Review Article

# The biomolecular era for thoracic surgeons: the example of the ESTS Biology Club

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**Abstract:** Understanding basic mechanisms of lung disease may help to move forward the management of our patients. Molecular biology has affected our diagnostic and therapeutic pathways in the direction of personalized medicine not only for thoracic malignancies. Accordingly, thoracic surgeons are becoming increasingly aware that specific knowledge of genetic and epigenetic alterations may influence their clinical behavior—from the ward to the operating room (OR). In this continuously evolving scenario, surgical societies have perceived the increasing relevance of biomolecular medicine in the practice of modern thoracic surgery. More recently, in the spirit of mutual collaboration between sister societies, the European Society of Thoracic Surgeons (ESTS) has adopted the concept of the American Association for Thoracic Surgery (AATS) incorporating one session dedicated to the Biology Club within the Annual Meeting Program. The aim of the ESTS Biology Club is to outline and sponsor the new profile of the surgeon scientist during the only world meeting exclusively focused on general thoracic surgery. The following article will summarize the significance of this and give an update on molecular biology tools for thoracic malignancies.

**Keywords:** Molecular biology; thoracic surgery; non-small cell lung cancer (NSCLC); mesothelioma; the European Society of Thoracic Surgeons (ESTS)

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## Introduction—the new era

Would it be possible today for thoracic surgeons to ignore the information resulting from the so-called "oncogenic addiction"—at least the *EGFR* mutation or the anaplastic lymphoma kinase (*ALK*) translocation in lung cancer? How much has the biomolecular era affected our diagnostic and therapeutic pathways when dealing with thoracic cancers? Thoracic surgeons would concur on the statement that their specialty has changed dramatically since the introduction of minimally invasive techniques facilitated by the refinement of anesthetic techniques, the new thresholds for surgery-related risk assessment, the implementation of quality metrics to assess performance, and the need to comply with cost-effectiveness criteria while running a surgical service (1).

The multidisciplinary approach to thoracic oncology based on the integration of competences is gaining an unprecedented momentum from the experience of lung cancer screening teams. In these groups, surgeons have a fundamental role in interpreting low-dose screening CT (LDCT) and suggesting the most appropriate diagnostic procedure for the screen-detected nodules (2). It is not by chance that the experience from a lung cancer screening program led by a surgeon has contributed to a five-fold reduction of the false positive results by adding the assessment of micro RNA (miRNA) signatures to LDCT (3). Accordingly, thoracic surgeons are becoming increasingly aware that specific knowledge of genetic and epigenetic alterations may influence their clinical behavior—from the ward to the operating room (OR) (1). In this setting,

it would be difficult to argue against the benefit on patient management of the recently introduced new classification of adenocarcinoma where the integration of pathological, biomolecular, radiological, and clinical features is crucial to the prediction of prognostic correlates of adenocarcinoma subtypes (4).

The future will depend on initiatives such as the Lungscape project from the European Thoracic Oncology Platform—a network of cancer centres (http://www.etop-eu.org)—providing an innovative platform to conduct biomolecular investigations into the nature and outcome of non-small cell lung cancer (NSCLC) and with Mesoscape of malignant pleural mesothelioma (MPM). The aims are to harmonize standards and improve the quality of genetic testing in cancer centres, and increase the knowledge about latest targeted therapies; both initiatives where thoracic surgeon are and will be further involved in the future. Moreover, the fundamental work by Pass and colleagues on fibulin 3 as a new biomarker for mesothelioma (5) has conclusively outlined the role of the surgeon scientist in modern medicine.

