



















- S, Shimizu M, Rattan S, Bullrich F, Negrini M, Croce CM. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc Natl Acad Sci USA* 2004;101:2999-3004.
26. Sevignani C, Calin GA, Nnadi SC, Shimizu M, Davuluri RV, Hyslop T, Demant P, Croce CM, Siracusa LD. MicroRNA genes are frequently located near mouse cancer susceptibility loci. *Proc Natl Acad Sci USA* 2007;104:8017-22.
  27. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. *Nat Rev Cancer* 2009;9:239-52.
  28. Korpala M, Lee ES, Hu G, Kang Y. The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2. *J Biol Chem* 2008;283:14910-4.
  29. Zhao C, Xu Y, Zhang Y, Tan W, Xue J, Yang Z, Zhang Y, Lu Y, Hu X. Downregulation of miR-145 contributes to lung adenocarcinoma cell growth to form brain metastases. *Oncol Rep* 2013;30:2027-34.
  30. Sachdeva M, Mo YY. MicroRNA-145 suppresses cell invasion and metastasis by directly targeting mucin 1. *Cancer Res* 2010;70:378-87.
  31. Götte M, Mohr C, Koo CY, Stock C, Vaske AK, Viola M, Ibrahim SA, Peddibhotla S, Teng YH, Low JY, Ebnet K, Kiesel L, Yip GW. miR-145-dependent targeting of junctional adhesion molecule A and modulation of fascin expression are associated with reduced breast cancer cell motility and invasiveness. *Oncogene* 2010;29:6569-80.
  32. Hanniford D, Zhong J, Koetz L, Gaziel-Sovran A, Lackaye DJ, Shang S, Pavlick A, Shapiro R, Berman R, Darvishian F, Shao Y, Osman I, Hernando E. A miRNA-Based Signature Detected in Primary Melanoma Tissue Predicts Development of Brain Metastasis. *Clin Cancer Res* 2015;21:4903-12.
  33. He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. *Nat Rev Genet* 2004;5:522-31.
  34. Cortez MA, Bueso-Ramos C, Ferdin J, Lopez-Berestein G, Sood A K, Calin GA. MicroRNAs in body fluids - the mix of hormones and biomarkers. *Nat Rev Clin Oncol* 2011;8:467-77.
  35. Corrado C, Raimondo S, Chiesi A, Ciccia F, De LG, Alessandro R. Exosomes as intercellular signaling organelles involved in health and disease: basic science and clinical applications. *Int J Mol Sci* 2013;14:5338-66.
  36. Azmi AS, Bao B, Sarkar FH. Exosomes in cancer development, metastasis, and drug resistance: a comprehensive review. *Cancer Metastasis Rev* 2013;32:623-42.
  37. Zhou W, Fong MY, Min Y, Somlo G, Liu L, Palomares MR, Yu Y, Chow A, O'Connor ST, Chin AR, Yen Y, Wang Y, Marcusson EG, Chu P, Wu J, Wu X, Li AX, Li Zi, Gao H, Ren X, Boldin MP, Lin PC, Wang SE. Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis. *Cancer Cell* 2014;25:501-15.
  38. Tominaga N, Kosaka N, Ono M, Katsuda T, Yoshioka Y, Tamura K, Lötval J, Nakagama H, Ochiya T. Brain metastatic cancer cells release microRNA-181c-containing extracellular vesicles capable of destructing blood-brain barrier. *Nat Commun* 2015;6:6716.
