

Tumorigenesis of malignant mesothelioma: The key role of genetics

INTRODUCTION

The literature review in this section focuses on several key concepts regarding the genetics and pathways involved in the tumorigenesis of malignant mesothelioma (MM). With this in mind, approximately 250 articles were analyzed and summarized below but we do not claim that this is an in-depth, exhaustive review, so please consult the bibliography at the end of this text for further further information.

MOLECULAR BIOLOGY OF MESOTHELIOMA

Malignant mesothelioma (MM) is caused by the abnormal proliferation of tumors in the pleura, pericardium, peritoneum, tunica vaginalis testis or ovarian epithelium (1,2).

Its incidence rate is increasing, and unfortunately the prognosis is often poor (3,4). A number of diverse pathogenetic hypotheses for this disease have been investigated in detail (5-8).

MM is characterized by a long latency period before the appearance of the initial symptoms that can lead to a diagnosis and during this long period, genetic mutations may occur and characterize the neoplastic changes (9-11). The purpose of this literature review is to focus on the genetics and pathogenetic pathways associated with this neoplasm.

GENES

The main chromosomes affected by this neoplasm are: 1, 3, 4, 6, 9, 13 and 14 (12).

The genetic abnormalities most commonly associated with malignant pleural mesothelioma (MPM), and which will be analyzed individually, are the following: p16^{INK4a}/p14^{ARF} (13,14), NF2 (15,16), p53 (17-20), PTEN (21-23), BAP-1 (24), LATS2 (25), PI3K/AKT/mTOR (22,26), EGFR (27,28), VEGF (29-31), pRb (32,33), BCL-2 (34-36), hippo (37-39) and Wnt (40,41).

p16^{INK4a}/p14^{ARF}

The p16^{INK4a}/p14^{ARF} gene is also known as CDKN2A/ARF and is located on chromosome 9p21.

This is a very important tumor suppressor gene that codifies for two proteins: p16^{INK4a} and p14^{ARF}. (42-43)

Protein p16^{INK4a} inhibits CDK, which inactivates pRb.

Protein p14^{ARF}, on the other hand, regulates the function of p53 and inhibits its degradation by interacting with MDM2 (27,44,45).

These modifications play a fundamental role in regulating the control of the cell cycle; these genetic mutations also appear to be associated with more aggressive tumors and a poorer prognosis (13,14).

These genes in particular are implicated in the development of different types of neoplasia (46-48). Similarly, the same type of genetic mutations may also occur in MPM (13, 50-54).

Scientific studies have shown that if this gene is “switched off”, cancerogenesis may be “accelerated” due to exposure to asbestos (55-59).

Gene therapy studies are aimed at reactivating the p16^{INK4a}/p14^{ARF} gene to restore the functions that have been lost if the gene is mutated. The studies have shown that reactivating this gene halts the cell cycle of mesothelioma cells, inhibits the phosphorylation of pRb, and decreases cell growth. All these modifications may therefore increase survival, increase the levels of protein p53, and boost cell apoptosis (60-63,12).

Gene therapy aimed at restoring the functions altered by the mutation of this gene has shown promising preliminary results.

NF2

NF2, the abbreviation for the type 2 neurofibromatosis gene, is a genetic trait that follows an autosomal dominant inheritance pattern leading to tumor predisposition syndrome, and is characterized by the development of bilateral vestibular schwannomas on the eighth cranial nerve and other brain tumors, including meningiomas and ependymomas.

This syndrome results from the lack of expression of the NF2 gene, which is a tumor suppressor.

Although known for the above syndrome, this gene is also associated with malignant mesothelioma (64-69).

The lack of protein activity associated with the codification of the mutated gene appears to be associated with a greater possibility of carcinogenesis, as opposed to patients who do not have this genetic mutation, and which is certainly greater for patients who have been exposed to asbestos (22,70). However, the precise functionality of this gene has not yet been fully defined.

Gene therapy associated with this gene involves trying to “over-express” it through the use of viral vectors. These studies have shown interesting results, such as controlling the cell cycle and proliferation (71-75).

Re-expression of the NF2 gene in patients with MM could certainly be of considerable help in inhibiting cell proliferation and tumor invasion (76).

BAP-1

Several clinical studies have sought to understand how there appears to be a genetic predisposition to MPM in certain localities. BAP-1 was found among the genes that were mutated and thus deemed to be involved in this disease (77-79).

Recent studies have also shown that BAP-1 is a tumor suppressor located on chromosome 3p21, which appears to play a role in regulating the cell cycle and responding to DNA damage (80-81).

This genetic mutation was found in patients with MM, especially the squamous histotype rather than the epithelial histotype (82-84).

This pathologic genetic modification seems to be particularly associated with a poorer prognosis (85-86), as well as the development of neoplasia (87).

Gene therapy is being investigated not only to find an effective treatment for patients with a genetic alteration of this gene, but also to eventually prevent MM in subjects with a mutated BAP-1 gene.

LATS2

The Large Tumor Suppressor (LATS) was the first tumor marker identified in *Drosophila* (88).

In humans, this gene is located in a region of chromosome 13 (13q11-12) and is often mutated in tumors (89-90).

Two forms of LATS have been identified: LATS1 and LATS2. LATS2 in particular is a centrosomal protein which appears to be involved in mitotic subdivision (91), regulating the inhibition of the growth of Hippo (37) and activating p53 (92-93).

This gene has been studied in MM, particularly in cell lines characterized by a deletion of chromosome 13q11-12. Comparative genomic hybridization techniques were used for these analyses, subsequently confirmed by PCR.

These studies have shown the presence of genetic mutations of LATS2 in MM cells (25).

According to these studies, LATS2 appears to play a role in cell proliferation and survival. However, further studies are needed to confirm whether this gene actually plays a causal role in the development of MM.

DNA methylation

Studies investigating DNA methylation in MM have shown promising results.

They have shown that the methylation profile can be a differentiating factor between the physiological pleura and their pathological mutations, especially those that are characteristic of mesothelioma (94).

Some studies maintain that the methylation profile could even be considered a diagnostic marker that can be used to identify primitive and secondary pleural tumors (95).

Other studies investigated the relationship between patient outcomes and their methylation status and have observed interesting differences in survival associated this genetic mutation (96).

Other studies have also analyzed diagnosis and an eventual epigenetic therapeutic approach (15,97).

MicroRNA

miRNA expression is another important mechanism in the development of tumors, which supports their ability to control different biological processes.

For this reason, many researchers have focused their attention on the profile of miRNA to verify if there are any discrepancies/associations between these various genetic expressions and the pleura (98-103).

Other genes

A component of the Hippo cascade, the salvador gene (SAV) was discovered in the *Drosophila* 81349 and is considered one of the gene suppressors altered in different neoplastic forms (16, 104-105). Deletion of the chromosome 14q22 was recently demonstrated in approximately 5% of mesothelioma cell lines; however, the actual role of this gene in the pathogenesis of this disease is still being studied (25).

Deletion of the β -catenin (CTNNB1) gene in MM cell lines was discovered in approximately 10% of cases (106). CTNNB1 appears to be a cell growth stimulation factor in different tumor forms (107), although further studies are needed in this case too to clarify their pathogenetic role.

Recent studies have suggested that the Hedgehog signal pathway is activated in MM cell lines (108). This pathway in fact appears to be regulated by 13 genes in cancer pathogenesis. However, only three of these genes were mutated in MM cell lines: PTCH1, SMO and SUFU (108-110).

The circadian rhythm is regulated by different genes and proteins that involve different processes: sleep, body temperature, hormones, the immune response and many others (111). Various studies have demonstrated a possible correlation between changes in the circadian rhythm and the development of cancer (112-113). Studies are investigating different genes with respect to MM, including the following: the clock genes PER (period), CRY (cryptochrome) BMAL1 (aryl hydrocarbonreceptor nuclear translocator-like) (114-116).

CONCLUSIONS

Genetic mutations associated with MM are being studied, with many already identified and many others being defined.

All these studies are aimed at increasing our knowledge about the genetics of MM, to understand how genetic mutations are associated with this disease.

Defining their pathogenetic role and cause would open up new avenues of research and certainly to potential experimental therapeutic strategies aimed at restoring the correct genetics whenever possible, which appear to be distorted in this disease.

BIBLIOGRAPHY

- [1] C. Tan, T. Treasure, Mesothelioma: time to take stock, *J. R. Soc. Med.* 98 (2005) 455–458.
- [2] M.R. Becklake, E. Bagatin, J.A. Neder, Asbestos-related diseases of the lungs and pleura: uses, trends and management over the last century, *Int. J. Tuberc. Lung Dis.* 11 (2007) 356–369.
- [3] H. Yang, J. Testa, M. Carbone, Mesothelioma epidemiology, carcinogenesis, and pathogenesis, *Curr. Treat. Options in Oncol.* 9 (2008) 147–157.
- [4] J.P. van Meerbeeck, R. Gaafar, C. Manegold, R.J. Van Klaveren, E.A. Van Marck, M. Vincent, C. Legrand, A. Bottomley, C. Debruyne, G. Giaccone, Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada, *J. Clin.*

Oncol. 23 (2005) 6881–6889.

[5] J.C. Wagner, C.A. Sleggs, P. Marchand, Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province, *Br. J. Ind. Med.* 17 (1960) 260–271.

[6] ATSDR, Public Health Statement for Asbestos, 2001.

[7] J.J. Manfredi, J. Dong, W.J. Liu, L. Resnick-Silverman, R. Qiao, P. Chahinian, M. Saric, A.R. Gibbs, J.I. Phillips, J. Murray, C.W. Axten, R.P. Nolan, S.A. Aaronson, Evidence against a role for SV40 in human mesothelioma, *Cancer Res.* 65 (2005) 2602–2609.

[8] P. Carthew, R. Hill, R. Edwards, P. Lee, Intrapleural administration of fibres induces mesothelioma in rats in the same relative order of hazard as occurs in man after exposure, *Hum. Exp. Toxicol.* 11 (1992) 530–534.

[9] F.E. Mott, Mesothelioma: a review, *Ochsner J.* 12 (2012) 70–79.

[10] D.A. Fennell, Genetics and molecular biology of mesothelioma, *Malignant Mesothelioma*, vol. 189, Springer, Berlin Heidelberg, 2012, pp. 149–167.

[11] M. Cheung, J. Talarchek, K. Schindeler, E. Saraiva, L.S. Penney, M. Ludman, J.R. Testa, Further evidence for germline BAP1 mutations predisposing to melanoma and malignant mesothelioma, *Cancer Genet.* 206 (2013) 206–210.

[12] C.T. Yang, L. You, C.C. Yeh, J.W.C. Chang, F. Zhang, F. McCormick, D.M. Jablons, Adenovirus-mediated p14ARF gene transfer in human mesothelioma cells, *J. Natl. Cancer Inst.* 92 (2000) 636–641.

[13] S. Xio, D. Li, J. Vijg, D.J. Sugarbaker, J.M. Corson, J.A. Fletcher, Codeletion of p15 and p16 in primary malignant mesothelioma, *Oncogene* 11 (1995) 511–515.