The new profile of the surgeon scientist indeed represents a cultural revolution in thoracic surgery. Excellence in the OR, in the intensive care unit and on the ward is coupled with an unprecedented attention to clinical and basic research which translats in focused knowledge of the biomolecular changes causing thoracic diseases. Concomitantly, a new measurement of performance has been inherited from the world of basic researchers and progressively popularized among academic surgeons. In spite of undisputed flaws and limitations, the widely accepted bibliometric parameters (i.e., the impact factor and the h-index) have become, especially in Europe, important criteria to define career progress and actual leadership in academic institutions (6). In this continuously evolving scenario, surgical societies have perceived the increasing relevance of biomolecular medicine in the practice of modern thoracic surgery. The American Association for Thoracic Surgery (AATS) has supported for years an ancillary event to the AATS Annual Meeting focused on the biology of thoracic conditions of surgical interest. The AATS General Thoracic Biology Club has gathered an ever increasing membership attracted by a program including presentations of experimental evidence of biomolecular pathways studied at highly respected international academic institutions. It is notable that the surgeons that have presented at this meeting have developed a successful research portfolio and have achieved important leadership positions.

More recently, in the spirit of mutual collaboration between sister societies, the European Society of Thoracic Surgeons (ESTS) has adopted this concept, incorporating one session dedicated to the Biology Club within the Annual Meeting Program, with the aim of outlining and sponsoring the new profile of the surgeon scientist during the only world meeting exclusively focused on general thoracic surgery. During the 2014 Annual Meeting in Copenhagen, for the first time in Europe, the ESTS leadership will award scholarships to support traveling fellowships in hosting academic institutions to facilitate exchange of expertise and knowledge among European highly qualified thoracic surgical centers.

## Molecular biology for thoracic surgeons

Substantial progress in understanding basic mechanisms of lung disease—still a substantial public health problem—may help to move forward clinical management of our patients. Molecular biology bears the opportunity to move forward in the direction of personalized medicine not only for thoracic malignancies.

Writing in *Nature* in 1961, Astbury described molecular biology as: "...not so much a technique as an approach, an approach from the viewpoint of the so-called basic sciences with the leading idea of searching below the large-scale manifestations of classical biology for the corresponding molecular plan. It is concerned particularly with the forms of biological molecules and [...] is predominantly three-dimensional and structural—which does not mean, however, that it is merely a refinement of morphology. It must at the same time inquire into genesis and function" (7).

So how does this translate into the thoracic surgeons practice and how is this applicable in the pathologies we treat? The following article will summarize the significance and give an update on molecular biology tools for thoracic malignancies.

## Molecular biology of NSCLC

There are two main types of lung cancer divided by histological, clinical and endocrine characteristics, NSCLC (80-85% of lung cancer) and small cell lung cancer (SCLC) (15-20% of lung cancer) (8). Lung cancers arise from lung epithelial cells, which accumulate genetic and epigenetic alterations resulting from chronic exposure to carcinogens in tobacco smoke. Epigenetic changes are accounted by aberrant promoter methylation or histone modifications resulting in alteration of transcription of genes without altering genetic code. Genetic alterations can occur at

 

the chromosomal level (loss or gain of genomic material, translocations, and microsatellite instability), and at the nucleotide level (mutations). These abnormalities that occurred to proto-oncogenes or tumor suppressor genes can affect both function and/or expression levels of the proteins causing up-regulation of survival pathways and out-growth of affected lung epithelial cells. NSCLC can be histologically classified into three other main subtypes according to recommendation of the World health organization (WHO) and the International Association for the Study of Lung Cancer (IASLC) (9). Lung adenocarcinoma is the most common subtype of NSCLC, accounting for about 40% of NSCLC. Later in 2011, an effort has been made to further sub-classify adenocarcinoma with the integration of clinical, radiological surgical, and molecular issues in addition to tumor histology (by the IASLC, American Thoracic Society, and European Respiratory Society) (4,10). A total of 70% of the NSCLC cases are diagnosed with stage IV and patients received platinum based chemotherapeutic agents as the first line treatment (11). Nevertheless, the molecular change in NSCLC is heterogeneous and leads to a broad range of disease outcomes even within the same histological subtype. In the last decades, there has been a development in high-throughput and high-resolution technology for determining genetic and epigenetic alterations in cancers such as next-generation sequencing (NGS) and genomic hybridization array, gene expression microarrays, and proteomics. This technology has brought several new insights into the molecular biology of NSCLC and further sub-divides NSCLC based on molecular changes.

