoda, and M. Tsuchiya. 1994. Gene expression of interstitial collagenase (matrix metalloproteinase 1) in gastrointestinal tract cancers. *J. Gastroenterol.* 29:391–397. <http://dx.doi.org/10.1007/BF02361233>
- Papadopoulou, S., A. Scorilas, N. Arnogianaki, B. Papapanayiotou, A. Tzimogianni, N. Agnantis, and M. Talieri. 2001. Expression of gelatinase-A (MMP-2) in human colon cancer and normal colon mucosa. *Tumour Biol.* 22:383–389. <http://dx.doi.org/10.1159/000050641>
- Papadopoulou, S., A. Scorilas, J. Yotis, N. Arnogianaki, G. Plataniotis, N. Agnanti, and M. Talieri. 2002. Significance of urokinase-type plasminogen activator and plasminogen activator inhibitor-1 (PAI-1) expression in human colorectal carcinomas. *Tumour Biol.* 23:170–178. <http://dx.doi.org/10.1159/000064033>
- Peng, Z.H., D.S. Wan, L.R. Li, G. Chen, Z.H. Lu, X.J. Wu, L.H. Kong, and Z.Z. Pan. 2011. Expression of COX-2, MMP-2 and VEGF in stage II and III colorectal cancer and the clinical significance. *Hepatogastroenterology.* 58:369–376.
- Pyke, C., P. Kristensen, E. Ralfkiaer, J. Grøndahl-Hansen, J. Eriksen, F. Blasi, and K. Danø. 1991. Urokinase-type plasminogen activator is expressed in stromal cells and its receptor in cancer cells at invasive foci in human colon adenocarcinomas. *Am. J. Pathol.* 138:1059–1067.
- Pyke, C., E. Ralfkiaer, K. Tryggvason, and K. Danø. 1993. Messenger RNA for two type IV collagenases is located in stromal cells in human colon cancer. *Am. J. Pathol.* 142:359–365.
- Qian, L.Y., P. Li, X.R. Li, D.J. Chen, and S.H. Zhu. 2012. Multivariate analysis of molecular indicators for postoperative liver metastasis in colorectal cancer cases. *Asian Pac. J. Cancer Prev.* 13:3967–3971. <http://dx.doi.org/10.7314/APJCP.2012.13.8.3967>
- Richter, K.K., L.M. Fink, B.M. Hughes, H.M. Shmaysani, C.C. Sung, and M. Hauer-Jensen. 1998. Differential effect of radiation on endothelial cell function in rectal cancer and normal rectum. *Am. J. Surg.* 176:642–647. [http://dx.doi.org/10.1016/S0002-9610\(98\)00280-3](http://dx.doi.org/10.1016/S0002-9610(98)00280-3)
- Ring, P., K. Johansson, M. Höyhty, K. Rubin, and G. Lindmark. 1997. Expression of tissue inhibitor of metalloproteinases TIMP-2 in human colorectal cancer—a predictor of tumour stage. *Br. J. Cancer.* 76:805–811. <http://dx.doi.org/10.1038/bjc.1997.466>
- Schwandner, O., A. Schlamp, R. Broll, and H.P. Bruch. 2007. Clinicopathologic and prognostic significance of matrix metalloproteinases in rectal cancer. *Int. J. Colorectal Dis.* 22:127–136. <http://dx.doi.org/10.1007/s00384-006-0173-y>
- Seetoo, D.Q., P.J. Crowe, P.J. Russell, and J.L. Yang. 2003. Quantitative expression of protein markers of plasminogen activation system in prognosis of colorectal cancer. *J. Surg. Oncol.* 82:184–193. <http://dx.doi.org/10.1002/jso.10210>
- Shiozawa, J., M. Ito, T. Nakayama, M. Nakashima, S. Kohno, and I. Sekine. 2000. Expression of matrix metalloproteinase-1 in human colorectal carcinoma. *Mod. Pathol.* 13:925–933. <http://dx.doi.org/10.1038/modpathol.3880169>
- Sier, C.F., C. Fellbaum, H.W. Verspaget, M. Schmitt, G. Griffioen, H. Graeff, H. Höfler, and C.B. Lamers. 1991. Immunolocalization of urokinase-type plasminogen activator in adenomas and carcinomas of the colorectum. *Histopathology.* 19:231–238. <http://dx.doi.org/10.1111/j.1365-2559.1991.tb00027.x>
- Sis, B., O. Sa ol, A. Küpelio lu, S. Sokmen, C. Terzi, M. Fuzun, E. Ozer, and P. Bishop. 2004. Prognostic significance of matrix metalloproteinase-2, cathepsin D, and tenascin-C expression in colorectal carcinoma. *Pathol. Res. Pract.* 200:379–387. <http://dx.doi.org/10.1016/j.prp.2004.02.012>
- Sordat, I., P. Chaubert, P. Protiva, L. Guillou, L. Mazzucchelli, E. Saraga, J. Benhattar, C. Trân-Thang, A.L. Blum, G. Dorta, and B. Sordat. 1997. In situ stromal expression of the urokinase/plasmin system correlates with epithelial dysplasia in colorectal adenomas. *Am. J. Pathol.* 150:283–295.