[14] M. Ladanyi, Implications of P16/CDKN2A deletion in pleural mesotheliomas, *Lung Cancer* 49 (2005) S95–S98 (Amsterdam, Netherlands).

[15] D. Jean, J. Daubriac, F.o. Le Pimpec-Barthes, F.o. Galateau-Salle, M.C. Jaurand, Molecular changes in mesothelioma with an impact on prognosis and treatment, *Arch. Pathol. Lab. Med.* 136 (2012) 277–293.

[16] K.P. Lee, J.H. Lee, T.S. Kim, T.H. Kim, H.D. Park, J.S. Byun, M.C. Kim, W.I. Jeong, D.F. Calvisi, J.M. Kim, D.S. Lim, The Hippo–Salvador pathway restrains hepatic oval cell proliferation, liver size, and liver tumorigenesis, *Proc. Natl. Acad. Sci.* 107 (2010) 8248–8253.

[17] C. Frezza, C.P. Martins, From tumor prevention to therapy: empowering p53 to fight back, *Drug Resist. Updat.* 15 (2012) 258–267.

[18] Y. Sekido, Genomic abnormalities and signal transduction dysregulation in malignant mesothelioma cells, *Cancer Sci.* 101 (2009) 1–6.

[19] A.A. Bahnassy, A.-R.N. Zekri, A.A. Abou-Bakr, M.M. El-Defar, A. El-Bastawisy, M.A. Sakr, G.M. El-sherif, R.M. Gaafar, Aberrant expression of cell cycle regulatory genes predicts overall and disease free survival in malignant pleural mesothelioma patients, *Exp. Mol. Pathol.* 93 (2012) 154–161.

[20] S.L. O'Kane, R.J. Pound, A. Campbell, N. Chaudhuri, M.J. Lind, L. Cawkwell, Expression of bcl-2 family members in malignant pleural mesothelioma, *Acta Oncol.* 45 (2006) 449–453.

[21] T. Maehama, J.E. Dixon, The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate, *J. Biol. Chem.* 273 (1998) 13375–13378.

[22] D.A. Altomare, H. You, G.H. Xiao, M.E. Ramos-Nino, K.L. Skele, A. De Rienzo, S.C. Jhanwar, B.T. Mossman, A.B. Kane, J.R. Testa, Human and mouse mesotheliomas exhibit elevated AKT/PKB activity,

which can be targeted pharmacologically to inhibit tumor cell growth, *Oncogene* 24 (2005) 6080–6089.

- [23] S.M. Wilson, D. Barbone, T.-M. Yang, D.M. Jablons, R. Bueno, D.J. Sugarbaker, S.L. Nishimura, G.J. Gordon, V.C. Broaddus, mTOR mediates survival signals in malignant mesothelioma grown as tumor fragment spheroids, *Am. J. Respir. Cell Mol. Biol.* 39 (2008) 576–583.
- [24] M. Carbone, L. Ferris, F. Baumann, A. Napolitano, C. Lum, E. Flores, G. Gaudino, A. Powers, P. Bryant-Greenwood, T. Krausz, E. Hyjek, R. Tate, J. Friedberg, T. Weigel, H. Pass, H. Yang, BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITs, *J. Transl. Med.* 10 (2012) 179.
- [25] H. Murakami, T. Mizuno, T. Taniguchi, M. Fujii, F. Ishiguro, T. Fukui, S. Akatsuka, Y. Horio, T. Hida, Y. Kondo, S. Toyokuni, H. Osada, Y. Sekido, LATS2 is a tumor suppressor gene of malignant mesothelioma, *Cancer Res.* 71 (2011) 873–883.
- [26] Y. Suzuki, H. Murakami, K. Kawaguchi, T. Taniguchi, M. Fujii, K. Shinjo, Y. Kondo, H. Osada, K. Shimokata, Y. Horio, Y. Hasegawa, T. Hida, Y. Sekido, Activation of the PI3K-AKT pathway in human malignant mesothelioma cells, *Mol. Med. Rep.* 2 (2009) 181–188.
- [27] A.Y. Lee, D.J. Raz, B. He, D.M. Jablons, Update on the molecular biology of malignant mesothelioma, *Cancer* 109 (2007) 1454–1461.
- [28] J.G. Edwards, D.E.B. Swinson, J.L. Jones, D.A. Waller, K.J. O'Byrne, EGFR expression: associations with outcome and clinicopathological variables in malignant pleural mesothelioma, *Lung Cancer* 54 (2006) 399–407 (Amsterdam, Netherlands).
- [29] D. Hanahan, J. Folkman, Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis, *Cell* 86 (1996) 353–364.
- [30] L. Strizzi, A. Catalano, G. Vianale, S. Orecchia, A. Casalini, G. Tassi, R. Puntoni, L. Mutti, A. Procopio, Vascular endothelial growth factor is an autocrine growth factor in human malignant mesothelioma, *J. Pathol.* 193 (2001) 468–475.
- [31] H.L. Kindler, Moving beyond chemotherapy: novel cytostatic agents for malignant mesothelioma, *Lung Cancer* 45 (2004) S125–S127 (Amsterdam, Netherlands).
- [32] R.A. Kratzke, G.A. Otterson, C.E. Lincoln, S. Ewing, H. Oie, J. Geradts, F.J. Kaye, Immunohistochemical analysis of the p16INK4 cyclin-dependent kinase inhibitor in malignant mesothelioma, *J. Natl. Cancer Inst.* 87 (1995) 1870–1875.
- [33] S.W. Lowe, C.J. Sherr, Tumor suppression by Ink4a-Arf: progress and puzzles, *Curr. Opin. Genet. Dev.* 13 (2003) 77–83.
- [34] K. Segers, M. Ramael, S.K. Singh, E. Marck, J. Weyler, J. Meerbeeck, P. Vermeire, Immunoreactivity for bcl-2 protein in malignant mesothelioma and nonneoplastic mesothelium, *Virchows Arch.* 424 (1994) 631–634.
- [35] Y. Soini, V. Kinnula, R. Kaarteenaho-Wiik, E. Kurttila, K. Linnainmaa, P. Pääkkö, Apoptosis and expression of apoptosis regulating proteins bcl-2, mcl-1, bcl-X, and bax in malignant mesothelioma, *Clin. Cancer Res.* 5 (1999) 3508–3515.
- [36] S. Hopkins-Donaldson, R. Cathomas, A.P. Simões-Wüst, S. Kurtz, L. Belyanskaya, R.A. Stahel, U. Zangemeister-Wittke, Induction of apoptosis and chemosensitization of mesothelioma cells by Bcl-2 and Bcl-xL antisense treatment, *Int. J. Cancer* 106 (2003) 160–166.

- [37] F.-X. Yu, K.-L. Guan, The Hippo pathway: regulators and regulations, *Genes Dev.* 27 (2013) 355–371.
- [38] T. Mizuno, H. Murakami, M. Fujii, F. Ishiguro, I. Tanaka, Y. Kondo, S. Akatsuka, S. Toyokuni, K. Yokoi, H. Osada, Y. Sekido, YAP induces malignant mesothelioma cell proliferation by upregulating transcription of cell cycle-promoting genes, *Oncogene* 31 (2012) 5117–5122.
- [39] M. Fujii, T. Toyoda, H. Nakanishi, Y. Yatabe, A. Sato, Y. Matsudaira, H. Ito, H. Murakami, Y. Kondo, E. Kondo, T. Hida, T. Tsujimura, H. Osada, Y. Sekido, TGF- β synergizes with defects in the Hippo pathway to stimulate human malignant mesothelioma growth, *J. Exp. Med.* 209 (2012) 479–494.
- [40] K. Saito-Diaz, T. Chen, X. Wang, C. Thorne, H. Wallace, A. Page-McCaw, E. Lee, The way Wnt works: components and mechanism, *Growth Factors* 31 (2013) 1–31.
- [41] K. Uematsu, S. Kanazawa, L. You, B. He, Z. Xu, K. Li, B.M. Peterlin, F. McCormick, D.M. Jablons, Wnt pathway activation in mesothelioma: evidence of disheveled overexpression and transcriptional activity of β -catenin, *Cancer Res.* 63 (2003) 4547–4551.
- [42] M. Ruas, G. Peters, The p16INK4a/CDKN2A tumor suppressor and its relatives, *Biochim. Biophys. Acta* 1378 (1998) F115–F177.
- [43] G. Thillainadesan, J.M. Chitilian, M. Iovic, J.N. Ablack, J.S. Mymryk, M. Tini, J. Torchia, TGF-beta-dependent active demethylation and expression of the p15ink4b tumor suppressor are impaired by the ZNF217/CoREST complex, *Mol. Cell* 46 (2012) 636–649.
- [44] P. Krimpenfort, A. Ijpenberg, J.Y. Song, M. van der Valk, M. Nawijn, J. Zevenhoven, A. Berns, p15Ink4b is a critical tumour suppressor in the absence of p16Ink4a, *Nature* 448 (2007) 943–946.
- [45] P. Berggren, R. Kumar, S. Sakano, L. Hemminki, T. Wada, G. Steineck, J. Adolfsson, P. Larsson, U. Norming, H. Wijkström, K. Hemminki, Detecting homozygous deletions in the CDKN2A(p16INK4a)/ARF(p14ARF) gene in urinary bladder cancer using real-time quantitative PCR, *Clin. Cancer Res.* 9 (2003) 235–242.
- [46] L.L. Chang, W.T. Yeh, S.Y. Yang, W.J. Wu, C.H. Huang, Genetic alterations of p16INK4a and p14ARF genes in human bladder cancer, *J. Urol.* 170 (2003) 595–600.
- [47] V.L. Brown, C.A. Harwood, T. Crook, J.G. Cronin, D.P. Kelsell, C.M. Proby, p16INK4a and p14ARF tumor suppressor genes are commonly inactivated in cutaneous squamous cell carcinoma, *J. Invest. Dermatol.* 122 (2004) 1284–1292.
- [48] J.L. Wang, B.Y. Zheng, X.D. Li, K. Nokelainen, T. Angstrom, M.S. Lindstrom, K.L. Wallin, p16INK4A and p14ARF expression pattern by immunohistochemistry in human papillomavirus-related cervical neoplasia, *Mod. Pathol.* 18 (2005) 629–637.
- [49] J.Q. Cheng, S.C. Jhanwar, W.M. Klein, D.W. Bell, W.-C. Lee, D.A. Altomare, T. Nobori, O.I. Olopade, A.J. Buckler, J.R. Testa, p16 Alterations and deletion mapping of 9p21–p22 in malignant mesothelioma, *Cancer Res.* 54 (1994) 5547–5551.
- [50] P.B. Illei, V.W. Rusch, M.F. Zakowski, M. Ladanyi, Homozygous deletion of CDKN2A and codeletion of the methylthioadenosine phosphorylase gene in the majority of pleural mesotheliomas, *Clin. Cancer Res.* 9 (2003) 2108–2113.
- [51] F.B. Onofre, A.S. Onofre, N. Pomjanski, B. Buckstegge, H.J. Grote, A. Bocking, 9p21 Deletion in the diagnosis of malignant mesothelioma in serous effusions additional to immunocytochemistry, DNA-ICM, and

AgNOR analysis, *Cancer* 114 (2008) 204–215.