### *Epigenetic aberrations*

Hypermethylation of tumor suppressor gene promoters causes silencing of gene transcription by inhibiting the binding of transcription factors to the promoter. The modification of histones such as methylation, acetylation, phosphorylation, ubiquitylation and ADP-ribosylation also takes part in the epigenetic regulation of genes by altering accessibility of chromatin. Gene promoter methylation profiling by genome wide methylation analysis has revealed that the methylation profile of several tumor suppressor genes such as *CDKN2A* and adenomatous polyposis coli (*APC*) served as prognostic and predictive markers (12). Methylation profile can also be identified in circulating DNA secreted in the liquid specimens such as blood, sputum, and bronchoalveolar lavage (BAL) (12). The investigation of DNA methylation in these specimens will potentially provide advantage in early and non-invasive detection of NSCLC. The methylation of gene promoters was operated by the enzyme DNA methyltransferase (DNMT) which could serve as a therapeutic target. Aza-dC or 5-azacytidine (AzaC), DNMT inhibitors, were approved by the US Food and Drug Administration (FDA) for the treatment of myelodysplastic syndrome (12). Histone de-acetylase inhibitor such as vorinostat has shown clinical activity in several cancers and is being tested in NSCLC under phase I/II clinical trials in combination with other agents (13).

### *Genetic aberrations*

NSCLC is a cancer with high level of gene instability. Structural alterations of chromosomes (gain, loss, translocation) in the region containing important oncogenes and tumor suppressor genes causes gain or loss of the allele (14). Loss of heterozygosity (LOH) where one allele of a tumor suppressor gene such as *CDKN2A* and *TP53* is missing has been involved in the initiation of malignant transformation of lung (15). Several oncogene mutations "driver mutations" have been discovered (16). Driver mutations are mutations that provide growth advantage to tumor cells and are critical for tumor cell survival. Tumor cells become dependent on driver mutations (addicted) therefore can serve as predictive factors and targets for therapy. Well established driver mutations include *EGFR*, *KRAS*, *HER2*, *BRAF*, *PIK3CA*, *AKT1*, *MEK1*, *NRAS*, echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK* and *MET* amplification (16). As the results; novel targeted therapy of NSCLC has been intensively developed based on the driver mutations and their corresponding molecular pathways and has been shown to improve clinical outcomes significantly. The promising treatment of NSCLC patients with *EGFR* mutations with the EGFR tyrosine kinase inhibitor, gefitinib and erlotinib led to the recommendation to test all patients with advance adenocarcinoma for *EGFR* mutation [accounting 20% of NSCLC (8) for the selection of treatment (4)]. On the other hand, patients with *KRAS* mutations (10-30%) or amplification of proto oncogenes such as *MET* receptor tyrosine kinase (7-21%) of NSCLC patients confer the resistance to treatment with these tyrosine kinase inhibitors (8). Recently, the discovery of *EML4-ALK* fusion oncoprotein has shed light on the treatment of NSCLC with *EML-ALK* fusion [accounting for about 6.7% of NSCLC (17)] with ALK tyrosine kinase receptor inhibitor. All the patients harboring *EML-ALK* fusion responded rapidly to these inhibitors such as crizotinib (PF-02341066) (18) which was

 

later approved by the US FDA in 2011.