  39. Hoshino A, Costa-Silva B, Shen TL, Rodrigues G, Hashimoto A, Tesic Mark M, Molina H, Kohsaka S, Di Giannatale A, Ceder S, Singh S, Williams C, Sotop N, Uryu K, Pharmed L, King T, Bojmar L, Davies AE, Ararso Y, Zhang T, Zhang H, Hernandez J, Weiss JM, Dumont-Cole VD, Kramer K, Wexler LH, Narendran A, Schwartz GK, Healey JH, Sandstrom P, Jørgen Labori K, Kure EH, Grandgenett PM, Hollingsworth MA, de Sousa M, Kaur S, Jain M, Mallya K, Batra SK, Jarnagin WR, Brady MS, Fodstad O, Muller V, Pantel K, Minn AJ, Bissell MJ, Garcia BA, Kang Y, Rajasekhar VK, Ghajar CM, Matei I, Peinado H, Bromberg J, Lyden D. Tumour exosome integrins determine organotropic metastasis. *Nature* 2015; doi: 10.1038/nature15756.
  40. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. *Neurobiol Dis* 2010;37:13-25.
  41. Klemke M, Weschenfelder T, Konstandin MH, Samstag Y. High affinity interaction of integrin alpha4beta1 (VLA-4) and vascular cell adhesion molecule 1 (VCAM-1) enhances migration of human melanoma cells across activated endothelial cell layers. *J Cell Physiol* 2007;212:368-74.
  42. Wu K, Fukuda K, Xing F, Zhang Y, Sharma S, Liu Y, Chan MD, Zhou X, Qasem SA, Pochampally R, Mo YY, Watabe K. Roles of the cyclooxygenase 2 matrix metalloproteinase 1 pathway in brain metastasis of breast cancer. *J Biol Chem* 2015;290:9842-54.
  43. Rolland Y, Demeule M, Fenart L, Beliveau R. Inhibition of melanoma brain metastasis by targeting melanotransferrin at the cell surface. *Pigment Cell Melanoma Res* 2009;22: 86-98.
  44. Perides G, Zhuge Y, Lin T, Stins MF, Bronson RT, Wu JK. The fibrinolytic system facilitates tumor cell migration across the blood-brain barrier in experimental melanoma brain metastasis. *BMC Cancer* 2006;6: 56.
  45. Fazakas C, Wilhelm I, Nagyoszi P, Farkas AE, Haskó J, Molnár J, Bauer H, Bauer HC, Ayaydin F, Dung NT, Siklós L, Krizbai IA. Transmigration of melanoma cells through the blood-brain barrier: role of endothelial tight junctions and melanoma-released serine proteases. *PLoS One* 2001;6:e20758.
  46. Lorger M, Felding-Habermann B. Capturing changes in the brain microenvironment during initial steps of breast cancer brain metastasis. *Am J Pathol* 2010;176:2958-71.
  47. Kiernast Y, von Baumgarten L, Fuhrmann M, Klinkert WE, Goldbrunner R, Herms J, Winkler F. Real-time imaging reveals the single steps of brain metastasis formation. *Nat Med* 2010;16:116-22.
  48. Blecharz KG, Colla R, Rohde V, Vajkoczy P. Control of the blood-brain barrier function in cancer cell metastasis. *Biol Cell* 2015;107:342-71.
  49. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015;523:337-41.
  50. Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, Wiig H, Alitalo K. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med* 2015;212:991-9.
  51. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, Sneed PK, Chao ST, Weil RJ, Suh J, Bhatt A, Jensen AW, Brown PD, Shih HA, Kirkpatrick J, Gaspar LE, Fiveash JB, Chiang V, Knisely JP, Sperduto CM, Lin N, Mehta M. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012;30:419-25.
  52. Oser MG, Niederst MJ, Sequist LV, Engelman JA. Transformation from non-small-cell lung cancer to small-cell lung cancer: molecular drivers and cells of origin. *Lancet Oncol* 2015;16:165-72.
  53. Ramakrishna R, Rostomily R. Seed, soil, and beyond: the basic biology of brain metastasis. *Surg Neurol Int* 2013;4:S256-64.
  54. St Hill CA. Interactions between endothelial selectins and cancer cells regulate metastasis. *Front Biosci* 2011;16:3233-51.