[52] M. Takeda, T. Kasai, Y. Enomoto, M. Takano, K. Morita, E. Kadota, N. Iizuka, H. Maruyama, A. Nonomura, Genomic gains and losses in malignant mesothelioma demonstrated by FISH analysis of paraffin-embedded tissues, *J. Clin. Pathol.* 65 (2012) 77–82.

[53] S. Chiosea, A. Krasinskas, P.T. Cagle, K.A. Mitchell, D.S. Zander, S. Dacic, Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas, *Mod. Pathol.* 21 (2008) 742–747.

[54] J.R. Fischer, U. Ohnmacht, N. Rieger, M. Zemaitis, C. Stoffregen, M. Kostrzewa, E. Buchholz, C. Manegold, H. Lahm, Promoter methylation of RASSF1A, RARÎ2 and DAPK predict poor prognosis of patients with malignant mesothelioma, *Lung Cancer* 54 (2006) 109–116.

[55] T. Kamijo, F. Zindy, M.F. Roussel, D.E. Quelle, J.R. Downing, R.A. Ashmun, G. Grosveld, C.J. Sherr, Tumor suppression at the mouse INK4a locus mediated by the alternative reading frame product p19ARF, *Cell* 91 (1997) 649–659.

[56] N.E. Sharpless, N. Bardeesy, K.H. Lee, D. Carrasco, D.H. Castrillon, A.J. Aguirre, E.A. Wu, J.W. Horner, R.A. DePinho, Loss of p16Ink4a with retention of p19Arf predisposes mice to tumorigenesis, *Nature* 413 (2001) 86–91.

[57] M. Serrano, H. Lee, L. Chin, C. Cordon-Cardo, D. Beach, R.A. DePinho, Role of the INK4a locus in tumor suppression and cell mortality, *Cell* 85 (1996) 27–37.

[58] D.A. Altomare, C.W. Menges, J. Pei, L. Zhang, K.L. Skele-Stump, M. Carbone, A.B. Kane, J.R. Testa, Activated TNF-alpha/NF-kappaB signaling via down-regulation of Fas-associated factor 1 in asbestos-induced mesotheliomas from Arf knockout mice, *Proc. Natl. Acad. Sci. U.S.A.* 106 (2009) 3420–3425.

[59] D.A. Altomare, C.W. Menges, J. Xu, J. Pei, L. Zhang, A. Tadevosyan, E. Neumann-Domer, Z. Liu, M. Carbone, I. Chudoba, A.J. Klein-Szanto, J.R. Testa, Losses of both products of the Cdkn2a/Arf locus contribute to asbestos-induced mesothelioma development and cooperate to accelerate tumorigenesis, *PLoS One* 6 (2011) e18828.

[60] S. Frizelle, J. Rubins, J. Zhou, D. Curiel, R. Kratzke, Gene therapy of established mesothelioma xenografts with recombinant p16INK4a adenovirus, *Cancer Gene Ther.* 7 (2000) 1421–1425.

[61] S. Frizelle, J. Rubins, J. Zhou, D. Curiel, R. Kratzke, Gene therapy of established mesothelioma xenografts with recombinant p16INK4a adenovirus, *Cancer Gene Ther.* 7 (2000) 1421–1425.

[62] C. Yang, L. You, Y. Lin, C. Lin, F. McCormick, D. Jablons, A comparison analysis of anti-tumor efficacy of adenoviral gene replacement therapy (p14ARF and p16INK4A) in human mesothelioma cells, *Anticancer Res.* 23 (2003) 33–38.

[63] Y. Tada, H. Shimada, K. Hiroshima, M. Tagawa, A potential therapeutic strategy for malignant mesothelioma with gene medicine, *Biomed. Res. Int.* 2013 (2013) 8.

[64] D.G.R. Evans, Neurofibromatosis 2 [bilateral acoustic neurofibromatosis, central neurofibromatosis, NF2, neurofibromatosis type II], *Genet. Med.* 11 (2009) 599.

[65] Y. Sekido, H.I. Pass, S. Bader, D.J.Y. Mew, M.F. Christman, A.F. Gazdar, J.D. Minna, Neurofibromatosis type 2 (NF2) gene is somatically mutated in mesothelioma but not in lung cancer, *Cancer Res.* 55 (1995) 1227–1231.

[66] A.B. Bianchi, S.I. Mitsunaga, J.Q. Cheng, W.M. Klein, S.C. Jhanwar, B. Seizinger, N. Kley, A.J. Klein-

- Szanto, J.R. Testa, High frequency of inactivating mutations in the neurofibromatosis type 2 gene (NF2) in primary malignant mesotheliomas, *Proc. Natl. Acad. Sci. U.S.A.* 92 (1995) 10854–10858.
- [67] P. Andujar, J.C. Pairon, A. Renier, A. Descatha, I. Hysi, I. Abd-Alsamad, M.A. Billon- Galland, H.I.n. Blons, B.n.d. Clin, C. Danel, D. Debrosse, F.o. Galateau-SallÃ©, B. Housset, P. Laurent-Puig, F.o. Le Pimpec-Barthes, M. Letourneau, I. Monnet, J.F.o. RÃ©gnard, P. Validire, J. Zucman-Rossi, M.C. Jaurand, D. Jean, Differential mutation profiles and similar intronic TP53 polymorphisms in asbestos-related lung cancer and pleural mesothelioma, *Mutagenesis* 28 (2013) 323–331.
- [68] H. Nemoto, G. Tate, K. Kishimoto, M. Saito, A. Shirahata, T. Umemoto, T. Matsubara, T. Goto, H. Mizukami, G. Kigawa, T. Mitsuya, K. Hibi, Heterozygous loss of NF2 is an early molecular alteration in well-differentiated papillary mesothelioma of the peritoneum, *Cancer Genet.* 205 (2012) 594–598.
- [69] M. Guled, L. Lahti, P.M. Lindholm, K. Salmenkivi, I. Bagwan, A.G. Nicholson, S. Knuutila, CDKN2A, NF2, and JUN are dysregulated among other genes by miRNAs in malignant mesothelioma—a miRNA microarray analysis, *Genes Chromosom. Cancer* 48 (2009) 615–623.
- [70] J. Jongasma, E. van Montfort, M. Vooijs, J. Zevenhoven, P. Krimpenfort, M. van der Valk, M. van de Vijver, A. Berns, A conditional mouse model for malignant mesothelioma, *Cancer Cell* 13 (2008) 261–271.
- [71] K. Ikeda, Y. Saeki, C. Gonzalez-Agosti, V. Ramesh, E.A. Chiocca, Inhibition of NF2-negative and NF2-positive primary human meningioma cell proliferation by overexpression of merlin due to vector-mediated gene transfer, *J. Neurosurg.* 91 (1999) 85–92.
- [72] K.M.M. Schulze, C.O. Hanemann, H.W. Müller, H. Hanenberg, Transduction of wild-type merlin into human schwannoma cells decreases schwannoma cell growth and induces apoptosis, *Hum. Mol. Genet.* 11 (2002) 69–76.
- [73] J. Fraenzer, H. Pan, L.J. Minimo, G. Smith, D. Knauer, G. Hung, Overexpression of the NF2 gene inhibits schwannoma cell proliferation through promoting PDGFR degradation, *Int. J. Oncol.* 2003 (2003) 1493–1500.
- [74] F.C. Morales, J.R. Molina, Y. Hayashi, M.-M. Georgescu, Overexpression of ezrin inactivates NF2 tumor suppressor in glioblastoma, *Neuro-Oncology* 12 (2010) 528–539.
- [75] P. Poulikakos, G. Xiao, R. Gallagher, S. Jablonski, S. Jhanwar, J. Testa, Re-expression of the tumor suppressor NF2/merlin inhibits invasiveness in mesothelioma cells and negatively regulates FAK, *Oncogene* 25 (2006) 5960–5980.
- [76] G.H. Xiao, R. Gallagher, J. Shetler, K. Skele, D.A. Altomare, R.G. Pestell, S. Jhanwar, J.R. Testa, The NF2 tumor suppressor gene product, merlin, inhibits cell proliferation and cell cycle progression by repressing cyclin D1 expression, *Mol. Cell. Biol.* 25 (2005) 2384–2394.
- [77] I. Roushdy-Hammady, J. Siegel, S. Emri, J.R. Testa, M. Carbone, Geneticsusceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey, *Lancet* 357 (2001) 444–445.
- [78] A.U. Dogan, Y.I. Baris, M. Dogan, S. Emri, I. Steele, A.G. Elmishad, M. Carbone, Genetic predisposition to fiber carcinogenesis causes a mesothelioma epidemic in Turkey, *Cancer Res.* 66 (2006) 5063–5068.
- [79] M. Metintas, G. Hillerdal, S. Metintas, P. Dumortier, Endemic malignant mesothelioma: exposure to erionite is more important than genetic factors, *Arch. Environ. Occup. Health* 65 (2010) 86–93.
- [80] J.R. Testa, M. Cheung, J. Pei, J.E. Below, Y. Tan, E. Sementino, N.J. Cox, A.U. Dogan, H.I. Pass, S.