- Sunami, E., N. Tsuno, T. Osada, S. Saito, J. Kitayama, S. Tomozawa, T. Tsuruo, Y. Shibata, T. Muto, and H. Nagawa. 2000. MMP-1 is a prognostic marker for hematogenous metastasis of colorectal cancer. *Oncologist.* 5:108–114. <http://dx.doi.org/10.1634/theoncologist.5-2-108>

- Šundov, Z., S. Tomić, K. Vilović, N. Kunac, M. Kalebić, and J. Bezić. 2008. Immunohistochemically detected high expression of matrix metalloproteinase-2 as predictor of poor prognosis in Duke's B colon cancer. *Croat. Med. J.* 49:636–642. <http://dx.doi.org/10.3325/cmj.2008.5.636>
- Svagzdys, S., V. Lesauskaite, D. Pangonyte, Z. Saladzinskas, A. Tamelis, and D. Pavalkis. 2011. Matrix metalloproteinase-9 is a prognostic marker to predict survival of patients who underwent surgery due to rectal carcinoma. *Tohoku J. Exp. Med.* 223:67–73. <http://dx.doi.org/10.1620/tjem.223.67>
- Takeha, S., Y. Fujiyama, T. Bamba, T. Sorsa, H. Nagura, and H. Ohtani. 1997. Stromal expression of MMP-9 and urokinase receptor is inversely associated with liver metastasis and with infiltrating growth in human colorectal cancer: a novel approach from immune/inflammatory aspect. *Jpn. J. Cancer Res.* 88:72–81. <http://dx.doi.org/10.1111/j.1349-7006.1997.tb00304.x>
- Tatsuta, S., S. Tanaka, K. Haruma, M. Yoshihara, K. Sumii, G. Kajiyama, and F. Shimamoto. 1997. Combined expression of urokinase-type plasminogen activator and proliferating cell nuclear antigen at the deepest invasive portion correlates with colorectal cancer prognosis. *Int. J. Oncol.* 10:125–129.
- Tutton, M.G., M.L. George, S.A. Eccles, S. Burton, R.I. Swift, and A.M. Abulafi. 2003. Use of plasma MMP-2 and MMP-9 levels as a surrogate for tumour expression in colorectal cancer patients. *Int. J. Cancer.* 107:541–550. <http://dx.doi.org/10.1002/ijc.11436>
- Unsal, D., N. Akyurek, A. Uner, O.P. Erpolat, U. Han, M. Akmansu, B.B. Mentes, and A. Dursun. 2008. Gelatinase B expression as a prognostic factor in patients with stage II/III rectal carcinoma treated by postoperative adjuvant therapy. *Am. J. Clin. Oncol.* 31:55–63. <http://dx.doi.org/10.1097/COC.0b013e318068b4e2>
- Unsal Kilic, D., A. Uner, N. Akyurek, P. Erpolat, A. Dursun, and Y. Pak. 2007. Matrix metalloproteinase-9 expression correlated with tumor response in patients with locally advanced rectal cancer undergoing preoperative chemoradiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 67:196–203. <http://dx.doi.org/10.1016/j.ijrobp.2006.08.010>
- Wong, J.C., S.K. Chan, D.F. Schaeffer, X. Sagaert, H.J. Lim, H. Kennecke, D.A. Owen, K.W. Suh, Y.B. Kim, and I.T. Tai. 2011. Absence of MMP2 expression correlates with poor clinical outcomes in rectal cancer, and is distinct from MMP1-related outcomes in colon cancer. *Clin. Cancer Res.* 17:4167–4176. <http://dx.doi.org/10.1158/1078-0432.CCR-10-1224>
- Xiong, B., T.J. Sun, W.D. Hu, F.L. Cheng, M. Mao, and Y.F. Zhou. 2005. Expression of cyclooxygenase-2 in colorectal cancer and its clinical significance. *World J. Gastroenterol.* 11:1105–1108. <http://dx.doi.org/10.3748/wjg.v11.i8.1105>
- Yang, B., J. Gao, Z. Rao, and Q. Shen. 2012. Clinicopathological significance and prognostic value of MMP-13 expression in colorectal cancer. *Scand. J. Clin. Lab. Invest.* 72:501–505. <http://dx.doi.org/10.3109/00365513.2012.699638>
- Yang, J.L., D. Seetoo, Y. Wang, M. Ranson, C.R. Berney, J.M. Ham, P.J. Russell, and P.J. Crowe. 2000. Urokinase-type plasminogen activator and its receptor in colorectal cancer: independent prognostic factors of metastasis and cancer-specific survival and potential therapeutic targets. *Int. J. Cancer.* 89:431–439. [http://dx.doi.org/10.1002/1097-0215\(20000920\)89:5<431::AID-IJC6>3.0.CO;2-V](http://dx.doi.org/10.1002/1097-0215(20000920)89:5<431::AID-IJC6>3.0.CO;2-V)
- Zlobec, I., S. Höller, L. Tornillo, L. Terracciano, and A. Lugli. 2009. Combined histomorphologic and immunohistochemical phenotype to predict the presence of vascular invasion in colon cancer. *Dis. Colon Rectum.* 52:1114–1121. <http://dx.doi.org/10.1007/DCR.0b013e31819eef49>
- Zlobec, I., P. Minoo, D. Baumhoer, K. Baker, L. Terracciano, J.R. Jass, and A. Lugli. 2008a. Multimarker phenotype predicts distant adverse survival in patients with lymph node-negative colorectal cancer. *Cancer.* 112:495–502. <http://dx.doi.org/10.1002/cncr.23208>
- Zlobec, I., L. Terracciano, L. Tornillo, U. Günthert, T. Vuong, J.R. Jass, and A. Lugli. 2008b. Role of RHAMM within the hierarchy of well-established prognostic factors in colorectal cancer. *Gut.* 57:1413–1419. <http://dx.doi.org/10.1136/gut.2007.141192>

### Studies of protease localization in human lung cancer

- Aljada, I.S., N. Ramnath, K. Donohue, S. Harvey, J.J. Brooks, S.M. Wiseman, T. Khoury, G. Loewen, H.K. Slocum, T.M. Anderson, et al. 2004. Upregulation of the tissue inhibitor of metalloproteinase-1 protein is associated with progression of human non-small-cell lung cancer. *J. Clin. Oncol.* 22:3218–3229. <http://dx.doi.org/10.1200/JCO.2004.02.110>
- Bolon, I., M. Devouassoux, C. Robert, D. Moro, C. Brambilla, and E. Brambilla. 1997. Expression of urokinase-type plasminogen activator, stromelysin 1, stromelysin 3, and matrilysin genes in lung carcinomas. *Am. J. Pathol.* 150:1619–1629.