  55. Li B, Zhao WD, Tan ZM, Fang WG, Zhu L, Chen YH. Involvement of Rho/ROCK signalling in small cell lung cancer migration through human brain microvascular endothelial cells. *FEBS Lett* 2006;580:4252-60.
  56. Liu Y, Liu YS, Wu PF, Li Q, Dai WM, Yuan S, Xu ZH, Liu TT, Miao ZW, Fang WG, Chen YH, Li B. Brain microvascular endothelium induced-annexin A1 secretion contributes to small cell lung cancer brain metastasis. *Int J Biochem Cell Biol* 2015;66:11-9.
  57. Biaoxue R, Xiling J, Shuangying Y, Wei Z, Xiguang C, Jinsui W, Min Z. Upregulation of Hsp90-beta and annexin A1 correlates with poor survival and lymphatic metastasis in lung cancer patients. *J Exp Clin Cancer Res* 2012;31:70.
  58. van Meerbeek JP1, Fennell DA, De Ruyscher DK. Small-cell lung cancer. *Lancet* 2011;12;378:1741-55.

59. Hodkinson PS, Elliott T, Wong WS, Rintoul RC, Mackinnon AC, Haslett C, Sethi T. ECM overrides DNA damage-induced cell cycle arrest and apoptosis in small-cell lung cancer cells through beta1 integrin-dependent activation of PI3-kinase. *Cell Death Differ* 2006;13:1776-88.
60. Ali A1, Goffin JR, Arnold A, Ellis PM. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. *Curr Oncol* 2013;20:300-6.
61. Goldstraw P, Ball D, Jett JR, Le Chevalier T, Lim E, Nicholson AG, Shepherd FA. Non-small-cell lung cancer. *Lancet* 2011;378:1727-40.
62. Ceresoli GL, Cappuzzo F, Gregorc V, Bartolini S, Crinò L, Villa E. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann Oncol* 2004;15:1042-7.
63. Lai CS, Boshoff C, Falzon M, Lee SM. Complete response to erlotinib treatment in brain metastases from recurrent NSCLC. *Thorax* 2006;61:91.
64. Prudkin L, Liu DD, Ozburn NC, Sun M, Behrens C, Tang X, Moran C, Wistuba II. Epithelial-to-mesenchymal transition in the development and progression of adenocarcinoma and squamous cell carcinoma of the lung. *Mod Pathol* 2009;22:668-78.
65. Seike M, Goto A, Okano T, Bowman ED, Schetter AJ, Horikawa I, Mathe EA, Jen J, Yang P, Sugimura H, Gemma A, Kudoh S, Croce CM, Harris CC. MiR-21 is an EGFR-regulated anti-apoptotic factor in lung cancer in never-smokers. *Proc Natl Acad Sci USA* 2009;106:12085-90.
66. Chin LJ, Ratner E, Leng S, Zhai R, Nallur S, Babar I, Muller RU, Straka E, Su L, Burki EA, Crowell RE, Patel R, Kulkarni T, Homer R, Zelterman D, Kidd KK, Zhu Y, Christiani DC, Belinsky SA, Slack FJ, Weidhaas JB. A SNP in a let-7 microRNA complementary site in the KRAS 3' untranslated region increases non-small cell lung cancer risk. *Cancer Res* 2008;68:8535-40.
67. Zhao C1, Xu Y, Zhang Y, Tan W, Xue J, Yang Z, Zhang Y, Lu Y, Hu X. Downregulation of miR-145 contributes to lung adenocarcinoma cell growth to form brain metastases. *Oncol Rep* 2013 Nov;30:2027-34.
68. Zhang Y, Lin Q. MicroRNA-145 inhibits migration and invasion by down-regulating FSCN1 in lung cancer. *Int J Clin Exp Med* 2015;8:8794-802.