- Trusa, M. Hesdorffer, M. Nasu, A. Powers, Z. Rivera, S. Comertpay, M. Tanji, G. Gaudino, H. Yang, M. Carbone, Germline BAP1 mutations predispose to malignant mesothelioma, *Nat. Genet.* 43 (2011) 1022–1025.
- [81] T. Popova, L. Hebert, V. Jacquemin, S. Gad, V. Caux-Moncoutier, C. Dubois-d Enghien, B. Richaudeau, X. Renaudin, J. Sellers, A. Nicolas, X. Sastre-Garau, L. Desjardins, G. Gyapay, V. Raynal, Olga M. Sinilnikova, N. Andrieu, E. Manié, A. de Pauw, P. Gesta, V. Bonadona, Christine M. Maugard, C. Penet, M.F. Avril, E. Barillot, O. Cabaret, O. Delattre, S. Richard, O. Caron, M. Benfodda, H.-H. Hu, N. Soufir, B. Bressac-de Paillerets, D. Stoppa-Lyonnet, M.-H. Stern, Germline BAP1 mutations predispose to renal cell carcinomas, *Am. J. Hum. Genet.* 92 (2013) 974–980.
- [82] M. Bott, M. Brevet, B.S. Taylor, S. Shimizu, T. Ito, L.Wang, J. Creaney, R.A. Lake, M.F. Zakowski, B. Reva, C. Sander, R. Delsite, S. Powell, Q. Zhou, R. Shen, A. Olshen, V. Rusch, M. Ladanyi, The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma, *Nat. Genet.* 43 (2011) 668–672.
- [83] Y. Yoshikawa, A. Sato, T. Tsujimura, M. Emi, T. Morinaga, K. Fukuoka, S. Yamada, A. Murakami, N. Kondo, S. Matsumoto, Y. Okumura, F. Tanaka, S. Hasegawa, T. Nakano, T. Hashimoto-Tamaoki, Frequent inactivation of the BAP1 gene in epithelioid-type malignant mesothelioma, *Cancer Sci.* 103 (2012) 868–874.
- [84] M. Zauderer, M. Bott, R. McMillan, C. Sima, V. Rusch, L. Krug, M. Ladanyi, Clinical characteristics of patients with malignant pleural mesothelioma harboring somatic BAP1 mutations, *J. Thorac. Oncol.* 8 (2013) 1430–1433.
- [85] L. Arzt, F. Quehenberger, I. Halbwedl, T. Mairinger, H. Popper, BAP1 protein is a progression factor in malignant pleural mesothelioma, *Pathol. Oncol. Res.* (2013) 1–7.
- [86] R. Murali, T. Wiesner, R. Scolyer, Tumours associated with BAP1 mutations, *Pathology* 45 (2013) 116–126.
- [87] R. Pilarski, C.M. Cebulla, J.B. Massengill, K. Rai, T. Rich, L. Strong, B. McGillivray, M.-J. Asrat, F.H. Davidorf, M.H. Abdel-Rahman, Expanding the clinical phenotype of hereditary BAP1 cancer predisposition syndrome, reporting three new cases, *Genes Chromosom. Cancer* 53 (2) (2013) 177–182.
- [88] R.W. Justice, O. Zilian, D.F. Woods, M. Noll, P.J. Bryant, The *Drosophila* tumor suppressor gene *warts* encodes a homolog of human myotonic dystrophy kinase and is required for the control of cell shape and proliferation, *Genes Dev.* 9 (1995) 534–546.
- [89] N. Yabuta, T. Fujii, N.G. Copeland, D.J. Gilbert, N.A. Jenkins, H. Nishiguchi, Y. Endo, S. Toji, H. Tanaka, Y. Nishimune, H. Nojima, Structure, expression, and chromosome mapping of LATS2, a mammalian homologue of the *Drosophila* tumor suppressor gene *lats/warts*, *Genomics* 63 (2000) 263–270.
- [90] C.F. Chen, S.H. Yeh, D.S. Chen, P.J. Chen, Y.S. Jou, Molecular genetic evidence supporting a novel human hepatocellular carcinoma tumor suppressor locus at 13q12.11, *Genes Chromosom. Cancer* 44 (2005) 320–328.
- [91] Y. Aylon, D. Michael, A. Shmueli, N. Yabuta, H. Nojima, M. Oren, A positive feedback loop between the p53 and Lats2 tumor suppressors prevents tetraploidization, *Genes Dev.* 20 (2006) 2687–2700.
- [92] Y. Aylon, Y. Ofir-Rosenfeld, N. Yabuta, E. Lapi, H. Nojima, X. Lu, M. Oren, The Lats2 tumor suppressor augments p53-mediated apoptosis by promoting the nuclear proapoptotic function of ASPP1, *Genes Dev.* 24 (2010) 2420–2429.

- [93] S. Visser, X. Yang, LATS tumor suppressor: a new governor of cellular homeostasis, *Cell Cycle* 9 (2010) 3922–3933.
- [94] B.C. Christensen, E.A. Houseman, J.J. Godleski, C.J. Marsit, J.L. Longacker, C.R. Roelofs, M.R. Karagas, M.R. Wrensch, R.-F. Yeh, H.H. Nelson, J.L. Wiemels, S. Zheng, J.K. Wiencke, R. Bueno, D.J. Sugarbaker, K.T. Kelsey, Epigenetic profiles distinguish pleural mesothelioma from normal pleura and predict lung asbestos burden and clinical outcome, *Cancer Res.* 69 (2009) 227–234.
- [95] Y. Goto, K. Shinjo, Y. Kondo, L. Shen, M. Toyota, H. Suzuki, W. Gao, B. An, M. Fujii, H. Murakami, H. Osada, T. Taniguchi, N. Usami, M. Kondo, Y. Hasegawa, K. Shimokata, K. Matsuo, T. Hida, N. Fujimoto, T. Kishimoto, J.-P.J. Issa, Y. Sekido, Epigenetic profiles distinguish malignant pleural mesothelioma from lung adenocarcinoma, *Cancer Res.* 69 (2009) 9073–9082.
- [96] J.R. Fischer, U. Ohnmacht, N. Rieger, M. Zemaitis, C. Stoffregen, M. Kostrzewa, E. Buchholz, C. Manegold, H. Lahm, Promoter methylation of RASSF1A, RAR β and DAPK predict poor prognosis of patients with malignant mesothelioma, *Lung Cancer* 54 (2006) 109–116.
- [97] F. Vandermeers, S. Neelature Sriramareddy, C. Costa, R. Hubaux, J.-P. Cosse, L. Willems, The role of epigenetics in malignant pleural mesothelioma, *Lung Cancer* 81 (2013) 311–318 (Amsterdam, Netherlands).
- [98] S.V. Ivanov, C.M.V. Goparaju, P. Lopez, J. Zavadil, G. Toren-Haritan, S. Rosenwald, M. Hoshen, A. Chajut, D. Cohen, H.I. Pass, Pro-tumorigenic effects of miR-31 loss in mesothelioma, *J. Biol. Chem.* 285 (2010) 22809–22817.
- [99] G. Reid, M.E. Pel, M.B. Kirschner, Y.Y. Cheng, N. Mugridge, J. Weiss, M. Williams, C. Wright, J.J.B. Edelman, M.P. Vallely, B.C. McCaughan, S. Klebe, H. Brahmbhatt, J.A. MacDiarmid, N. van Zandwijk, Restoring expression of miR-16: a novel approach to therapy for malignant pleural mesothelioma, *Ann. Oncol.* 24 (12) (2013) 3128–3135.
- [100] G.V. Gee, D.C. Koestler, B.C. Christensen, D.J. Sugarbaker, D. Ugolini, G.P. Ivaldi, M.B. Resnick, E.A. Houseman, K.T. Kelsey, C.J. Marsit, Downregulated microRNAs in the differential diagnosis of malignant pleural mesothelioma, *Int. J. Cancer* 127 (2010) 2859–2869.
- [101] M.B. Kirschner, Y.Y. Cheng, B. Badrian, S.C. Kao, J. Creaney, J.J. Edelman, N.J. Armstrong, M.P. Vallely, A.W. Musk, B.W. Robinson, B.C. McCaughan, S. Klebe, S.E. Mutsaers, N. van Zandwijk, G. Reid, Increased circulating miR-625–3p: a potential biomarker for patients with malignant pleural mesothelioma, *J Thorac Oncol* 7 (2012) 1184–1191.
- [102] T. Muraoka, J. Soh, S. Toyooka, K. Aoe, N. Fujimoto, S. Hashida, Y. Maki, N. Tanaka, K. Shien, M. Furukawa, H. Yamamoto, H. Asano, K. Tsukuda, T. Kishimoto, T. Otsuki, S. Miyoshi, The degree of microRNA-34b/c methylation in serum-circulating DNA is associated with malignant pleural mesothelioma, *Lung Cancer* 82 (3) (2013) 485–490.
- [103] M. Cioce, F. Ganci, V. Canu, A. Sacconi, F. Mori, C. Canino, E. Korita, B. Casini, G. Alessandrini, A. Cambria, M.A. Carosi, R. Blandino, V. Panebianco, F. Facciolo, P. Visca, S. Volinia, P. Muti, S. Strano, C.M. Croce, H.I. Pass, G. Blandino, Protumorigenic effects of mir-145 loss in malignant pleural mesothelioma, *Oncogene* (2013), in press, (Epub ahead of print).
- [104] N. Tapon, K.F. Harvey, D.W. Bell, D.C.R. Wahrer, T.A. Schiripo, D.A. Haber, I.K. Hariharan, Salvador Promotes both cell cycle exit and apoptosis in *Drosophila* and is mutated in human cancer cell lines, *Cell* 110

(2002) 467–478.

[105] L. Lu, Y. Li, S.M. Kim, W. Bossuyt, P. Liu, Q. Qiu, Y. Wang, G. Halder, M.J. Finegold, J.-S. Lee, R.L. Johnson, Hippo signaling is a potent in vivo growth and tumor suppressor pathway in the mammalian liver, *Proc. Natl. Acad. Sci.* 107 (2010) 1437–1442.

[106] K. Shigemitsu, Y. Sekido, N. Usami, S.Mori, M. Sato, Y. Horio, Y. Hasegawa, S. Bader, A. Gazdar, J. Minna, T. Hida, H. Yoshioka, M. Imaizumi, Y. Ueda, M. Takahashi, K. Shimokata, Genetic alteration of the beta-catenin gene (CTNNB1) in human lung cancer and malignant mesothelioma and identification of a new 3p21.3 homozygous deletion, *Oncogene* 20 (2001) 4249–4257.

[107] N. Usami, Y. Sekido, O. Maeda, K. Yamamoto, J. Minna, Y. Hasegawa, H. Yoshioka, M. Imaizumi, Y. Ueda, M. Takahashi, K. S., Beta-catenin inhibits cell growth of a malignant mesothelioma cell line, NCI-H28, with a 3p21.3 homozygous deletion, *Oncogene* 22 (2003) 7923–7930.

[108] M. You, J. Varona-Santos, S. Singh, D.J. Robbins, N. Savaraj, D.M. Nguyen, Targeting of the Hedgehog signal transduction pathway suppresses survival of malignant pleural mesothelioma cells in vitro, *J. Thorac. Cardiovasc. Surg.* 147 (1) (2013) 508–516.

[109] C.B. Lim, C.M. Prêle, H.M. Cheah, Y.Y. Cheng, S. Klebe, G. Reid, D.N. Watkins, S. Baltic, P.J. Thompson, S.E. Mutsaers, Mutational analysis of hedgehog signaling pathway genes in human malignant mesothelioma, *PLoS One* 8 (2013) e66685.

[110] G. Klorin, E. Rozenblum, O. Glebov, R.L. Walker, Y. Park, P.S. Meltzer, I.R. Kirsch, F.J. Kaye, A.V. Roschke, Integrated high-resolution array CGH and SKY analysis of homozygous deletions and other genomic alterations present in malignant mesothelioma cell lines, *Cancer Genet.* 206 (2013) 191–205.

[111] C. Savvidis, M. Koutsilieris, Circadian rhythm disruption in cancer biology, *Mol. Med.* 18 (2012) 1249–1260.

[112] R.G. Stevens, Circadian disruption and breast cancer: from melatonin to clock genes, *Epidemiology* 16 (2005) 254–258.