- Bolon, I., V. Gouyer, M. Devouassoux, B. Vandenbunder, N. Wernert, D. Moro, C. Brambilla, and E. Brambilla. 1995. Expression of c-ets-1, collagenase 1, and urokinase-type plasminogen activator genes in lung carcinomas. *Am. J. Pathol.* 147:1298–1310.
- Byun, J.H., M.A. Lee, S.Y. Roh, B.Y. Shim, S.H. Hong, Y.H. Ko, S.J. Ko, I.S. Woo, J.H. Kang, Y.S. Hong, et al. 2006. Association between cyclooxygenase-2 and matrix metalloproteinase-2 expression in non-small cell lung cancer. *Jpn. J. Clin. Oncol.* 36:263–268. <http://dx.doi.org/10.1093/jcco/hyl024>
- Cox, G., J.L. Jones, A. Andi, D.A. Waller, and K.J. O'Byrne. 2001. A biological staging model for operable non-small cell lung cancer. *Thorax.* 56:561–566. <http://dx.doi.org/10.1136/thorax.56.7.561>
- D'Amico, T.A., T.A. Aloja, M.B. Moore, D.H. Conlon, J.E. Herndon II, M.S. Kinch, and D.H. Harpole Jr. 2001. Predicting the sites of metastases from lung cancer using molecular biologic markers. *Ann. Thorac. Surg.* 72:1144–1148. [http://dx.doi.org/10.1016/S0003-4975\(01\)02979-4](http://dx.doi.org/10.1016/S0003-4975(01)02979-4)
- Dong, B., M. Sato, A. Sakurada, M. Sagawa, C. Endo, S. Wu, S. Yamanaka, A. Horii, and T. Kondo. 2005. Computed tomographic images reflect the biologic behavior of small lung adenocarcinoma: they correlate with cell proliferation, microvascularization, cell adhesion, degradation of extracellular matrix, and K-ras mutation. *J. Thorac. Cardiovasc. Surg.* 130:733–739. <http://dx.doi.org/10.1016/j.jtcvs.2005.05.013>
- Fan, J., F.Y. Wu, L. Wang, G.N. Jiang, and W. Gao. 2011. Comparative expression of matrix metalloproteinases in low-grade mucoepidermoid carcinoma and typical lung cancer. *Oncol. Lett.* 2:1269–1273.
- Frey, A.B., A. Wali, H. Pass, and F. Lonardo. 2007. Osteopontin is linked to p65 and MMP-9 expression in pulmonary adenocarcinoma but not in malignant pleural mesothelioma. *Histopathology.* 50:720–726. <http://dx.doi.org/10.1111/j.1365-2559.2007.02675.x>
- Gaeta, M., A. Blandino, S. Pergolizzi, S. Mazziotti, R. Caruso, M. Barone, and S. Cascinu. 2003. Patterns of recurrence of bronchioloalveolar cell carcinoma after surgical resection: a radiological, histological, and immunohistochemical study. *Lung Cancer.* 42:319–326. [http://dx.doi.org/10.1016/S0169-5002\(03\)00362-3](http://dx.doi.org/10.1016/S0169-5002(03)00362-3)
- Galateau-Salle, F.B., R.E. Luna, K. Horiba, M.N. Sheppard, T. Hayashi, M.V. Fleming, T.V. Colby, W. Bennett, C.C. Harris, W.G. Stetler-Stevenson, et al. 2000. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in bronchial squamous preinvasive lesions. *Hum. Pathol.* 31:296–305. [http://dx.doi.org/10.1016/S0046-8177\(00\)80242-7](http://dx.doi.org/10.1016/S0046-8177(00)80242-7)
- Grossi, F., R. Spizzo, D. Bordo, V. Cacitti, F. Valent, C. Rossetto, A. Follador, S. Di Terlizzi, M. Aita, A. Morelli, et al. 2010. Prognostic stratification of stage IIIA pN2 non-small cell lung cancer by hierarchical clustering analysis of tissue microarray immunostaining data: an Alpe Adria Thoracic Oncology Multidisciplinary Group study (ATOM 014). *J. Thorac. Oncol.* 5:1354–1360. <http://dx.doi.org/10.1097/JTO.0b013e3181e77a78>
- Guo, C.B., S. Wang, C. Deng, D.L. Zhang, F.L. Wang, and X.Q. Jin. 2007. Relationship between matrix metalloproteinase 2 and lung cancer progression. *Mol. Diagn. Ther.* 11:183–192. <http://dx.doi.org/10.1007/BF03256240>
- Herbst, R.S., S. Yano, H. Kuniyasu, F.R. Khuri, C.D. Bucana, F. Guo, D. Liu, B. Kemp, J.J. Lee, W.K. Hong, and I.J. Fidler. 2000. Differential expression of E-cadherin and type IV collagenase genes predicts outcome in patients with stage I non-small cell lung carcinoma. *Clin. Cancer Res.* 6:790–797.