69. Donzelli S, Mori F, Bellissimo T, Sacconi A, Casini B, Frixia T, Roscilli G, Aurisicchio L, Facciolo F, Pompili A, Carosi MA, Pescarmona E, Segatto O, Pond G, Muti P, Telera S, Strano S, Yarden Y, Blandino G. Epigenetic silencing of miR-145-5p contributes to brain metastasis. *Oncotarget* 2015;6:35183-201.
70. Arora S, Ranade AR, Tran NL, Nasser S, Sridhar S, Korn RL, Ross JT, Dhruv H, Foss KM, Sibenaller Z, Ryken T, Gotway MB, Kim S, Weiss GJ. MicroRNA-328 is associated with (non-small) cell lung cancer (NSCLC) brain metastasis and mediates NSCLC migration. *Int J Cancer* 2011;129:2621-31.
71. Tano K, Akimitsu N. Long noncoding RNAs in cancer progression. *Front genet* 2012;3:219.
72. Shen L, Chen L, Wang Y, Jiang X, Xia H, Zhuang Z. Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. *J Neurooncol* 2015;121:101-8.
73. Mittelbronn M, Warth A, Meyermann R, Goodman S, Weller M. Expression of integrins alphavbeta3 and alphavbeta5 and their ligands in primary and secondary central nervous system neoplasms. *Histol Histopathol* 2012;33:405-12.
74. Vogetseder A, Thies S, Ingold B, Roth P, Weller M, Schraml P, Goodman SL, Moch H. Alphav-Integrin isoform expression in primary human tumors and brain metastases. *Int J Cancer* 2013;133:2362-71.
75. Lorgier M, Krueger JS, O'Neal M, Staffin K, Felding-Habermann B. Activation of tumor cell integrin  $\alpha\beta3$  controls angiogenesis and metastatic growth in the brain. *Proc Natl Acad Sci USA* 2009;106:10666-71.
76. Berghoff AS, Kovanda AK, Melchardt T, Bartsch R, Hainfellner JA, Sipos B, Schittenhelm J, Zielinski CC, Widhalm G, Dieckmann K, Weller M, Goodman SL, Birner P, Preusser M.  $\alpha\beta3$ ,  $\alpha\beta5$  and  $\alpha\beta6$  integrins in brain metastases of lung cancer. *Clin Exp Metastasis* 2014;31:841-51.
77. Deryugina EI, Quigley JP. Tumor angiogenesis: MMP-mediated induction of intravasation- and metastasis-sustaining neovasculature. *Matrix Biol* 2015;44-46:94-112.
78. Rojiani MV, Alidina J, Esposito N, Rojiani AM. Expression of MMP-2 correlates with increased angiogenesis in CNS metastasis of lung carcinoma. *Int J Clin Exp Pathol* 2010;3:775-81.
79. Preusser M, Berghoff AS, Berger W, Ilhan-Mutlu A, Dinhof C, Widhalm G, Dieckmann K, Wöhrer A, Hackl M, von Deimling A, Streubel B, Birner P. High rate of FGFR1 amplifications in brain metastases of squamous and non-squamous lung cancer. *Lung Cancer* 2014;8:83-9.
80. Lee HW, Seol HJ, Choi YL, Ju HJ, Joo KM, Ko YH, Lee JI, Nam DH. Genomic copy number alterations associated with the early brain metastasis of non-small cell lung cancer. *Int J Oncol* 2012;4:2013-20.
81. Prat A, Perou CM. Deconstructing the molecular portraits of breast cancer. *Mol Oncol* 2011, 5;5-23.
82. Niikura N, Saji S, Tokuda Y, Iwata H. Brain metastases in breast cancer. *Jpn J Clin Oncol* 2014;44:1133-40.
83. Hung MH, Liu CY, Shiau CY, Hsu CY, Tsai YF, Wang YL, Tai LC, King KL, Chao TC, Chiu JH, Su CH, Lo SS, Tzeng CH, Shyr YM, Tseng LM. Effect of age and biological subtype on the risk and timing of brain metastasis in breast cancer patients. *PLoS One* 2014;9:e89389.