[113] S. Giacchetti, G. Bjarnason, C. Garufi, D. Genet, S. Iacobelli, M. Tampellini, R. Smaaland, C. Focan, B. Coudert, Y. Humblet, J.L. Canon, A. Adenis, G.L. Re, C. Carvalho, J. Schueller, N. Anciaux, M.A. Lentz, B.t. Baron, T. Gorlia, F. Lévi, Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy Group, *J. Clin. Oncol.* 24 (2006) 3562–3569.

[114] O.D. Røe, E. Anderssen, E. Helge, C.H. Pettersen, K.S. Olsen, H. Sandeck, R. Haaverstad, S. Lundgren, E. Larsson, Genome-wide profile of pleural mesothelioma versus parietal and visceral pleura: the emerging gene portrait of the mesothelioma phenotype, *PLoS One* 4 (2009) e6554.

[115] M. Elshazley, M. Sato, T. Hase, R. Yamashita, K. Yoshida, S. Toyokuni, F. Ishiguro, H. Osada, Y. Sekido, K. Yokoi, N. Usami, D.S. Shames, M. Kondo, A.F. Gazdar, J.D. Minna, Y. Hasegawa, The circadian clock gene BMAL1 is a novel therapeutic target for malignant pleural mesothelioma, *Int. J. Cancer* 131 (2012) 2820–2831.

[116] M. Brevet, S. Shimizu, M.J. Bott, N. Shukla, Q. Zhou, A.B. Olshen, V. Rusch, M. Ladanyi, Coactivation of receptor tyrosine kinases in malignant mesothelioma as a rationale for combination targeted therapy, *J.*

Thorac. Oncol. 6 (2011) 864–874.

REFERENZE AGGIUNTIVE

- R. Pilarski, C.M. Cebulla, J.B. Massengill, K. Rai, T. Rich, L. Strong, B. McGillivray, M.-J. Asrat, F.H. Davidorf, M.H. Abdel-Rahman, Expanding the clinical phenotype of hereditary BAP1 cancer predisposition syndrome, reporting three new cases, *Genes Chromosom. Cancer* 53 (2) (2013) 177–182.
- R.W. Justice, O. Zilian, D.F. Woods, M. Noll, P.J. Bryant, The *Drosophila* tumor suppressor gene *warts* encodes a homolog of human myotonic dystrophy kinase and is required for the control of cell shape and proliferation, *Genes Dev.* 9 (1995) 534–546.
- N. Yabuta, T. Fujii, N.G. Copeland, D.J. Gilbert, N.A. Jenkins, H. Nishiguchi, Y. Endo, S. Toji, H. Tanaka, Y. Nishimune, H. Nojima, Structure, expression, and chromosome mapping of LATS2, a mammalian homologue of the *Drosophila* tumor suppressor gene *lats/warts*, *Genomics* 63 (2000) 263–270.
- C.F. Chen, S.H. Yeh, D.S. Chen, P.J. Chen, Y.S. Jou, Molecular genetic evidence supporting a novel human hepatocellular carcinoma tumor suppressor locus at 13q12.11, *Genes Chromosom. Cancer* 44 (2005) 320–328.
- Y. Aylon, D. Michael, A. Shmueli, N. Yabuta, H. Nojima, M. Oren, A positive feedback loop between the p53 and *Lats2* tumor suppressors prevents tetraploidization, *Genes Dev.* 20 (2006) 2687–2700.
- Y. Aylon, Y. Ofir-Rosenfeld, N. Yabuta, E. Lapi, H. Nojima, X. Lu, M. Oren, The *Lats2* tumor suppressor augments p53-mediated apoptosis by promoting the nuclear proapoptotic function of ASPP1, *Genes Dev.* 24 (2010) 2420–2429.
- S. Visser, X. Yang, LATS tumor suppressor: a new governor of cellular homeostasis, *Cell Cycle* 9 (2010) 3922–3933.
- B.C. Christensen, E.A. Houseman, J.J. Godleski, C.J. Marsit, J.L. Longacker, C.R. Roelofs, M.R. Karagas, M.R. Wrensch, R.-F. Yeh, H.H. Nelson, J.L. Wiemels, S. Zheng, J.K. Wiencke, R. Bueno, D.J. Sugarbaker, K.T. Kelsey, Epigenetic profiles distinguish pleural mesothelioma from normal pleura and predict lung asbestos burden and clinical outcome, *Cancer Res.* 69 (2009) 227–234.
- Y. Goto, K. Shinjo, Y. Kondo, L. Shen, M. Toyota, H. Suzuki, W. Gao, B. An, M. Fujii, H. Murakami, H. Osada, T. Taniguchi, N. Usami, M. Kondo, Y. Hasegawa, K. Shimokata, K. Matsuo, T. Hida, N. Fujimoto, T. Kishimoto, J.-P.J. Issa, Y. Sekido, Epigenetic profiles distinguish malignant pleural mesothelioma from lung adenocarcinoma, *Cancer Res.* 69 (2009) 9073–9082.
- J.R. Fischer, U. Ohnmacht, N. Rieger, M. Zemaitis, C. Stoffregen, M. Kostrzewa, E. Buchholz, C. Manegold, H. Lahm, Promoter methylation of RASSF1A, RAR β and DAPK predict poor prognosis of patients with malignant mesothelioma, *Lung Cancer* 54 (2006) 109–116.
- F. Vandermeers, S. Neelature Sriramareddy, C. Costa, R. Hubaux, J.-P. Cosse, L. Willems, The role of epigenetics in malignant pleural mesothelioma, *Lung Cancer* 81 (2013) 311–318 (Amsterdam, Netherlands).
- S.V. Ivanov, C.M.V. Goparaju, P. Lopez, J. Zavadil, G. Toren-Haritan, S. Rosenwald, M. Hoshen, A. Chajut, D. Cohen, H.I. Pass, Pro-tumorigenic effects of miR-31 loss in mesothelioma, *J. Biol. Chem.* 285 (2010) 22809–

22817.

- G. Reid, M.E. Pel, M.B. Kirschner, Y.Y. Cheng, N. Mugridge, J. Weiss, M. Williams, C. Wright, J.J.B. Edelman, M.P. Vallely, B.C. McCaughan, S. Klebe, H. Brahmabhatt, J.A. MacDiarmid, N. van Zandwijk, Restoring expression of miR-16: a novel approach to therapy for malignant pleural mesothelioma, *Ann. Oncol.* 24 (12) (2013) 3128–3135.
- G.V. Gee, D.C. Koestler, B.C. Christensen, D.J. Sugarbaker, D. Ugolini, G.P. Ivaldi, M.B. Resnick, E.A. Houseman, K.T. Kelsey, C.J. Marsit, Downregulated microRNAs in the differential diagnosis of malignant pleural mesothelioma, *Int. J. Cancer* 127 (2010) 2859–2869.
- M.B. Kirschner, Y.Y. Cheng, B. Badrian, S.C. Kao, J. Creaney, J.J. Edelman, N.J. Armstrong, M.P. Vallely, A.W. Musk, B.W. Robinson, B.C. McCaughan, S. Klebe, S.E. Mutsaers, N. van Zandwijk, G. Reid, Increased circulating miR-625-3p: a potential biomarker for patients with malignant pleural mesothelioma, *J Thorac Oncol* 7 (2012) 1184–1191.
- T. Muraoka, J. Soh, S. Toyooka, K. Aoe, N. Fujimoto, S. Hashida, Y. Maki, N. Tanaka, K. Shien, M. Furukawa, H. Yamamoto, H. Asano, K. Tsukuda, T. Kishimoto, T. Otsuki, S. Miyoshi, The degree of microRNA-34b/c methylation in serum-circulating DNA is associated with malignant pleural mesothelioma, *Lung Cancer* 82 (3) (2013) 485–490.
- M. Cioce, F. Ganci, V. Canu, A. Sacconi, F. Mori, C. Canino, E. Korita, B. Casini, G. Alessandrini, A. Cambria, M.A. Carosi, R. Blandino, V. Panebianco, F. Facciolo, P. Visca, S. Volinia, P. Muti, S. Strano, C.M. Croce, H.I. Pass, G. Blandino,
- Protumorigenic effects of mir-145 loss in malignant pleural mesothelioma, *Oncogene* (2013), in press, (Epub ahead of print).
- N. Tapon, K.F. Harvey, D.W. Bell, D.C.R. Wahrer, T.A. Schiripo, D.A. Haber, I.K. Hariharan, Salvador Promotes both cell cycle exit and apoptosis in *Drosophila* and is mutated in human cancer cell lines, *Cell* 110 (2002) 467–478.
- L. Lu, Y. Li, S.M. Kim, W. Bossuyt, P. Liu, Q. Qiu, Y. Wang, G. Halder, M.J. Finegold, J.-S. Lee, R.L. Johnson, Hippo signaling is a potent in vivo growth and tumor suppressor pathway in the mammalian liver, *Proc. Natl. Acad. Sci.* 107 (2010) 1437–1442.
- K. Shigemitsu, Y. Sekido, N. Usami, S. Mori, M. Sato, Y. Horio, Y. Hasegawa, S. Bader, A. Gazdar, J. Minna, T. Hida, H. Yoshioka, M. Imaizumi, Y. Ueda, M. Takahashi, K. Shimokata, Genetic alteration of the beta-catenin gene (CTNNB1) in human lung cancer and malignant mesothelioma and identification of a new 3p21.3 homozygous deletion, *Oncogene* 20 (2001) 4249–4257.
- N. Usami, Y. Sekido, O. Maeda, K. Yamamoto, J. Minna, Y. Hasegawa, H. Yoshioka,
- M. Imaizumi, Y. Ueda, M. Takahashi, K. S., Beta-catenin inhibits cell growth of a malignant mesothelioma cell line, NCI-H28, with a 3p21.3 homozygous deletion, *Oncogene* 22 (2003) 7923–7930.
- M. You, J. Varona-Santos, S. Singh, D.J. Robbins, N. Savaraj, D.M. Nguyen, Targeting of the Hedgehog signal transduction pathway suppresses survival of malignant pleural mesothelioma cells in vitro, *J. Thorac. Cardiovasc. Surg.* 147 (1) (2013) 508–516.
- C.B. Lim, C.M. Prêle, H.M. Cheah, Y.Y. Cheng, S. Klebe, G. Reid, D.N. Watkins, S. Baltic, P.J. Thompson,