- Hoikkala, S., P. Pääkkö, Y. Soini, R. Mäkitaro, V. Kinnula, and T. Turpeenniemi-Hujanen. 2006. Tissue MMP-2 and MMP-9 [corrected] are better prognostic factors than serum MMP-2/TIMP-2—complex or TIMP-1 [corrected] in stage [corrected] I-III lung carcinoma. *Cancer Lett.* 236:125–132. <http://dx.doi.org/10.1016/j.canlet.2005.05.012>
- Iizasa, T., T. Fujisawa, M. Suzuki, S. Motohashi, K. Yasufuku, T. Yasukawa, M. Baba, and M. Shiba. 1999. Elevated levels of circulating plasma matrix metalloproteinase 9 in non-small cell lung cancer patients. *Clin. Cancer Res.* 5:149–153.



- Ishikawa, S., K. Takenaka, K. Yanagihara, R. Miyahara, Y. Kawano, Y. Otake, S. Hasegawa, H. Wada, and F. Tanaka. 2004. Matrix metalloproteinase-2 status in stromal fibroblasts, not in tumor cells, is a significant prognostic factor in non-small-cell lung cancer. *Clin. Cancer Res.* 10:6579–6585. <http://dx.doi.org/10.1158/1078-0432.CCR-04-0272>
- Kawano, N., H. Osawa, T. Ito, Y. Nagashima, F. Hirahara, Y. Inayama, Y. Nakatani, S. Kimura, H. Kitajima, N. Koshikawa, et al. 1997. Expression of gelatinase A, tissue inhibitor of metalloproteinases-2, matrylsin, and trypsin(ogen) in lung neoplasms: an immunohistochemical study. *Hum. Pathol.* 28:613–622. [http://dx.doi.org/10.1016/S0046-8177\(97\)90085-X](http://dx.doi.org/10.1016/S0046-8177(97)90085-X)
- Kerr, K.M., S.J. MacKenzie, S. Ramasami, G.I. Murray, N. Fyfe, A.D. Chapman, M.C. Nicolson, and G. King. 2004. Expression of Fhit, cell adhesion molecules and matrix metalloproteinases in atypical adenomatous hyperplasia and pulmonary adenocarcinoma. *J. Pathol.* 203:638–644. <http://dx.doi.org/10.1002/path.1557>
- Kim, T.H., J.Y. Jung, H.J. Roh, K.Y. Chung, and M.R. Roh. 2014. Comparative Expression of Matrix Metalloproteinases in Internal Malignancies and Paired Cutaneous Metastatic Lesions. *Am. J. Dermatopathol.* In press. <http://dx.doi.org/10.1097/DAD.0000000000000184>
- Kitamura, H., Y. Oosawa, N. Kawano, Y. Kameda, H. Hayashi, Y. Nakatani, N. Udaka, T. Ito, and K. Miyazaki. 1999. Basement membrane patterns, gelatinase A and tissue inhibitor of metalloproteinase-2 expressions, and stromal fibrosis during the development of peripheral lung adenocarcinoma. *Hum. Pathol.* 30:331–338. [http://dx.doi.org/10.1016/S0046-8177\(99\)90013-8](http://dx.doi.org/10.1016/S0046-8177(99)90013-8)
- Kodate, M., T. Kasai, H. Hashimoto, K. Yasumoto, Y. Iwata, and H. Manabe. 1997. Expression of matrix metalloproteinase (gelatinase) in T1 adenocarcinoma of the lung. *Pathol. Int.* 47:461–469. <http://dx.doi.org/10.1111/j.1440-1827.1997.tb04525.x>
- Kumaki, F., K. Matsui, T. Kawai, Y. Ozeki, Z.X. Yu, V.J. Ferrans, and W.D. Travis. 2001. Expression of matrix metalloproteinases in invasive pulmonary adenocarcinoma with bronchioloalveolar component and atypical adenomatous hyperplasia. *Am. J. Pathol.* 159:2125–2135. [http://dx.doi.org/10.1016/S0002-9440\(10\)63064-7](http://dx.doi.org/10.1016/S0002-9440(10)63064-7)
- Leinonen, T., R. Pirinen, J. Böhm, R. Johansson, and V.M. Kosma. 2008. Increased expression of matrix metalloproteinase-2 (MMP-2) predicts tumour recurrence and unfavourable outcome in non-small cell lung cancer. *Histol. Histopathol.* 23:693–700.
