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Biochimica et Biophysica Acta 1762 (2006) 587–591

BIOCHIMICA ET BIOPHYSICA ACTA

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Review

Autoantibody biomarkers in the detection of cancer

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Received 15 February 2006; received in revised form 24 March 2006; accepted 4 April 2006
Available online 19 April 2006

Abstract

By definition, tumor biomarkers are selective molecules that can distinguish between patients with cancer and controls. Serum tumor markers have been the most widely used approach for cancer detection. However, the limitations of these markers, which are based on the measurement of tumor antigens, preclude their general use in cancer screening and diagnosis. Here we give an overview of recent cancer biomarker developments based on the detection of autoantibodies produced against tumor antigens in patients' sera. This new detection method can measure the autoantibodies for a spectrum of tumor antigens in a single assay, with sensitivity and specificity exceeding those obtained using the conventional antigen determination method. Autoantibodies against serum cancer biomarkers offer a novel technology for cancer detection.
Published by Elsevier B.V.

Keywords: Autoantibody-based EIA; Cancer detection; Biomarker; Autoantibody ECPKA; cAMP-dependent protein kinase

1. Introduction

An ideal tumor biomarker would allow a simple blood test to detect cancer. Due to a lack of sensitivity and specificity, however, no single marker has been recognized as a true cancer marker. Currently available serum biomarkers are based on the measurement of cancer antigens [1]. For example, the prostate-specific antigen (PSA) is measured for prostate cancer biomarker [2], the carcinoembryonic antigen (CEA) for colorectal cancer [3], the cancer antigen CA15-3 for breast cancer [4], the cancer antigen CA19-9 for gastrointestinal cancer [5], and the cancer antigen CA125 for ovarian cancer [6]. In addition to these novel markers, some other proteins, hormones, and enzymes have been used as markers for the past 30 years [1,7]. But these markers show limited specificity and sensitivity, and levels also increase under benign conditions and during gestation. There is great need to discover novel biomarkers and translate them into routine clinical use. An extensive literature review is not intended for this review. Only selected reviews describe the development of a specific new approach: "autoantibody detection in cancer diagnosis."

2. Discovery of autoantibody ECPKA—a universal cancer biomarker

In normal mammalian cells, cAMP-dependent protein kinase A (PKA) is an intracellular enzyme [8,9]. Intriguingly, however, in cells of various cancer types, it is secreted into the conditioned medium [10,11]. This PKA, designated as extracellular protein kinase A (ECPKA), is markedly up-regulated in the serum of cancer patients [10,11], and surgical removal of tumors leads to decreased ECPKA levels [12]. Modulation of intracellular levels of PKA type I regulates ECPKA levels [10].

There is increasing evidence for an immune response to cancer in humans, demonstrated in part by the identification of autoantibodies against a number of intracellular and surface antigens in patients with different tumor types [13–16]. Such autoantibodies could have diagnostic and prognostic utility.

With the speculation that ECPKA excretion might elicit the induction of serum autoantibodies and that the presence of such autoantibodies could serve as a cancer diagnostic, a novel enzyme immunoassay (EIA) that measures IgG autoantibody against ECPKA was developed [17]. This autoantibody was found to be elevated in patients with a wide range of active cancers in various stages of malignancies in different cell types, including bladder, breast, cervical, colon, esophageal, gastric,

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0925-4439/$ - see front matter. Published by Elsevier B.V.
doi:10.1016/j.bbadis.2006.04.001

liver, lung, ovarian, pancreatic, prostate, renal, renal cell, small bowel, rectal, adenocystic carcinomas, melanoma, sarcoma and thyoma, liposarcoma, and leiomyosarcoma [17].

The sera-presence of an autoantibody directed against ECPKA was highly correlated to cancer. High anti-ECPKA autoantibody titers (frequency = 90%, mean titer = 3.6) were found in cancer patients, whereas low or negative titers (frequency = 13%, mean titer = 1.0) were found in the control group. The ROC plot showed that autoantibody EIA exhibited 90% sensitivity, and 87% specificity, whereas the enzymatic assay (antigen determination method) exhibited 83% sensitivity and 80% specificity. These results show that the autoantibody detection method exhibits higher sensitivity and specificity than the antigen determination method [17].