### *micro RNAs (miRNAs)*

miRNAs are small RNAs which do not encode protein, however they play a key role in the regulation of gene expression. miRNAs bind to the 3'-untranslated region of mRNA of the target gene by using imperfect complementary sequence and induce the degradation of target mRNAs or block their translation into protein. After the first finding of the involvement of miRNAs in human diseases and cancer in 2002, almost 2,000 miRNAs with identified targets have been discovered to date. miRNAs are stable molecules and can also be analyzed in blood, liquid effusions as well as archived formalin fixed paraffin embedded tissues. Using high throughput methods such as miRNA profiling by PCR assay or miRNA arrays or sequencing, miRNA expression signature has been developed for several purposes such as diagnosis, prognosis, chemotherapeutic resistance, and response (19). miRNA Let-7, functions as tumor suppressor and the reduced expression correlates with poor prognosis of NSCLC. Let-7 targets to suppress the expression of several oncoproteins such as Myc proto-oncogene protein and Ras (19). miR-372 acts as oncogene has been shown to be involved in the neutralization of cyclin dependent kinases (CDK) inhibition by p53 (20). Later miRNA signature (hsa-let-7a, hsa-miR-221, hsa-miR-137, hsa-miR-372, and hsa-miR-182*) was discovered to be associated with survival and relapse of NSCLC patients (21). Antagonists to oncogenic miRNAs which overexpress or replacement of tumor suppressor miRNAs lost in cancer provide attractive treatment approaches. *In vitro* experiment and systemic delivery in *in vivo* pre-clinical models revealed efficient anti-tumor activity and was well tolerated (22). After several successes in pre-clinical models, a multicenter phase I study of miR-34 injected in liposome (MRX34) is being conducted in hematologic malignancies and solid tumors (ClinicalTrials.gov Identifier: NCT01829971).

So far it has been realized that targeting specific molecules or molecular pathways personalized to individual defects of each tumor provides the most effective treatment.

## Molecular biology of malignant pleural mesothelioma (MPM)

MPM is one of the most aggressive tumors mainly derived from the pleura and predominantly associated with exposure to asbestos which remains the major causative factor. It is usually resistant to conventional therapies, and the prognosis of patients is particularly severe. Despite remarkable effort to determine the molecular mechanisms involved in MPM carcinogenesis, to date, findings have not led to develop an appropriate treatment approach and the molecular basis for this malignancy suffers from the relative lack of strong evidence.

Intrinsic resistance and poor response to the traditional treatment modalities (i.e., surgery, radiation, and chemotherapy) have driven researchers to explore thoroughly the molecular mechanisms that underlie mesothelioma carcinogenesis.

Over the past decade, emerging evidences have pinpointed derangements in several cellular pathways that involve cell cycle regulators, apoptosis, growth factors, and angiogenesis [reviewed in Zucali *et al*., 2011 (23)]. Epigenetic modifications also have been explored in MPM to dissect alterations of genes expression [reviewed in Vandermeers *et al*., 2013 (24)] even though promoter methylation coupled with gene expression modification is a frequent phenomenon in MPM, thus playing a role in oncogenesis, no valid biomarkers have been identified for diagnosis or prognosis.

Here we address new insights into molecular characteristics and the major genetic alterations that have been associated with MPM. Exploring this active area of research may have a great impact on the identification and the development of new therapeutic targets.

## Chromosomal alterations

Karyotypic studies and comparative genomic hybridization (CGH) analyses using MPM specimens and cell lines have shed light on the genetic alterations involved in the carcinogenesis of MPM. Although there is no specific chromosomal aberration common to all cases of malignant mesothelioma, numerous prominent sites of chromosome loss have been described [reviewed in Carbone *et al*., 2002 (25)]. These include monosomy of chromosome 22 (26) which is the most frequent alteration found in 70% of MPMs [reviewed in Carbone *et al*., 2002 (25)]. Moreover, recurrent regions of loss have been identified at 1p, 3p, 6q, 9p, 13q, 14q, 15q, 17p, and 22q (27,28). This pattern of chromosomal loss emphasized the possible involvement of suppressor genes (TSG) in the initiation and the progression of MPM malignancy.

## Gene mutations

New methods, known as NGS, have revolutionized the genetic analysis of mesothelioma (29). Transcriptome analysis was used to characterize particular genes, mutational profile for four to MPM tumors that do not exist in control tissue. Using this approach, the authors identified uncharacterized human cancer mutations including somatic mutation, gene deletions or silencing, and RNA editing (30). Indeed, deeper investigations in sequencing should provide precious guidance to detect true-driver mutations in MPM to target for efficacious therapy. Only a couple of gene mutations critically located on chromosomes 22q, 9p, and 3p have shown a high rate in MPM malignancy.