- Li, G.H., Y.S. Cui, Q.Y. Wu, X.J. Zhang, and Y.F. Gao. 2013. Clinicopathologic significance of  $\beta$ -catenin and matrix metalloproteinase-2 expression in non-small cell lung cancer. *Med. Oncol.* 30:437. <http://dx.doi.org/10.1007/s12032-012-0437-z>
- Li, M., T. Xiao, Y. Zhang, L. Feng, D. Lin, Y. Liu, Y. Mao, S. Guo, N. Han, X. Di, et al. 2010. Prognostic significance of matrix metalloproteinase-1 levels in peripheral plasma and tumour tissues of lung cancer patients. *Lung Cancer.* 69:341–347. <http://dx.doi.org/10.1016/j.lungcan.2009.12.007>
- Lim, B.J., S.S. Jung, S.Y. Choi, and C.S. Lee. 2010. Expression of metastasis-associated molecules in non-small cell lung cancer and their prognostic significance. *Mol. Med. Rep.* 3:43–49.
- Lin, T.S., S.H. Chiou, L.S. Wang, H.H. Huang, S.F. Chiang, A.Y. Shih, Y.L. Chen, C.Y. Chen, C.P. Hsu, N.Y. Hsu, et al. 2004. Expression spectra of matrix metalloproteinases in metastatic non-small cell lung cancer. *Oncol. Rep.* 12:717–723.
- Liu, Y., D. Lin, T. Xiao, Y. Ma, Z. Hu, H. Zheng, S. Zheng, Y. Liu, M. Li, L. Li, et al. 2011. An immunohistochemical analysis-based decision tree model for estimating the risk of lymphatic metastasis in pN0 squamous cell carcinomas of the lung. *Histopathology.* 59:882–891. <http://dx.doi.org/10.1111/j.1365-2559.2011.04013.x>
- Matsuo, Y., S. Hashimoto, T. Koga, Y. Yonemitsu, I. Yoshino, K. Sugimachi, H. Honda, K. Masuda, and K. Sueishi. 2004. Growth pattern correlates with the distribution of basement membrane and prognosis in lung adenocarcinoma. *Pathol. Res. Pract.* 200:517–529. <http://dx.doi.org/10.1016/j.prp.2004.05.002>
- Michael, M., B. Babic, R. Khokha, M. Tsao, J. Ho, M. Pintilie, K. Leco, D. Chamberlain, and F.A. Shepherd. 1999. Expression and prognostic significance of metalloproteinases and their tissue inhibitors in patients with small-cell lung cancer. *J. Clin. Oncol.* 17:1802–1808.
- Mino, N., K. Takenaka, M. Sonobe, R. Miyahara, K. Yanagihara, Y. Otake, H. Wada, and F. Tanaka. 2007. Expression of tissue inhibitor of metalloproteinase-3 (TIMP-3) and its prognostic significance in resected non-small cell lung cancer. *J. Surg. Oncol.* 95:250–257. <http://dx.doi.org/10.1002/jso.20663>
- Morita, S., A. Sato, H. Hayakawa, H. Ihara, T. Urano, Y. Takada, and A. Takada. 1998. Cancer cells overexpress mRNA of urokinase-type plasminogen activator, its receptor and inhibitors in human non-small-cell lung cancer tissue: analysis by Northern blotting and in situ hybridization. *Int. J. Cancer.* 78:286–292. [http://dx.doi.org/10.1002/\(SICI\)1097-0215\(19981029\)78:3<286::AID-IJC4>3.0.CO;2-R](http://dx.doi.org/10.1002/(SICI)1097-0215(19981029)78:3<286::AID-IJC4>3.0.CO;2-R)
- Nakagawa, H., and S. Yagihashi. 1994. Expression of type IV collagen and its degrading enzymes in squamous cell carcinoma of lung. *Jpn. J. Cancer Res.* 85:934–938. <http://dx.doi.org/10.1111/j.1349-7006.1994.tb02971.x>
- Nakstad, B., and T. Lyberg. 1991. Immunohistochemical localization of coagulation, fibrinolytic and antifibrinolytic markers in adenocarcinoma of the lung. *APMIS.* 99:981–988. <http://dx.doi.org/10.1111/j.1699-0463.1991.tb01288.x>
- Nawrocki, B., M. Polette, V. Marchand, M. Monteau, P. Gillery, J.M. Tournier, and P. Birembaut. 1997. Expression of matrix metalloproteinases and their inhibitors in human bronchopulmonary carcinomas: quantitative and morphological analyses. *Int. J. Cancer.* 72:556–564. [http://dx.doi.org/10.1002/\(SICI\)1097-0215\(19970807\)72:4<556::AID-IJC2>3.0.CO;2-P](http://dx.doi.org/10.1002/(SICI)1097-0215(19970807)72:4<556::AID-IJC2>3.0.CO;2-P)
- Oka, T., T. Ishida, T. Nishino, and K. Sugimachi. 1991. Immunohistochemical evidence of urokinase-type plasminogen activator in primary and metastatic tumors of pulmonary adenocarcinoma. *Cancer Res.* 51:3522–3525.