3. It is an all-in-one assay that screens for a spectrum of serum biomarker autoantibodies

The known serum tumor markers might also produce autoantibodies, as was shown for ECPKA, and the autoantibody-based EIA developed for ECPKA could also be used to assay for these serum tumor marker autoantibodies, which led to assay for the known serum tumor markers using the ECPKA autoantibody EIA. The same serum samples were used for determination of both the autoantibody assay and the antigen kits. The results indicated that the single method of ECPKA autoantibody EIA is applicable for the detection of autoantibodies specific to each of 10 tumor markers [17]. The parallel results (ROC curves almost superimposable) obtained with the autoantibody EIA and antigen kit assays for some tumor markers, and the superior ROC curves obtained with autoantibody EIA compared to the antigen kit assays obtained for other tumor markers, support the autoantibody EIA method presented here as a universal screen for serum tumor markers.

4. Conclusions from these studies

(1) The data show a sensitive method for measuring IgG autoantibodies against a spectrum of serum tumor markers in a single assay; the method is easy to perform, reproducible, rapid, and inexpensive (for example, one kit instead of 10 kits) [17].
(2) The autoantibody EIA exhibits enhanced sensitivity and specificity for the tumor markers VEGF, CA125, AFP, and ECPKA, compared to those obtained with the antigen kits; for CA15-3, hCG, Her-2, CEA, and CA19-9 markers, the data obtained with the autoantibody EIA and the antigen kits are similar [17]. Results indicate that serum tumor markers may all produce autoantibodies and that the autoantibody EIA is a novel screening method for cancer detection.
(3) This new assay, an autoantibody detection method, could make it possible to distinguish between the increased levels of tumor markers caused by cancer and those caused by inflammation. Known cancer markers all depend on the measurement of cancer antigens, and an increase in such antigens can occur temporarily with inflammation, but such an increase might not increase autoantibodies.
(4) The results indicate the probable utility of this new autoantibody detection EIA as a cancer screening tool for cancer diagnosis without the false positives associated with conventional testing. It could thus provide a novel technology for cancer detection.

5. SEREX and cancer immunomics

The use of SEREX (serological analysis of recombinant tumor cDNA expression libraries) [18–23] led to the identification of a large group of autoantigens in cancer patients' sera. This emerging area of research, termed "cancer immunomics," allows a global analysis of the autoantibodies produced by neoplasms against their antigens. Hundreds of autoantigens have been cloned with recognition of antibodies in patients' sera; however, efforts to predict malignant disease based on autoimmunity to individual antigens have thus far been largely unsuccessful. Although in aggregate these studies strongly suggest that autoantibodies have potential as biomarkers, thus far they have not resulted in serological markers with definitive predictive ability for cancer in the clinical arena [24,25], and none have been selected for cancer diagnosis [24,25]. One important problem inherent to autoantibody-based methods for identifying tumor-related antigens is demonstrating their tumor relevance. Cited below are examples of studies showing such relevance.

6. Autoantibody signatures in prostate cancer

The use of PSA-based screening for prostate cancer has risen dramatically since its introduction in the late 1980s [26,27]. However, reliance on PSA for the detection of early prostate cancer is still unsatisfactory, especially because of a high rate of false positive results [2] as high as 80%.

This study [28] presents findings of new biomarkers: autoantibody signatures in prostate cancer. Using protein microarrays, autoantibodies produced by prostate tumors against tumor antigens were identified in patients with prostate cancer. Specifically, phage-protein microarrays were screened to identify phage-peptide clones that bind autoantibodies in serum samples from patients with prostate cancer but not in those from controls. The results were consistent across a range of clinical and pathological features, including PSA level, Gleason grade, stage, and presence or absence of PSA recurrence. It was concluded that autoantibodies against peptides derived from prostate cancer tissue could be used as the basis for improving a screening test for serum biomarkers for prostate cancer.

7. Autoantibodies to annexin XI-A in the diagnosis of breast cancer

Efforts to diagnose breast cancer based on autoantibodies to the hundreds of individual antigens that have been cloned have thus far been largely unsuccessful. Although the range of

possible serological tumor markers for breast cancer reported in the literature is broad [14,29], few have been incorporated into routine oncologic practice, and none is thought to be of value for the diagnosis of ductal carcinoma in situ (DCIS) of the breast.

Annexin XI is a member of the annexin superfamily of Ca^{2+} signal transduction proteins associated with cell growth and differentiation.

This study [30] reports on the identification of autoantigens commonly recognized by sera from patients with breast cancer. They selected 10 sera from patients with invasive ductal carcinoma (IDC) of the breast with high titer IgG autoantibodies for biopanning of a T7 phage breast cancer DNA display library.