The two most abundant alterations in MPM concern *CDKN2A* and *NF2*. Indeed, mesothelioma lack expression of both *CDKN2A* encoded proteins, p16 and ARF, due to gene deletion or methylation [reviewed in Jean *et al*. (31)].

Mutations in the tumor suppressor neurofibromatosis type II (*NF2*; Merlin) gene have been found in 40% of mesothelioma (32-34). In MPM tumors with no detectable genetic alterations of *NF2*, its activity is downregulated. It was observed that expression levels of the protein kinase C-potentiated phosphatase inhibitor of 17 KDa (CPI-17), which inhibits the phosphatase reactivating NF2, were significantly higher in 17% of MPM with no detectable *NF2* mutations (35). Furthermore PTEN immunostaining was shown to be absent in over 60% of MPM patients and correlated with worst outcome (36). Absence of PTEN would result in increased AKT activity and NF2 degradation. It has been proposed that genes which are inactivated in a given tumor type and directly regulate tumor growth by either inhibiting growth or promoting death are "gatekeeper" genes (37). According to the data mentioned above, NF2 does correspond to this definition and should be considered a "gatekeeper" in mesothelioma. A role of NF2 in tissue repair is supported by the observation that the active form of NF2 suppresses tumorigenesis by migrating into the nucleus where it inhibits the E3 ubiquitin ligase CRL4 and through that controls a subset of Hippo pathway target genes (38). This observation is consistent with previous evidence of NF2 signalling-dependent activation of the Hippo pathway (39). The latter is an essential regulator of cell proliferation during tumorigenesis (40) [reviewed in Book chapter Mesothelioma by Felley-Bosco and Opitz in (41)].

Cyclin-dependent kinase inhibitor 2A (*CDKN2A*) is a tumor suppressor gene that maps to the 9p21 chromosomal locus that encodes p16, a CDK inhibitor regulating cell cycle during G1/S phase as well as other alternate transcript variants (42). *CDKN2A* is homozygously deleted at high frequency in MPM cell lines and tumor specimens (33,43-46). Cells lacking p16 lose their cell cycle control and undergo a malignant transformation. Indeed, increasing evidence suggests that *CDKN2A* loss could be used as negative prognostic factor, and represents an ideal candidate for gene therapy (41).

In the last decade, investigations have been conducted to identify *BAP1* gene (*BRCA1* associated protein-1) as a tumor suppressor gene that is frequently lost in MPM (47,48). *BAP1* maps to the 3p21.1 locus and encodes for an ubiquitin COOH-terminal hydrolase. It is believed that BAP1 mediate its effects through chromatin modulation, transcriptional regulation, and possibly via the ubiquitin-proteasome system and the DNA damage response pathway (49). Growing evidence from clinical and molecular studies suggested that when individuals with *BAP1* mutations are exposed to asbestos, mesothelioma predominates. Those authors pointed the fact that *BAP1* mutation, alone, might be sufficient to cause mesothelioma (47,50).

The *TP53* gene controls cell cycle and apoptosis and is mutated in many types of human cancers, and in about 20% in human MPM, a fairly low rate in comparison with other human cancers (51). Point mutations are the main types of alterations in mesothelioma. The International Agency for Research on Cancer p53 database indicates 6 point mutations, 5 missense mutations, and 1 stop mutation (http://www. p53.iarc.fr, accessed June 11, 2011) (31). The clinical significance of *TP53* mutations remains unclear so far.