- Okudera, K., Y. Kamata, S. Takanashi, Y. Hasegawa, T. Tushima, Y. Ogura, K. Nakanishi, H. Sato, and K. Okumura. 2006. Small adenocarcinoma of the lung: prognostic significance of central fibrosis chiefly because of its association with angiogenesis and lymphangiogenesis. *Pathol. Int.* 56:494–502. <http://dx.doi.org/10.1111/j.1440-1827.2006.01997.x>
- Ornstein, D.L., L.R. Zacharski, V.A. Memoli, W. Kisiel, B.J. Kudryk, J. Hunt, S.M. Rousseau, and D.C. Stump. 1991. Coexisting macrophage-associated fibrin formation and tumor cell urokinase in squamous cell and adenocarcinoma of the lung tissues. *Cancer.* 68:1061–1067. [http://dx.doi.org/10.1002/1097-0142\(19910901\)68:5<1061::AID-CNCR2820680525>3.0.CO;2-D](http://dx.doi.org/10.1002/1097-0142(19910901)68:5<1061::AID-CNCR2820680525>3.0.CO;2-D)
- Passlick, B., W. Siene, R. Seen-Hibler, W. Wöckel, O. Thetter, W. Mutschler, and K. Pantel. 2000. Overexpression of matrix metalloproteinase 2 predicts unfavorable outcome in early-stage non-small cell lung cancer. *Clin. Cancer Res.* 6:3944–3948.
- Passmore, M.R., M. Nataatmadja, and J.F. Fraser. 2012. Assessment of control tissue for gene and protein expression studies: a comparison of three alternative lung sources. *ScientificWorldJournal.* 2012:523840. <http://dx.doi.org/10.1100/2012/523840>
- Polette, M., B. Nawrocki, C. Gilles, H. Sato, M. Seiki, J.M. Tournier, and P. Birembaut. 1996. MT-MMP expression and localisation in human lung and breast cancers. *Virchows Arch.* 428:29–35. <http://dx.doi.org/10.1007/BF00192924>
- Pritchard, S.C., M.C. Nicolson, C. Lloret, J.A. McKay, V.G. Ross, K.M. Kerr, G.I. Murray, and H.L. McLeod. 2001. Expression of matrix metalloproteinases 1, 2, 9 and their tissue inhibitors in stage II non-small cell lung cancer: implications for MMP inhibition therapy. *Oncol. Rep.* 8:421–424.
- Robert, C., I. Bolon, S. Gazzeri, S. Veyrenc, C. Brambilla, and E. Brambilla. 1999. Expression of plasminogen activator inhibitors 1 and 2 in lung cancer and their role in tumor progression. *Clin. Cancer Res.* 5:2094–2102.
- Shao, W., W. Wang, X.G. Xiong, C. Cao, T.D. Yan, G. Chen, H. Chen, W. Yin, J. Liu, Y. Gu, et al. 2011. Prognostic impact of MMP-2 and MMP-9 expression in pathologic stage IA non-small cell lung cancer. *J. Surg. Oncol.* 104:841–846. <http://dx.doi.org/10.1002/jso.22001>
- Shou, Y., T. Hirano, Y. Gong, Y. Kato, K. Yoshida, T. Ohira, N. Ikeda, C. Konaka, Y. Ebihara, F. Zhao, and H. Kato. 2001. Influence of angiogenetic factors and matrix metalloproteinases upon tumour progression in non-small-cell lung cancer. *Br. J. Cancer.* 85:1706–1712. <http://dx.doi.org/10.1054/bjoc.2001.2137>
- Song, S.H., J.K. Lee, J.Y. Hur, I. Kim, H.S. Saw, and Y.K. Park. 2006. The expression of epidermal growth factor receptor, vascular endothelial growth factor, matrix metalloproteinase-2, and cyclooxygenase-2 in relation to human papilloma viral load and persistence of human papillomavirus after conization with negative margins. *Int. J. Gynecol. Cancer.* 16:2009–2017. <http://dx.doi.org/10.1111/j.1525-1438.2006.00727.x>
- Stenvold, H., T. Donnem, S. Andersen, S. Al-Saad, K. Al-Shibli, L.T. Busund, and R.M. Bremnes. 2012. Overexpression of matrix metalloproteinase-7 and -9 in NSCLC tumor and stromal cells: correlation with a favorable clinical outcome. *Lung Cancer.* 75:235–241. <http://dx.doi.org/10.1016/j.lungcan.2011.06.010>

- Tang, C., D. Luo, H. Yang, Q. Wang, R. Zhang, G. Liu, and X. Zhou. 2013. Expression of SHP2 and related markers in non-small cell lung cancer: a tissue microarray study of 80 cases. *Appl. Immunohistochem. Mol. Morphol.* 21:386–394. <http://dx.doi.org/10.1097/PAL.0b013e31827da3f9>
- Thomas, P., R. Khokha, F.A. Shepherd, R. Feld, and M.S. Tsao. 2000. Differential expression of matrix metalloproteinases and their inhibitors in non-small cell lung cancer. *J. Pathol.* 190:150–156. [http://dx.doi.org/10.1002/\(SICI\)1096-9896\(200002\)190:2<150::AID-PATH510>3.0.CO;2-W](http://dx.doi.org/10.1002/(SICI)1096-9896(200002)190:2<150::AID-PATH510>3.0.CO;2-W)
- Tolnay, E., T. Wiethege, C. Kuhnen, M. Wulf, B. Voss, and K.M. Müller. 1997. Expression of type IV collagenase correlates with the expression of vascular endothelial growth factor in primary non-small cell lung cancer. *J. Cancer Res. Clin. Oncol.* 123:652–658. <http://dx.doi.org/10.1007/s004320050120>
- Urbanski, S.J., D.R. Edwards, A. Maitland, K.J. Leco, A. Watson, and A.E. Kossakowska. 1992. Expression of metalloproteinases and their inhibitors in primary pulmonary carcinomas. *Br. J. Cancer.* 66:1188–1194. <http://dx.doi.org/10.1038/bjc.1992.434>
- Volm, M., J. Mattern, and R. Koomagi. 1999. Relationship of urokinase and urokinase receptor in non-small cell lung cancer to proliferation, angiogenesis, metastasis and patient survival. *Oncol. Rep.* 6:611–615.