However, autoantigens cloned by immunoscreening cDNA expression libraries by breast cancer patient sera are not necessarily related to breast cancer. A number of phage inserts cloned with sera from patients with IDC of the breast were significantly recognized by normal control sera and not by cancer patient sera. The significance of the presence of these autoantibodies in the non-cancer control sera is unknown, but it is clear that despite the origin of the cloning sera obtained from patients with breast cancer, these autoantigens are irrelevant to breast cancer and might be related to autoimmunity in degenerative brain diseases or to other causes.

In view of these findings, it is likely that probing this autoantigen microarray prospectively with sera from a large cohort of breast cancer patients could allow the identification of biomarkers with diagnostic significance and perhaps identification of discrete antigen phenotypes with clinical significance. The high prevalence of IgG autoantibodies in the sera of patients with DCIS and IDC of the breast suggests that they are potentially excellent candidates as biomarkers for the early diagnosis of breast cancer.

8. Serum osteopontin determination in lung cancer

Pleural mesothelioma is an asbestos-related cancer with a median survival of 8 to 12 months [31]. Patients with stage 1A disease, however, can survive for five or more years if the tumor is promptly resected. Unfortunately, it means that less than 5% of patients with pleural mesothelioma present with stage 1A disease. Therefore, a marker or series of biomarkers that can predict the development of mesothelioma or detect pleural mesothelioma in its early stages in populations with exposure to asbestos would be of considerable value. The authors undertook the present study [32] to test their hypothesis that osteopontin is a useful biomarker in pleural mesothelioma and, more specifically, to compare serum levels of osteopontin in a cohort of subjects with asbestos-related nonmalignant disease with preoperative levels in patients with surgically treated pleural mesothelioma.

An analysis of serum osteopontin levels comparing the receiver-operating-characteristic curve in the group exposed to asbestos with that of the group with mesothelioma had a sensitivity of 77.6% and a specificity of 85.5% at a cutoff value of 48.3 ng of osteopontin per milliliter. Subgroup analysis comparing patients with stage I mesothelioma with subjects with exposure to asbestos revealed a sensitivity of 84.6% and a specificity of 88.4% at a cutoff value of 62.4 ng of osteopontin per milliliter. The authors concluded that serum osteopontin levels can be used to distinguish persons with exposure to asbestos who do not have cancer from those with exposure to asbestos who have pleural mesothelioma [32].

It will be intriguing to question if autoantibody determination rather than antigen determination of serum osteopontin levels could improve the early diagnosis of this deadly disease.

9. Autoantibody against p53 protein in pancreatic cancer

In addition to molecular and immunohistochemical analysis, a serological analysis can be performed to identify p53 changes. Antibodies against p53 protein have been detected in the serum of patients with breast carcinoma [14], Burkitt's lymphoma [33], and lung carcinoma [16]. Several studies have shown that those antibodies are usually associated with the presence of a mutant p53 protein accumulated in tumor cells.

Specific markers for pancreatic or biliary cancers have been developed in the past few years. CA19-9 has a good sensitivity, but it is also increased in benign cholestasis. Mutations in the p53 gene are commonly reported in pancreatic cancer and can be detected by a serological analysis. This study [29] shows the presence of autoantibodies against p53 determined by EIA in patients with pancreatic cancer, biliary tract cancer, and benign biliary or pancreatic diseases as controls. It is concluded that the presence of p53 antibodies in the serum of patients with pancreatic and biliary diseases is specific for malignancy and independent of the presence of cholestatic disease.

10. The power and failure of traditional biomarkers

Protein markers, ideally detectable in serum samples, are most convenient for clinical routine. PSA or CEA are biomarkers routinely used in clinical practice to predict the presence of a tumor or therapeutic response. However, because PSA is not tumor-specific, serum levels can increase even during benign prostate diseases.

The "ideal" tumor marker defined for a specific cancer should have three defining characteristics. First, the marker should be expressed exclusively by a particular tumor. It should only be expressed in a specific cancer and not under physiologic conditions. Second, ease of specimen collection for the tumor marker assay is important, ideally being a serological sample. Assay cost could be adversely affected by more challenging types of specimen collection. Third, the tumor marker assay should be easy to perform, reproducible, rapid, and inexpensive. However, such an ideal tumor marker does not yet exist for cancer screening.

CEA is expressed in a variety of extra-intestinal tumors, such as lung, breast, ovarian, and bladder cancers [3]. CEA has the distinct advantage that serum levels can be determined accurately, reproducibly, and relatively inexpensively. This led many to believe that CEA could be used as a serological screening tool for early colorectal cancer (CRC) detection. Subsequent studies have demonstrated, however, that it

possesses neither the sensitivity nor the specificity to be used in this capacity [3]. It is least sensitive for stage I CRC.