- S.E. Mutsaers, Mutational analysis of hedgehog signaling pathway genes in human malignant mesothelioma, *PLoS One* 8 (2013) e66685.
- G. Klorin, E. Rozenblum, O. Glebov, R.L. Walker, Y. Park, P.S. Meltzer, I.R. Kirsch, F.J. Kaye, A.V. Roschke, Integrated high-resolution array CGH and SKY analysis of homozygous deletions and other genomic alterations present in malignant mesothelioma cell lines, *Cancer Genet.* 206 (2013) 191–205.
 - C. Savvidis, M. Koutsilieris, Circadian rhythm disruption in cancer biology, *Mol. Med.* 18 (2012) 1249–1260.
 - R.G. Stevens, Circadian disruption and breast cancer: from melatonin to clock genes, *Epidemiology* 16 (2005) 254–258.
 - S. Giacchetti, G. Bjarnason, C. Garufi, D. Genet, S. Iacobelli, M. Tampellini, R. Smaaland, C. Focan, B. Coudert, Y. Humblet, J.L. Canon, A. Adenis, G.L. Re, C. Carvalho, J. Schueller, N. Anciaux, M.A. Lentz, B.t. Baron, T. Gorlia, F. Lévi, Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy Group, *J. Clin. Oncol.* 24 (2006) 3562–3569 O.D. Røe, E. Anderssen, E. Helge, C.H. Pettersen, K.S. Olsen, H. Sandeck, R. Haaverstad, S. Lundgren, E. Larsson, Genome-wide profile of pleuralmesothelioma versus parietal and visceral pleura: the emerging gene portrait of the mesothelioma phenotype, *PLoS One* 4 (2009) e6554.
 - M. Elshazley, M. Sato, T. Hase, R. Yamashita, K. Yoshida, S. Toyokuni, F. Ishiguro, H. Osada, Y. Sekido, K. Yokoi, N. Usami, D.S. Shames, M. Kondo, A.F. Gazdar, J.D. Minna, Y. Hasegawa, The circadian clock gene *BMAL1* is a novel therapeutic target for malignant pleural mesothelioma, *Int. J. Cancer* 131 (2012) 2820–2831.
 - M. Brevet, S. Shimizu, M.J. Bott, N. Shukla, Q. Zhou, A.B. Olshen, V. Rusch, M. Ladanyi, Coactivation of receptor tyrosine kinases in malignant mesothelioma as a rationale for combination targeted therapy, *J. Thorac. Oncol.* 6 (2011) 864–874.
 - M.A. Lemmon, J. Schlessinger, Cell signaling by receptor tyrosine kinases, *Cell* 141 (2010) 1117–1134.
 - V. Agarwal, M.J. Lind, L. Cawkwell, Targeted epidermal growth factor receptor therapy in malignant pleural mesothelioma: where do we stand? *Cancer Treat. Rev.* 37 (2011) 533–542.
 - H. Kothmaier, F. Quehenberger, I. Halbwedl, P. Morbini, F. Demirag, H. Zeren, C.E. Comin, B. Murer, P.T. Cagle, R. Attanoos, A.R. Gibbs, F. Galateau-Salle, H.H. Popper, EGFR and PDGFR differentially promote growth in malignant epithelioid mesothelioma of short and long term survivors, *Thorax* 63 (2008) 345–351.
 - A. Destro, G.L. Ceresoli, M. Falleni, P.A. Zucali, E. Morengi, P. Bianchi, C. Pellegrini, N. Cordani, V. Vaira, M. Alloisio, A. Rizzi, S. Bosari, M. Roncalli, EGFR overexpression in malignant pleural mesothelioma: an immunohistochemical and molecular study with clinico-pathological correlations, *Lung Cancer* 51 (2006) 207–215 (Amsterdam, Netherlands).
 - R. Govindan, R.A. Kratzke, J.E. Herndon, G.A. Niehans, R. Vollmer, D. Watson, M.R. Green, H.L. Kindler, Gefitinib in patients with malignant mesothelioma: a phase II study by the cancer and leukemia group B, *Clin. Cancer Res.* 11 (2005) 2300–2304.
 - L.L. Garland, C. Rankin, D.R. Gandara, S.E. Rivkin, K.M. Scott, R.B. Nagle, A.J.P. Klein-Szanto, J.R. Testa, D.A. Altomare, E.C. Borden, Phase II study of Erlotinib in patients with malignant pleural mesothelioma: a

- southwest oncology group study, *J. Clin. Oncol.* 25 (2007) 2406–2413.
- C. Linder, S. Linder, E. Munck-Wikland, H. Strander, Independent expression of serum vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in patients with carcinoma and sarcoma, *Anticancer Res.* 18 (1998) 2063–2068.
 - S. Kumar-Singh, J. Weyler, M.J. Martin, P.B. Vermeulen, E. Van Marck, Angiogenic cytokines in mesothelioma: a study of VEGF, FGF-1 and -2, and TGF beta expression, *J. Pathol.* 189 (1999) 72–78.
 - F. Demirag, E. Uˆnsal, A. Yilmaz, A. Cı̇şagı̇rler, Prognostic significance of vascular endothelial growth factor, tumor necrosis, and mitotic activity index in malignant pleural mesothelioma*, *Chest J.* 128 (2005) 3382–3387.
 - K. Aoe, A. Hiraki, T. Tanaka, K.-I. Gemba, K. Taguchi, T. Murakami, N. Sueoka, T. Kamei, H. Ueoka, K. Sugi, T. Yoshino, T. Kishimoto, Expression of vascular endothelial growth factor in malignant mesothelioma, *Anticancer Res.* 26 (2006) 4833–4836.
 - R.E. Favoni, A. Daga, P. Malatesta, T. Florio, Preclinical studies identify novel targeted pharmacological strategies for treatment of human malignant pleural mesothelioma, *Br. J. Pharmacol.* 166 (2012) 532–553.
 - D.M. Jackman, H.L. Kindler, B.Y. Yeap, P. Fidias, R. Salgia, J. Lucca, L.K. Morse, P.A. Ostler, B.E. Johnson, P.A. Jˆanne, Erlotinib plus bevacizumab in previously treated patients with malignant pleural mesothelioma, *Cancer* 113 (2008) 808–814.
 - B.A. Whitson, R.A. Kratzke, Molecular pathways in malignant pleural mesothelioma, *Cancer Lett.* 239 (2006) 183–189.
 - C.D. Hoang, J. D'Cunha, M.G. Kratzke, C.E. Casmey, S.P. Frizelle, M.A. Maddaus, R.A. Kratzke, Gene expression profiling identifies matrix metalloproteinase overexpression in malignant mesothelioma, *Chest* 125 (2004) 1843–1852.
 - C.D. Hoang, X. Zhang, P.D. Scott, T.J. Guillaume, M.A. Maddaus, D. Yee, R.A. Kratzke, Selective activation of insulin receptor substrate-1 and -2 in pleural mesothelioma cells: association with distinct malignant phenotypes, *Cancer Res.* 64 (2004) 7479–7485.
 - N. Kalra, J. Zhang, Y. Yu, M. Ho, M. Merino, L. Cao, R. Hassan, Efficacy of anti-insulinlike growth factor I receptor monoclonal antibody cixutumumab in mesothelioma is highly correlated with insulin growth factor-I receptor sites/cell, *Int. J. Cancer* 131 (2012) 2143–2152.
 - H.I. Pass, C. Goparaju, S. Ivanov, J. Donington, M. Carbone, M. Hoshen, D. Cohen, A. Chajut, S. Rosenwald, H. Dan, S. Benjamin, R. Aharonov, hsa-miR-29c* is linked to the prognosis of malignant pleural mesothelioma, *Cancer Res.* 70 (2010) 1916–1924.
 - S. Busacca, S. Germano, L. De Cecco, M. Rinaldi, F. Comoglio, F. Favero, B. Murer, L. Mutti, M. Pierotti, G. Gaudino, microRNA signature of malignant mesothelioma with potential diagnostic and prognostic implications, *Am. J. Respir. Cell Mol. Biol.* 42 (2010) 312–319.
 - I. Thirkettle, P. Harvey, P.S. Hasleton, R.Y. Ball, R.M. Warn, Immunoreactivity for cadherins, HGF/SF, met, and erbB-2 in pleural malignant mesotheliomas, *Histopathology* 36 (2000) 522–528.
 - R. Jagadeeswaran, P.C. Ma, T.Y. Seiwert, S. Jagadeeswaran, O. Zumba, V. Nallasura, S. Ahmed, R. Filiberti, M. Paganuzzi, R. Puntoni, R.A. Kratzke, G.J. Gordon, D.J. Sugarbaker, R. Bueno, V. Janamanchi, V.P.

- Bindokas, H.L. Kindler, R. Salgia, Functional analysis of c-Met/hepatocyte growth factor pathway in malignant pleural mesothelioma, *Cancer Res.* 66 (2006) 352–361.
- K. Kawaguchi, H. Murakami, T. Taniguchi, M. Fujii, S. Kawata, T. Fukui, Y. Kondo, H.
 - Osada, N. Usami, K. Yokoi, Y. Ueda, Y. Yatabe, M. Ito, Y. Horio, T. Hida, Y. Sekido, Combined inhibition of MET and EGFR suppresses proliferation of malignant mesothelioma cells, *Carcinogenesis* 30 (2009) 1097–1105.
 - T. Mukohara, G. Civiello, I.J. Davis, M.L. Taffaro, J. Christensen, D.E. Fisher, B.E. Johnson, P.A. Jänne, Inhibition of the Met receptor in mesothelioma, *Clin. Cancer Res.* 11 (2005) 8122–8130.
 - J.A. McCubrey, L.S. Steelman, W.H. Chappell, S.L. Abrams, E.W.T. Wong, F. Chang, B. Lehmann, D.M. Terrian, M. Milella, A. Tafuri, F. Stivala, M. Libra, J. Basecke, C. Evangelisti, A.M. Martelli, R.A. Franklin, Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance, *Biochim. Biophys. Acta, Mol. Cell. Res.* 1773 (2007) 1263–1284.
 - D. Díez, F. Sánchez-Jiménez, J. Ranea, Evolutionary expansion of the Ras switch regulatory module in eukaryotes, *Nucleic Acids Res.* 39 (13) (2011) 5526–5537.
 - L. Santarpia, S.M. Lippman, A.K. El-Naggar, Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy, *Expert Opin. Ther. Targets* 16 (2012) 103–119.
 - Y. Mebratu, Y. Tesfagzi, How ERK1/2 activation controls cell proliferation and cell death: is subcellular localization the answer? *Cell Cycle* 8 (2009) 1168–1175.
 - H. Davies, G.R. Bignell, C. Cox, P. Stephens, S. Edkins, S. Clegg, J. Teague, H. Woffendin, M.J. Garnett, W. Bottomley, N. Davis, E. Dicks, R. Ewing, Y. Floyd, K. Gray, S. Hall, R. Hawes, J. Hughes, V. Kosmidou, A. Menzies, C. Mould, A. Parker, C. Stevens, S. Watt, S. Hooper, R. Wilson, H. Jayatilake, B.A. Gusterson, C. Cooper, J. Shipley, D. Hargrave, K. Pritchard-Jones, N. Maitland, G. Chenevix-Trench, G.J. Riggins, D.D. Bigner, G. Palmieri, A. Cossu, A. Flanagan, A. Nicholson, J.W. Ho, S.Y. Leung, S.T. Yuen, B.L. Weber, H.F. Seigler, T.L. Darrow, H. Paterson, R. Marais, C.J. Marshall, R. Wooster, M.R. Stratton, P.A. Futreal, Mutations of the BRAF gene in human cancer, *Nature* 417 (2002) 949–954.
 - M.d. Melo, M.W. Gerbase, J. Curran, J.C. Pache, Phosphorylated extracellular signal-regulated kinases are significantly increased in malignant mesothelioma, *J. Histochem. Cytochem.* 54 (2006) 855–861.
 - L. Vintman, S. Nielsen, A. Berner, R. Reich, B. Davidson, Mitogen-activated protein kinase expression and activation does not differentiate benign from malignant mesothelial cells, *Cancer* 103 (2005) 2427–2433.
 - C.L. Zanella, J. Posada, T.R. Tritton, B.T. Mossman, Asbestos causes stimulation of the extracellular signal-regulated kinase 1 mitogen-activated protein kinase cascade after phosphorylation of the epidermal growth factor receptor, *Cancer Res.* 56 (1996) 5334–5338.
 - A.B. Cummins, C. Palmer, B.T. Mossman, D.J. Taatjes, Persistent localization of activated extracellular signal-regulated kinases (ERK1/2) is epithelial cell-specific in an inhalation model of asbestosis, *Am. J. Pathol.* 162 (2003) 713–720.
 - A. Shukla, J.M. Hillegass, M.B. MacPherson, S.L. Beuschel, P.M. Vacek, K.J. Butnor, H.I. Pass, M. Carbone, J.R. Testa, N.H. Heintz, B.T. Mossman, ERK2 is essential for the growth of human epithelioid malignant mesotheliomas, *Int. J. Cancer* 129 (2011) 1075–1086.