- Yamamura, T., K. Nakanishi, S. Hiroi, F. Kumaki, H. Sato, S. Aida, and T. Kawai. 2002. Expression of membrane-type-1-matrix metalloproteinase and metalloproteinase-2 in nonsmall cell lung carcinomas. *Lung Cancer.* 35:249–255. [http://dx.doi.org/10.1016/S0169-5002\(01\)00431-7](http://dx.doi.org/10.1016/S0169-5002(01)00431-7)
- Yao, L., B. Sun, X. Zhao, X. Zhao, Q. Gu, X. Dong, Y. Zheng, J. Sun, R. Cheng, H. Qi, and J. An. 2014. Overexpression of Wnt5a promotes angiogenesis in NSCLC. *Biomed. Res. Int.* 2014:832562. <http://dx.doi.org/10.1155/2014/832562>
- Yoshino, H., Y. Endo, Y. Watanabe, and T. Sasaki. 1998. Significance of plasminogen activator inhibitor 2 as a prognostic marker in primary lung cancer: association of decreased plasminogen activator inhibitor 2 with lymph node metastasis. *Br. J. Cancer.* 78:833–839. <http://dx.doi.org/10.1038/bjc.1998.588>
- Zhang, Z., A. Wang, B. Sun, Z. Zhan, K. Chen, and C. Wang. 2013. Expression of CLDN1 and CLDN10 in lung adenocarcinoma in situ and invasive lepidic predominant adenocarcinoma. *J. Cardiothorac. Surg.* 8:95. <http://dx.doi.org/10.1186/1749-8090-8-95>
- Zhou, H., A. Wu, W. Fu, Z. Lv, and Z. Zhang. 2014. Significance of semaphorin-3A and MMP-14 protein expression in non-small cell lung cancer. *Oncol. Lett.* 7:1395–1400.

### Studies of protease localization in human prostate cancer

- Behnsawy, H.M., H. Miyake, K. Harada, and M. Fujisawa. 2013. Expression patterns of epithelial-mesenchymal transition markers in localized prostate cancer: significance in clinicopathological outcomes following radical prostatectomy. *BJU Int.* 111:30–37. <http://dx.doi.org/10.1111/j.1464-410X.2012.11551.x>
- Boag, A.H., and I.D. Young. 1994. Increased expression of the 72-kd type IV collagenase in prostatic adenocarcinoma. Demonstration by immunohistochemistry and in situ hybridization. *Am. J. Pathol.* 144:585–591.
- Bodey, B., B. Bodey Jr., S.E. Siegel, and H.E. Kaiser. 2001. Immunocytochemical detection of matrix metalloproteinase expression in prostate cancer. *In Vivo.* 15:65–70.
- Boxler, S., V. Djonov, T.M. Kessler, R. Hlushchuk, L.M. Bachmann, U. Held, R. Markwalder, and G.N. Thalmann. 2010. Matrix metalloproteinases and angiogenic factors: predictors of survival after radical prostatectomy for clinically organ-confined prostate cancer? *Am. J. Pathol.* 177:2216–2224. <http://dx.doi.org/10.2353/ajpath.2010.091190>
- Brehmer, B., S. Biesterfeld, and G. Jakse. 2003. Expression of matrix metalloproteinases (MMP-2 and -9) and their inhibitors (TIMP-1 and -2) in prostate cancer tissue. *Prostate Cancer Prostatic Dis.* 6:217–222. <http://dx.doi.org/10.1038/sj.pcan.4500657>
- Cardillo, M.R., F. Di Silverio, and V. Gentile. 2006. Quantitative immunohistochemical and in situ hybridization analysis of metalloproteinases in prostate cancer. *Anticancer Res.* 26(2A):973–982.