84. Venkitaraman R, Joseph T, Dhadda A, Chaturvedi A, Upadhyay S. Prognosis of patients with triple-negative breast cancer and brain metastasis. *Clin Oncol* 2009;21:729-30.
85. Niikura N, Liu J, Hayashi N, Mittendorf EA, Gong Y, Palla SL, Tokuda Y, Gonzalez-Angulo AM, Hortobagyi GN, Ueno NT. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. *J Clin Oncol* 2012;30:593-9.
86. Bos PD, Zhang XH, Nadal C, Shu W, Gomis RR, Nguyen DX, Minn AJ, van de Vijver MJ, Gerald WL, Foekens JA, Massagué J. Genes that mediate breast cancer metastasis to the brain. *Nature* 2009;459:1005-9.
87. Gupta GP, Nguyen DX, Chiang AC, Bos PD, Kim JY, Nadal C, Gomis RR, Manova-Todorova K, Massagué J. Mediators of vascular remodelling co-opted for sequential steps in lung metastasis. *Nature* 2007;446:765-70.
88. Fan C, Oh DS, Wessels L, Weigelt B, Nuyten DS, Nobel AB, van't Veer LJ, Perou CM. Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med* 2006;355:560-9.
89. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. *Nature Rev Cancer* 2002;2:161-74.
90. Padua D, Zhang XH, Wang Q, Nadal C, Gerald WL, Gomis RR, Massagué J. TGFbeta primes breast tumors for lung metastasis seeding through angiopoietin-like 4. *Cell* 2008;133:66-77.
91. Adams JC. Roles of fascin in cell adhesion and motility. *Curr Opin Cell Biol* 2004;16:590-6.
92. Dall'Olio F, Chiricolo M. Sialyltransferases in cancer. *Glycoconj J* 2001;18:841-50.
93. Palmieri D, Fitzgerald D, Shreeve SM, Hua E, Bronder JL, Weil RJ, Davis S, Stark AM, Merino MJ, Kurek R, Mehdorn HM, Davis G, Steinberg SM, Meltzer PS, Aldape K, Steeg PS. Analyses of resected human brain metastases of breast cancer reveal the association between up-regulation of hexokinase 2 and poor prognosis. *Mol Cancer Res* 2009;7:1438-45.
94. Smith TA. Mammalian hexokinases and their abnormal expression in cancer. *Br J Biomed Sci* 2000;57:170-8.
95. Brastianos PK, Carter SL, Santagata S, Cahill DP, Taylor-Weiner A, Jones RT, Van Allen EM, Lawrence MS, Horowitz PM, Cibulskis K, Ligon KL, Taberner J, Seoane J, Martinez-Saez E, Curry WT,

- Dunn IF, Paek SH, Park SH, McKenna A, Chevalier A, Rosenberg M, Barker FG 2nd, Gill CM, Van Hummelen P, Thorner AR, Johnson BE, Hoang MP, Choueiri TK, Signoretti S, Sougnez C, Rabin MS, Lin NU, Winer EP, Stemmer-Rachamimov A, Meyerson M, Garraway L, Gabriel S, Lander ES, Beroukhi R, Batchelor TT, Baselga J, Louis DN, Getz G, Hahn WC. Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets. *Cancer Discov* 2015;5:1164-77.
96. Ray PS, Wang J, Qu Y, Sim MS, Shamonki J, Bagaria SP, Ye X, Liu B, Elashoff D, Hoon DS, Walter MA, Martens JW, Richardson AL, Giuliano AE, Cui X. FOXC1 is a potential prognostic biomarker with functional significance in basal-like breast cancer. *Cancer Res* 2010;70:3870-6.
  97. Sizemore ST, Keri RA. The forkhead box transcription factor FOXC1 promotes breast cancer invasion by inducing matrix metalloproteinase 7 (MMP7) expression. *J Biol Chem* 2012;287:24631-40.