- R. Katso, K. Okkenhaug, K. Ahmadi, S. White, J. Timms, M.D. Waterfield, Cellular function of phosphoinositide 3-kinases: implications for development, immunity, homeostasis, and cancer, *Annu. Rev. Cell Dev. Biol.* 17 (2001) 615–675.
- J.A. Engelman, J. Luo, L.C. Cantley, The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism, *Nat. Rev. Genet.* 7 (2006) 606–619.
- N. Chalhoub, S.J. Baker, PTEN and the PI3-kinase pathway in cancer, *Annu. Rev. Pathol.* 4 (2009) 127–150.
- M. Chen, A. Cassidy, J. Gu, G.L. Delclos, F. Zhen, H. Yang, M.A. Hildebrandt, J. Lin, Y. Ye, R.M. Chamberlain, C.P. Dinney, X. Wu, Genetic variations in PI3K-AKT-mTOR pathway and bladder cancer risk, *Carcinogenesis* 30 (2009) 2047–2052.
- T.L. Yuan, L.C. Cantley, PI3K pathway alterations in cancer: variations on a theme, *Oncogene* 27 (2008) 5497–5510.
- B.D. Manning, L.C. Cantley, AKT/PKB signaling: navigating downstream, *Cell* 129 (2007) 1261–1274.
- A. Mora, D. Komander, D.M. van Aalten, D.R. Alessi, PDK1, the master regulator of AGC kinase signal transduction, *Semin. Cell Dev. Biol.* 15 (2004) 161–170.
- C.B. Ching, D.E. Hansel, Expanding therapeutic targets in bladder cancer: the PI3K/Akt/mTOR pathway, *Lab. Invest.* 90 (2010) 1406–1414.
- N. Sonenberg, A.C. Gingras, The mRNA 5' cap-binding protein eIF4E and control of cell growth, *Curr. Opin. Cell Biol.* 10 (1998) 268–275.
- N. Pullen, G. Thomas, Themodular phosphorylation and activation of p70s6k, *FEBS Lett.* 410 (1997) 78–82.
- M.E. Ramos-Nino, G. Vianale, T. Sabo-Attwood, L. Mutti, C. Porta, N. Heintz, B.T. Mossman, Human mesothelioma cells exhibit tumor cell-specific differences in phosphatidylinositol 3-kinase/AKT activity that predict the efficacy of Onconase, *Mol. Cancer Ther.* 4 (2005) 835–842.
- Y. Mamane, E. Petroulakis, L. Rong, K. Yoshida, L.W. Ler, N. Sonenberg, eIF4E—from translation to transformation, *Oncogene* 23 (2004) 3172–3179.
- G.G. Chiang, R.T. Abraham, Targeting the mTOR signaling network in cancer, *Trends Mol. Med.* 13 (2007) 433–442.
- C. Eng, PTEN: one gene, many syndromes, *Hum. Mutat.* 22 (2003) 183–198.
- S. Tanno, S. Tanno, Y. Mitsuuchi, D.A. Altomare, G.H. Xiao, J.R. Testa, AKT activation up-regulates insulin-like growth factor I receptor expression and promotes invasiveness of human pancreatic cancer cells, *Cancer Res.* 61 (2001) 589–593.
- Y. Samuels, Z. Wang, A. Bardelli, N. Silliman, J. Ptak, S. Szabo, H. Yan, A. Gazdar, S.M. Powell, G.J. Riggins, J.K. Willson, S. Markowitz, K.W. Kinzler, B. Vogelstein, V.E. Velculescu, High frequency of mutations of the PIK3CA gene in human cancers, *Science* 304 (2004) 554.
- A.-x. Liu, J.R. Testa, T.C. Hamilton, R. Jove, S.V. Nicosia, J.Q. Cheng, AKT2, a member of the protein kinase B family, is activated by growth factors, v-Ha-ras, and v-src through phosphatidylinositol 3-kinase in human ovarian epithelial cancer cells, *Cancer Res.* 58 (1998) 2973–2977.
- B. Actor, J.M. Cobbers, R. Buschges, M. Wolter, C.B. Knobbe, P. Lichter, G. Reifenberger, R.G. Weber, Comprehensive analysis of genomic alterations in gliosarcoma and its two tissue components, *Gene*

- Chromosome Cancer 34 (2002) 416–427.
- C.B. Knobbe, G. Reifenberger, Genetic alterations and aberrant expression of genes related to the phosphatidylinositol-3'-kinase/protein kinase B (Akt) signal transduction pathway in glioblastomas, *Brain Pathol.* 13 (2003) 507–518.
 - J.M. Pedrero, D.G. Carracedo, C.M. Pinto, A.H. Zapatero, J.P. Rodrigo, C.S. Nieto, M.V. Gonzalez, Frequent genetic and biochemical alterations of the PI 3-K/AKT/PTEN pathway in head and neck squamous cell carcinoma, *Int. J. Cancer* 114 (2005) 242–248 L.M. Chow, S.J. Baker, PTEN function in normal and neoplastic growth, *Cancer Lett.* 241 (2006) 184–196.
 - K.-U. Kim, S.M. Wilson, K.S. Abayasiriwardana, R. Collins, L. Fjellbirkeland, Z. Xu, D.M. Jablons, S.L. Nishimura, V.C. Broaddus, A novel in vitro model of human mesothelioma for studying tumor biology and apoptotic resistance, *Am. J. Respir. Cell Mol. Biol.* 33 (2005) 541–548.
 - I. Mohiuddin, X. Cao, M.K. Ozvaran, L. Zumstein, S. Chada, W.R. Smythe, Phosphatase and tensin analog gene overexpression engenders cellular death in human malignant mesothelioma cells via inhibition of AKT phosphorylation, *Ann. Surg. Oncol.* 9 (2002) 310–316.
 - M.A.S. Cedrés, P. Montero, A. Martinez, V. Martinez, D. Rodríguez-Freixinós, A. Torrejon, M. Gabaldon, S. Salcedo, Ramon y Cajal, E. Felip, Exploratory analysis of activation of PTEN–PI3K pathway and downstream proteins in malignant pleural mesothelioma (MPM), *Lung Cancer* 77 (2012) 192–198(Amsterdam, Netherlands).
 - L. Zhao, P.K. Vogt, Hot-spot mutations in p110alpha of phosphatidylinositol 3-kinase (pI3K): differential interactions with the regulatory subunit p85 and with RAS, *Cell Cycle* 9 (2010) 596–600.
 - P.K. Vogt, S. Kang, M.A. Elsliger, M. Gymnopoulos, Cancer-specific mutations in phosphatidylinositol 3-kinase, *Trends Biochem. Sci.* 32 (2007) 342–349.
 - S. Varghese, Z. Chen, D.L. Bartlett, J.F. Pingpank, S.K. Libutti, S.M. Steinberg, J. Wunderlich, H.R. Alexander, Activation of the phosphoinositide-3-kinase and mammalian target of rapamycin signaling pathways are associated with shortened survival in patients with malignant peritoneal mesothelioma, *Cancer* 117 (2011) 361–371.
 - D.A. Fennell, R.M. Rudd, Defective core-apoptosis signalling in diffuse malignant pleural mesothelioma: opportunities for effective drug development, *Lancet Oncol.* 5 (2004) 354–362.
 - B. Bedogni, S.M. Welford, A.C. Kwan, J. Ranger-Moore, K. Saboda, M.B. Powell, Inhibition of phosphatidylinositol-3-kinase and mitogen-activated protein kinase kinase 1/2 prevents melanoma development and promotes melanoma regression in the transgenic TPRas mouse model, *Mol. Cancer Ther.* 5 (2006) 3071–3077.
 - G.W. Cole, A.M. Alleva, J.T. Zuo, S.S. Sehgal, W.-S. Yeow, D.S. Schrupp, D.M. Nguyen, Suppression of Pro-metastasis phenotypes expression in malignant pleural mesothelioma by the PI3K inhibitor LY294002 or the MEK inhibitor UO126, *Anticancer Res.* 26 (2006) 809–821.
 - D. Barbone, T.M. Yang, J.R. Morgan, G. Gaudino, V.C. Broaddus, Mammalian target of rapamycin contributes to the acquired apoptotic resistance of human mesothelioma multicellular spheroids, *J. Biol. Chem.* 283 (2008) 13021–13030.