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## References

1. Rocco G. The surgeon's role in molecular biology. J Thorac Cardiovasc Surg 2012;144:S18-22.
2. Rocco G, Allen MS, Altorki NK, et al. Clinical statement on the role of the surgeon and surgical issues relating to computed tomography screening programs for lung cancer. Ann Thorac Surg 2013;96:357-60.
3. Sozzi G, Boeri M, Rossi M, et al. Clinical utility of a

 

plasma-based miRNA signature classifier within computed tomography lung cancer screening: a correlative MILD trial study. J Clin Oncol 2014;32:768-73.
4. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-85.
5. Pass HI, Levin SM, Harbut MR, et al. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma. N Engl J Med 2012;367:1417-27.
6. Rocco G. A view from above. Eur J Cardiothorac Surg 2009;35:385-91.
7. Astbury WT. Molecular biology or ultrastructural biology? Nature 1961;190:1124.
8. Larsen JE, Minna JD. Molecular biology of lung cancer: clinical implications. Clin Chest Med 2011;32:703-40.
9. Travis WD. eds. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus, and Heart. World Health Organization Classification of Tumours. Lyon, France: IARC Press, 2004.
10. Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-68.
11. Saintigny P, Burger JA. Recent advances in non-small cell lung cancer biology and clinical management. Discov Med 2012;13:287-97.
12. Heller G, Zielinski CC, Zochbauer-Muller S. Lung cancer: from single-gene methylation to methylome profiling. Cancer Metastasis Rev 2010;29:95-107.
13. Reguart N, Rosell R, Cardenal F, et al. Phase I/II trial of vorinostat (SAHA) and erlotinib for non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations after erlotinib progression. Lung Cancer 2014;84:161-7.
14. Czarnecka KH, Migdalska-Sek M, Antczak A, et al. Allelic imbalance in 1p, 7q, 9p, 11p, 12q and 16q regions in non-small cell lung carcinoma and its clinical association: a pilot study. Mol Biol Rep 2013;40:6671-84.
15. Ogiwara H, Kohno T, Nakanishi H, et al. Unbalanced translocation, a major chromosome alteration causing loss of heterozygosity in human lung cancer. Oncogene 2008;27:4788-97.
16. Yu Y, He J. Molecular classification of non-small-cell lung cancer: diagnosis, individualized treatment, and prognosis. Front Med 2013;7:157-71.
17. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.
18. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-703.
19. Lin PY, Yu SL, Yang PC. MicroRNA in lung cancer. Br J Cancer 2010;103:1144-8.
20. Dalmay T, Edwards DR. MicroRNAs and the hallmarks of cancer. Oncogene 2006;25:6170-5.
21. Yu SL, Chen HY, Chang GC, et al. MicroRNA signature predicts survival and relapse in lung cancer. Cancer Cell 2008;13:48-57.
22. Skrzypski M, Dziadziuszko R, Jassem J. MicroRNA in lung cancer diagnostics and treatment. Mutation research 2011;717:25-31.
23. Zucali PA, Giovannetti E, Destro A, et al. Thymidylate synthase and excision repair cross-complementing group-1 as predictors of responsiveness in mesothelioma patients treated with pemetrexed/carboplatin. Clin Cancer Res 2011;17:2581-90.
24. Vandermeers F, Neelature Sriramareddy S, Costa C, et al. The role of epigenetics in malignant pleural mesothelioma. Lung Cancer 2013;81:311-8.
25. Carbone M, Kratzke RA, Testa JR. The pathogenesis of mesothelioma. Semin Oncol 2002;29:2.
26. Cheng JQ, Lee WC, Klein MA, et al. Frequent mutations of NF2 and allelic loss from chromosome band 22q12 in malignant mesothelioma: evidence for a two-hit mechanism of NF2 inactivation. Genes Chromosomes Cancer 1999;24:238-42.
27. Björkqvist AM, Tammilehto L, Anttila S, et al. Recurrent DNA copy number changes in 1q, 4q, 6q, 9p, 13q, 14q and 22q detected by comparative genomic hybridization in malignant mesothelioma. Br J Cancer 1997;75:523-7.
28. Shivapurkar N, Virmani AK, Wistuba II, et al. Deletions of chromosome 4 at multiple sites are frequent in malignant mesothelioma and small cell lung carcinoma. Clin Cancer Res 1999;5:17-23.
29. Biesecker LG. Hypothesis-generating research and predictive medicine. Genome Res 2013;23:1051-3.
30. Sugarbaker DJ, Richards WG, Gordon GJ, et al. Transcriptome sequencing of malignant pleural mesothelioma tumors. Proc Natl Acad Sci U S A 2008;105:3521-6.
31. Jean D, Daubriac J, Le Pimpec-Barthes F, et al. Molecular changes in mesothelioma with an impact on prognosis and treatment. Arch Pathol Lab Med 2012;136:277-93.
32. Sekido Y, Pass HI, Bader S, et al. Neurofibromatosis type 2 (NF2) gene is somatically mutated in mesothelioma but