- Cozzi, P.J., J. Wang, W. Delprado, M.C. Madigan, S. Fairy, P.J. Russell, and Y. Li. 2006. Evaluation of urokinase plasminogen activator and its receptor in different grades of human prostate cancer. *Hum. Pathol.* 37:1442–1451. <http://dx.doi.org/10.1016/j.humpath.2006.05.002>
- Escaff, S., J.M. Fernández, L.O. González, A. Suárez, S. González-Reyes, J.M. González, and F.J. Vizoso. 2011a. Collagenase-3 expression by tumor cells and gelatinase B expression by stromal fibroblast-like cells are associated with biochemical recurrence after radical prostatectomy in patients with prostate cancer. *World J. Urol.* 29:657–663. <http://dx.doi.org/10.1007/s00345-010-0595-6>
- Escaff, S., J.M. Fernández, L.O. González, A. Suárez, S. González-Reyes, J.M. González, and F.J. Vizoso. 2011b. Comparative study of stromal metalloproteinases expression in patients with benign hyperplasia and prostate cancer. *J. Cancer Res. Clin. Oncol.* 137:551–555. <http://dx.doi.org/10.1007/s00432-010-0906-8>
- Fernandez-Gomez, J., S. Escaf, L.O. Gonzalez, A. Suarez, S. Gonzalez-Reyes, J. González, O. Miranda, and F. Vizoso. 2011. Relationship between metalloproteinase expression in tumour and stromal cells and aggressive behaviour in prostate carcinoma: Simultaneous high-throughput study of multiple metalloproteinases and their inhibitors using tissue array analysis of radical prostatectomy samples. *Scand. J. Urol. Nephrol.* 45:171–176. <http://dx.doi.org/10.3109/00365599.2010.545074>
- Gavrilov, D., O. Kenzior, M. Evans, R. Calaluze, and W.R. Folk. 2001. Expression of urokinase plasminogen activator and receptor in conjunction with the ets family and AP-1 complex transcription factors in high grade prostate cancers. *Eur. J. Cancer.* 37:1033–1040. [http://dx.doi.org/10.1016/S0959-8049\(01\)00077-6](http://dx.doi.org/10.1016/S0959-8049(01)00077-6)
- Gupta, A., Y. Lotan, R. Ashfaq, C.G. Roehrborn, G.V. Raj, C.C. Aragaki, F. Montorsi, and S.F. Shariat. 2009. Predictive value of the differential expression of the urokinase plasminogen activation axis in radical prostatectomy patients. *Eur. Urol.* 55:1124–1134. <http://dx.doi.org/10.1016/j.eururo.2008.06.054>
- Kogianni, G., M.M. Walker, J. Waxman, and J. Sturge. 2009. Endo180 expression with cofunctional partners MT1-MMP and uPAR-uPA is correlated with prostate cancer progression. *Eur. J. Cancer.* 45:685–693. <http://dx.doi.org/10.1016/j.ejca.2008.11.023>
- Kumano, M., H. Miyake, M. Muramaki, J. Furukawa, A. Takenaka, and M. Fujisawa. 2009. Expression of urokinase-type plasminogen activator system in prostate cancer: correlation with clinicopathological outcomes in patients undergoing radical prostatectomy. *Urol. Oncol.* 27:180–186. <http://dx.doi.org/10.1016/j.urolonc.2008.01.012>
- Kuniyasu, H., P. Troncso, D. Johnston, C.D. Bucana, E. Tahara, I.J. Fidler, and C.A. Pettaway. 2000. Relative expression of type IV collagenase, E-cadherin, and vascular endothelial growth factor/vascular permeability factor in prostatectomy specimens distinguishes organ-confined from pathologically advanced prostate cancers. *Clin. Cancer Res.* 6:2295–2308.
- Kuniyasu, H., R. Ukai, D. Johnston, P. Troncso, I.J. Fidler, and C.A. Pettaway. 2003. The relative mRNA expression levels of matrix metalloproteinase to E-cadherin in prostate biopsy specimens distinguishes organ-confined from advanced prostate cancer at radical prostatectomy. *Clin. Cancer Res.* 9:2185–2194.
- Madigan, M.C., E.A. Kingsley, P.J. Cozzi, W.J. Delprado, P.J. Russell, and Y. Li. 2008. The role of extracellular matrix metalloproteinase inducer protein in prostate cancer progression. *Cancer Immunol. Immunother.* 57:1367–1379. <http://dx.doi.org/10.1007/s00262-008-0473-x>
- Maruta, S., H. Sakai, S. Kanda, T. Hayashi, H. Kanetake, and Y. Miyata. 2009. E1AF expression is associated with extra-prostatic growth and matrix metalloproteinase-7 expression in prostate cancer. *APMIS.* 117:791–796. <http://dx.doi.org/10.1111/j.1600-0463.2009.02534.x>
- Matuszak, E.A., and N. Kyprianou. 2013. Expression patterns of epithelial-mesenchymal transition markers in localized prostate cancer: significance in clinicopathological outcomes following radical prostatectomy. *BJU Int.* 111:6–7. <http://dx.doi.org/10.1111/j.1464-410X.2012.11566.x>
- Min, H.J., Y. Lee, X.F. Zhao, Y.K. Park, M.K. Lee, J.W. Lee, and S. Kim. 2014. TMPPRS4 upregulates uPA gene expression through JNK signaling activation to induce cancer cell invasion. *Cell. Signal.* 26:398–408. <http://dx.doi.org/10.1016/j.cellsig.2013.08.002>
- Miyake, H., M. Muramaki, T. Kurahashi, A. Takenaka, and M. Fujisawa. 2010. Expression of potential molecular markers in prostate cancer: correlation with clinicopathological outcomes in patients undergoing radical prostatectomy. *Urol. Oncol.* 28:145–151. <http://dx.doi.org/10.1016/j.urolonc.2008.08.001>
- Montironi, R., G. Lucarini, C. Castaldini, C.M. Galluzzi, G. Biagini, and G. Fabris. 1996. Immunohistochemical evaluation of type IV collagenase (72-kd metalloproteinase) in prostatic intraepithelial neoplasia. *Anticancer Res.* 16(4A):2057–2062.