- Z.A. Knight, K.M. Shokat, Chemically targeting the PI3K family, *Biochem. Soc. Trans.* 35 (2007) 245–249.
- B.T. Hennessy, D.L. Smith, P.T. Ram, Y. Lu, G.B. Mills, Exploiting the PI3K/AKT pathway for cancer drug discovery, *Nat. Rev. Drug Discov.* 4 (2005) 988–1004.
- L. Yang, H.C. Dan, M. Sun, Q. Liu, X.-m. Sun, R.I. Feldman, A.D. Hamilton, M. Polokoff, S.V. Nicosia, M. Herlyn, S.M. Sebti, J.Q. Cheng, Akt/protein kinase B signaling inhibitor-2, a selective small molecule inhibitor of Akt signaling with antitumor activity in cancer cells overexpressing Akt, *Cancer Res.* 64 (2004) 4394–4399.
- D. Hanahan, R.A. Weinberg, The hallmarks of cancer, *Cell* 100 (2000) 57–70.
- L.E. Leard, V.C. Broaddus, Mesothelial cell proliferation and apoptosis, *Respirology* 9 (2004) 292–299.
- S.R. Narasimhan, L. Yang, B.I. Gerwin, V.C. Broaddus, Resistance of pleural mesothelioma cell lines to apoptosis: relation to expression of Bcl-2 and Bax, *Am. J. Physiol.* 275 (1998) L165–L171.
- L. Zhang, J. Yu, B.H. Park, K.W. Kinzler, B. Vogelstein, Role of BAX in the apoptotic response to anticancer agents, *Science* 290 (2000) 989–992.
- M. Raisova, A.M. Hossini, J. Eberle, C. Riebeling, T. Wieder, I. Sturm, P.T. Daniel, C.E. Orfanos, C.C. Geilen, The Bax/Bcl-2 ratio determines the susceptibility of human melanoma cells to CD95/Fas-mediated apoptosis, *J. Invest. Dermatol.* 117 (2001) 333–340.
- X. Cao, C. Rodarte, L. Zhang, C.D. Morgan, J. Littlejohn, W.R. Smythe, Bcl2/bcl-xL inhibitor engenders apoptosis and increases chemosensitivity in mesothelioma, *Cancer Biol. Ther.* 6 (2007) 246–252.
- S.W. Fesik, Promoting apoptosis as a strategy for cancer drug discovery, *Nat. Rev. Cancer* 5 (2005) 876–885.
- X.X. Cao, I. Mohiuddin, F. Ece, D.J. McConkey, W.R. Smythe, Histone deacetylase inhibitor downregulation of bcl-xl gene expression leads to apoptotic cell death in mesothelioma, *Am. J. Respir. Cell Mol. Biol.* 25 (2001) 562–568.
- W.R. Smythe, I. Mohiuddin, M. Ozveran, X.X. Cao, Antisense therapy for malignant mesothelioma with oligonucleotides targeting the bcl-xl gene product, *J. Thorac. Cardiovasc. Surg.* 123 (2002) 1191–1198.
- J.E. Littlejohn, X. Cao, S.D. Miller, M.K. Ozvaran, D. Jupiter, L. Zhang, C. Rodarte, W.R. Smythe, Bcl-xL antisense oligonucleotide and cisplatin combination therapy extends survival in SCID mice with established mesothelioma xenografts, *Int. J. Cancer* 123 (2008) 202–208.
- E. Varin, C. Denoyelle, E. Brotin, M. Meryet-Figuière, F. Giffard, E. Abeilard, D. Goux, P. Gauduchon, P. Icard, L. Poulain, Downregulation of Bcl-xL and Mcl-1 is sufficient to induce cell death in mesothelioma cells highly refractory to conventional chemotherapy, *Carcinogenesis* 31 (2010) 984–993.
- X. Cao, J. Yap, M. Newell-Rogers, C. Peddaboina, W. Jiang, H. Papaconstantinou, D. Jupiter, A. Rai, K.-Y. Jung, R. Tubin, W. Yu, K. Vanommeslaeghe, P. Wilder, A. MacKerell, S. Fletcher, R. Smythe, The novel BH3 alpha-helix mimetic JY-1-106 induces apoptosis in a subset of cancer cells (lung cancer, colon cancer and mesothelioma) by disrupting Bcl-xL and Mcl-1 protein–protein interactions with Bak, *Mol. Cancer* 12 (2013) 42.
- B.Z. Yuan, J.A. Chapman, S.H. Reynolds, Proteasome inhibitor MG132 induces apoptosis and inhibits invasion of human malignant pleural mesothelioma cells, *Transl. Oncol.* 1 (2008) 129–140.
- K.A. Morrow, L.A. Shevde, Merlin: the wizard requires protein stability to function as a tumor suppressor, *Biochim. Biophys. Acta, Rev. Cancer* 1826 (2012) 400–406.

- S. Tsukita, K. Oishi, N. Sato, J. Sagara, A. Kawai, ERM family members as molecular linkers between the cell surface glycoprotein CD44 and actin-based cytoskeletons, *J. Cell Biol.* 126 (1994) 391–401.
- I. Stamenkovic, Q. Yu, Merlin, a “Magic” linker between the extracellular cues and intracellular signaling pathways that regulate cell motility, proliferation, and survival, *Curr. Protein Pept. Sci.* 11 (2010) 471–484.
- R. Rong, X. Tang, D.H. Gutmann, K. Ye, Neurofibromatosis 2 (NF2) tumor suppressor merlin inhibits phosphatidylinositol 3-kinase through binding to PIKE-L, *Proc. Natl. Acad. Sci.* 101 (2004) 18200–18205.
- M.F. James, S. Han, C. Polizzano, S.R. Plotkin, B.D. Manning, A.O. Stemmer-Rachamimov, J.F. Gusella, V. Ramesh, NF2/Merlin is a novel negative regulator of mTOR complex 1, and activation of mTORC1 is associated with meningioma and schwannoma growth, *Mol. Cell. Biol.* 29 (2009) 4250–4261.
- M. Curto, B.K. Cole, D. Lallemand, C.H. Liu, A.I. McClatchey, Contact-dependent inhibition of EGFR signaling by Nf2/Merlin, *J. Cell Biol.* 177 (2007) 893–903.
- C. Thurneysen, I. Opitz, S. Kurtz, W. Weder, R.A. Stahel, E. Felley-Bosco, Functional inactivation of NF2/merlin in human mesothelioma, *Lung Cancer* 64 (2009) 140–147 (Amsterdam, Netherlands).
- T. Yokoyama, H. Osada, H. Murakami, Y. Tatematsu, T. Taniguchi, Y. Kondo, Y. Yatabe, Y. Hasegawa, K. Shimokata, Y. Horio, T. Hida, Y. Sekido, YAP1 is involved in mesothelioma development and negatively regulated by Merlin through phosphorylation, *Carcinogenesis* 29 (2008) 2139–2146.
- C.Y. Logan, R. Nusse, The WNT signaling pathway in development and disease, *Annu. Rev. Cell Dev. Biol.* 20 (2004) 781–810.
- A. Klaus, W. Birchmeier, Wnt signalling and its impact on development and cancer, *Nat. Rev. Cancer* 8 (2008) 387–398.
- B.T. MacDonald, K. Tamai, X. He, Wnt/2-catenin signaling: components, mechanisms, and diseases, *Dev. Cell* 17 (2009) 9–26.
- A.Y. Lee, B. He, L. You, S. Dadfarmay, Z. Xu, J. Mazieres, I. Mikami, F. McCormick, D.M. Jablons, Expression of the secreted frizzled-related protein gene family is downregulated in human mesothelioma, *Oncogene* 23 (2004) 6672–6676.
- S. Batra, Y. Shi, K.M. Kuchenbecker, B. He, N. Reguart, I. Mikami, L. You, Z. Xu, Y.-C. Lin, G.v. Clément, D.M. Jablons, Wnt inhibitory factor-1, a Wnt antagonist, is silenced by promoter hypermethylation in malignant pleural mesothelioma, *Biochem. Biophys. Res. Commun.* 342 (2006) 1228–1232.
- H. Kohno, V.J. Amatya, Y. Takeshima, K. Kushitani, N. Hattori, N. Kohno, K. Inai, Aberrant promoter methylation of WIF-1 and SFRP1, 2, 4 genes in mesothelioma, *Oncol. Rep.* 24 (2010) 423–431.
- A.S. Abutaily, J.E. Collins, W.R. Roche, Cadherins, catenins and APC in pleural malignant mesothelioma, *J. Pathol.* 201 (2003) 355–362.
- W. Anani, R. Bruggeman, D.S. Zander, Beta-catenin expression in benign and malignant pleural disorders, *Int. J. Clin. Exp. Pathol.* 4 (2011) 742–747.
- S.A. Fox, A.K. Richards, I. Kusumah, V. Perumal, E.M. Bolitho, S.E. Mutsaers, A.M. Dharmarajan, Expression profile and function of Wnt signaling mechanisms in malignant mesothelioma cells, *Biochem. Biophys. Res. Commun.* 440 (2013) 82–87.
- M. Kobayashi, C.L. Huang, M. Sonobe, R. Kikuchi, M. Ishikawa, J. Kitamura, R. Miyahara, T. Menju, S.

- Iwakiri, K. Itoi, R. Yasumizu, H. Date, Intratumoral Wnt2B expression affects tumor proliferation and survival in malignant pleural mesothelioma patients, *Exp. Ther. Med.* 3 (2012) 952–958.
- J. Mazieres, L. You, B. He, Z. Xu, S. Twogood, A.Y. Lee, N. Reguart, S. Batra, I. Mikami, D.M. Jablons, Wnt2 as a new therapeutic target in malignant pleural mesothelioma, *Int. J. Cancer* 117 (2005) 326–332.
 - B. He, L. You, K. Uematsu, Z. Xu, A.Y. Lee, M. Matsangou, F. McCormick, D.M. Jablons, A monoclonal antibody against Wnt-1 induces apoptosis in human cancer cells, *Neoplasia* 6 (2004) 7–14.
 - Y. Dai, C.W.M. Bedrossian, C.W. Michael, The expression pattern of β -catenin in mesothelial proliferative lesions and its diagnostic utilities, *Diagn. Cytopathol.* 33 (2005) 320–324.
 - T. Taniguchi, S. Karnan, T. Fukui, T. Yokoyama, H. Tagawa, K. Yokoi, Y. Ueda, T.
 - Mitsudomi, Y. Horio, T. Hida, Y. Yatabe, M. Seto, Y. Sekido, Genomic profiling of malignant pleural mesothelioma with array-based comparative genomic hybridization shows frequent non-random chromosomal alteration regions including JUN amplification on 1p32, *Cancer Sci.* 98 (2007) 438–446.
 - N. Usami, T. Fukui, M. Kondo, T. Taniguchi, T. Yokoyama, S. Mori, K. Yokoi, Y. Horio, K. Shimokata, Y. Sekido, T. Hida, Establishment and characterization of four malignant pleural mesothelioma cell lines from Japanese patients, *Cancer Sci.* 97 (2006) 387–394.
 - N. Tochigi, R. Attanoos, L.R. Chirieac, T.C. Allen, P.T. Cagle, S. Dacic, p16 deletion in sarcomatoid tumors of the lung and pleura, *Arch. Pathol. Lab. Med.* 137 (2013) 632–636.
 - S. Matsumoto, K. Nabeshima, T. Kamei, K. Hiroshima, K. Kawahara, S. Hata, K. Marukawa, Y. Matsuno, K. Taguchi, T. Tsujimura, Morphology of 9p21 homozygous deletion-positive pleural mesothelioma cells analyzed using fluorescence in situ hybridization and virtual microscope system in effusion cytology, *Cancer Cytopathol.* 121 (2013) 415–422.
 - J.Q. Cheng, W.C. Lee, M.A. Klein, G.Z. Cheng, S.C. Jhanwar, J.R. Testa, Frequent mutations of NF2 and allelic loss from chromosome band 22q12 in malignant mesothelioma: evidence for a two-hit mechanism of NF2 inactivation, *Genes Chromosom. Cancer* 24 (1999) 238–242.
 - B. Deguen, L. Goutebroze, M. Giovannini, C. Boisson, R. van der Neut, M.C. Jaurand, G. Thomas, Heterogeneity of mesothelioma cell lines as defined by altered genomic structure and expression of the NF2 gene, *Int. J. Cancer* 77 (1998) 554–560