  98. Yu M, Bardia A, Wittner BS, Stott SL, Smas ME, Ting DT, Isakoff SJ, Ciciliano JC, Wells MN, Shah AM, Concannon KF, Donaldson MC, Sequist LV, Brachtel E, Sgroi D, Baselga J, Ramaswamy S, Toner M, Haber DA, Maheswaran S. Circulating breast tumor cells exhibit dynamic changes in epithelial and mesenchymal composition. *Science* 2013;339:580-4.
  99. Miller AJ, Mihm MC, Jr. Melanoma. *N Engl J Med* 2006;355:51-65.
  100. Damsky WE, Theodosakis N, Bosenberg M. Melanoma metastasis: new concepts and evolving paradigms. *Oncogene* 2014;33:2413-22.
  101. The International Agency for Research on Cancer. Pathology and Genetics of Skin Tumours (IARC WHO Classification of Tumours). Lyon: IARC Press; 2006.
  102. Fidler IJ. The Biology of brain metastasis: challenges for therapy. *Cancer J* 2015;21:284-93.
  103. Berghoff AS, Preusser M. BRAF alterations in brain tumours: molecular pathology and therapeutic opportunities. *Curr Opin Neurol* 2014;27:689-96.
  104. Muñoz-Couselo E, García JS, Pérez-García JM, Cebrián VO, Castán JC. Recent advances in the treatment of melanoma with BRAF and MEK inhibitors. *Ann Transl Med* 2015;3:207.
  105. Cancer Genome Atlas Network. Genomic Classification of Cutaneous Melanoma. *Cell* 2015;161:1681-96.
  106. Thompson EW, Newgreen DF, Tarin D. Carcinoma invasion and metastasis: a role for epithelial-mesenchymal transition? *Cancer Res* 2005;65:5991-5.
  107. Caramel J, Papadogeorgakis E, Hill L, Browne GJ, Richard G, Wierinckx A, Saldanha G, Osborne J, Hutchinson P, Tse G, Lachuer J, Puisieux A, Pringle JH, Ansieau S, Tulchinsky E. A switch in the expression of embryonic EMT-inducers drives the development of malignant melanoma. *Cancer Cell* 2013;24:466-80.
  108. Van Roy F. Beyond E-cadherin: roles of other cadherin superfamily members in cancer. *Nat Rev Cancer* 2014;14:121-34.
  109. Wilmott JS, Haydu LE, Menzies AM, Lum T, Hyman J, Thompson JF, Hersey P, Kefford RF, Scolyer RA, Long GV. Dynamics of chemokine, cytokine, and growth factor serum levels in BRAF-mutant melanoma patients during BRAF inhibitor treatment. *J Immunol* 2014;192:2505-13.
  110. Robertson GP. Functional and therapeutic significance of Akt deregulation in malignant melanoma. *Cancer Metastasis Rev* 2005;24:273-85.
  111. Stahl JM, Cheung M, Sharma A, Trivedi NR, Shanmugam S, Robertson GP. Loss of PTEN promotes tumor development in malignant melanoma. *Cancer Res* 2003;63:2881-90.
  112. Mumford BS, Robertson GP. Circulating melanoma cells in the diagnosis and monitoring of melanoma: an appraisal of clinical potential. *Mol Diagn Ther* 2014;18:175-83.
  113. Lin Q, Balasubramanian K, Fan D, Kim SJ, Guo L, Wang H, Bar-Eli M, Aldape KD, Fidler IJ. Reactive astrocytes protect melanoma cells from chemotherapy by sequestering intracellular calcium through gap junction communication channels. *Neoplasia* 2010;12:748-54.
  114. Wilhelm I, Krizbai IA. *In vitro* models of the blood-brain barrier for the study of drug delivery to the brain. *Mol Pharm* 2014;11:1949-63.
  115. Hopkins AM, DeSimone E, Chwalek K, Kaplan DL. 3D *in vitro* modeling of the central nervous system. *Prog Neurobiol* 2015;125:1-25.