 

not in lung cancer. Cancer Res 1995;55:1227-31.
33. Bianchi AB, Mitsunaga SI, Cheng JQ, et al. High frequency of inactivating mutations in the neurofibromatosis type 2 gene (NF2) in primary malignant mesotheliomas. Proc Natl Acad Sci U S A 1995;92:10854-8.
34. Deguen B, Goutebroze L, Giovannini M, et al. Heterogeneity of mesothelioma cell lines as defined by altered genomic structure and expression of the NF2 gene. Int J Cancer 1998;77:554-60.
35. Thurneysen C, Opitz I, Kurtz S, et al. Functional inactivation of NF2/merlin in human mesothelioma. Lung Cancer 2009;64:140-7.
36. Opitz I, Soltermann A, Abaecherli M, et al. PTEN expression is a strong predictor of survival in mesothelioma patients. Eur J Cardiothorac Surg 2008;33:502-6.
37. Kinzler KW, Vogelstein B. Cancer-susceptibility genes. Gatekeepers and caretakers. Nature 1997;386:761, 763.
38. Li W, You L, Cooper J, et al. Merlin/NF2 suppresses tumorigenesis by inhibiting the E3 ubiquitin ligase CRL4(DCAF1) in the nucleus. Cell 2010;140:477-90.
39. Lau YK, Murray LB, Houshmandi SS, et al. Merlin is a potent inhibitor of glioma growth. Cancer Res 2008;68:5733-42.
40. Zhao B, Lei QY, Guan KL. The Hippo-YAP pathway: new connections between regulation of organ size and cancer. Curr Opin Cell Biol 2008;20:638-46.
41. Felley-Bosco E, Opitz I. Mesothelioma. In: Stahel RA. eds. Lung Cancer Therapy Annual 7. CRC Press, 2012.
42. Romagosa C, Simonetti S, Lopez-Vicente L, et al. p16(Ink4a) overexpression in cancer: a tumor suppressor gene associated with senescence and high-grade tumors. Oncogene 2011;30:2087-97.
43. Wong L, Zhou J, Anderson D, et al. Inactivation of p16INK4a expression in malignant mesothelioma by methylation. Lung Cancer 2002;38:131-6.
44. Xio S, Li D, Vijg J, et al. Codeletion of p15 and p16 in primary malignant mesothelioma. Oncogene 1995;11:511-5.
45. Illei PB, Ladanyi M, Rusch VW, et al. The use of CDKN2A deletion as a diagnostic marker for malignant mesothelioma in body cavity effusions. Cancer 2003;99:51-6.
46. Ladanyi M. Implications of P16/CDKN2A deletion in pleural mesotheliomas. Lung Cancer 2005;49 Suppl 1:S95-8.
47. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet 2011;43:1022-5.
48. Bott M, Brevet M, Taylor BS, et al. The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma. Nat Genet 2011;43:668-72.
49. Murali R, Wiesner T, Scolyer RA. Tumours associated with BAP1 mutations. Pathology 2013;45:116-26.
50. Carbone M, Yang H, Pass HI, et al. BAP1 and cancer. Nat Rev Cancer 2013;13:153-9.
51. Sekido Y. Genomic abnormalities and signal transduction dysregulation in malignant mesothelioma cells. Cancer Sci 2010;101:1-6.

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