Other tumor antigens that have been used as CRC markers include tumor-associated glycoprotein-72 (TAG-72), a high molecular weight mucin-like glycoprotein expressed in a variety of human cancers; carbohydrate antigen CA19-9, an oligosaccharide related to the Lewis A blood group substance; and lipid-associated sialic acid (LASA). As with CEA, these tumor markers show low sensitivity and specificity in CRC and have proven ineffective as screening and diagnostic tools.

Although PSA has affected prostate cancer detection positively, problems with specificity remain. One important contributing factor is the fact that PSA is organ specific and not cancer specific. Serum PSA level does not change only because of cancer, but also with inflammation, trauma, or benign proliferation [2]. There is considerable overlap in PSA levels among men with prostate cancer and those with benign disease.

The discovery of new molecular forms of PSA, such as free PSA (fPSA) and complex derivatives of PSA, offers the potential for improved diagnostic discrimination of prostate cancer from benign conditions [2]. Research showing the altered serum distribution of molecular derivatives of PSA in men with cancer and those with benign disease lends itself to novel methods of risk stratification.

The PSA revolution that has occurred over the past two decades has positively affected the detection and treatment of men with prostate cancer. Although methods to improve specificity have shown promise, meaningful interpretation has yet to be uniformly accepted within clinical practice. The identification of other molecular forms of PSA within serum has led to a new era in PSA markers. Although the discovery of various free forms of PSA has introduced the potential for improved specificity in detection, further evaluation is anticipated. The development of improved methods to detect and measure cPSA has the potential to replace PSA as a standard diagnostic test in cancer screening [2].

11. Conclusion and perspective

It is evident that a wide variety of tumor markers exists with the potential for clinical use in cancer diagnosis and for the determination of postoperative prognosis and response to treatment in cases of metastatic disease. Each tumor marker, however, has limitations, and none is ideal.

The identification of circulating tumor antigens or their related autoantibodies provides a means for early cancer diagnosis as well as a lead for therapy. A test based on the demonstration of autoantibodies to tumor antigens in sera of patients could be of great importance for early detection of cancer because of the prolonged time course of carcinogenesis and because a detectable level of antibodies against carcinogen stimulus could form well before the tumor phenotype arises.

This review highlights the development of a new biomarker that screens cancers of various cell types. Because autoantibodies for cancer antigens have never been carefully examined and because the current cancer biomarker detection methodologies that are based on tumor antigen measurement have failed to detect cancers, the autoantibody measurement against the new biomarker, ECPKA was developed.

The anti-ECPKA autoantibody, whose presence has been highly correlated to cancer [17], measures malignant transformation in all cells and is not specific to one type of cancer. Unlike tests such as CEA, which measures less well-defined antigens and whose serum levels tend to be inconsistent but elevated late in the disease [3], the anti-ECPKA autoantibody test measures the autoantibody of a well-defined cancer antigen, ECPKA, whose serum levels are specifically up-regulated in cancer patients' sera and are regulated by the intracellular levels of PKA-I [10].

Because an increase in PKA-I expression has been shown to occur at the very early phase of carcinogenesis, well before the tumor phenotype manifests [34], it is probable that the ECPKA-autoantibody detection in patients' sera could serve as an early diagnostic method for cancers of various cell types.

Most importantly, this new assay, the ECPKA autoantibody assay, could be used as a universal screening method to detect serum tumor markers. The detection of autoantibodies for a spectrum of serum tumor markers, demonstrated in an all-in-one assay [17], suggests that this new assay, the autoantibody screening method, might facilitate the accurate and early detection of cancer.

Whether ECPKA-autoantibody expression could be affected by any temporal physiological or pathological conditions other than cancer remains to be established. Ideally, biomarkers should fulfill several key requirements: they should be easy to measure using standardized and inexpensive methods, they should be expressed in accessible material (e.g., cells and body fluids), they should have a clearly defined cutoff value (which might differ between different patient strata), and they should have high predictive power (high sensitivity and specificity). The autoantibody-based EIA method presented here shows its utility as a routine diagnostic procedure to detect cancer of various cell types by measuring various serum tumor biomarkers in a single assay. Thus, the autoantibody biomarker-detecting EIA is better than antigen-determining EIA kits in saving time for diagnosis and costs imposed on patients for these diagnostic kits. This new assay, detection of autoantibodies against serum cancer biomarkers rather than measuring tumor antigens, offers a novel technology for cancer detection.

Acknowledgements

This research was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute (P.I., Y.S. Cho-Chung), Bethesda, MD.

References

[1] C.T. Garrett, S. Sell, Cellular Cancer Markers, Humana Press, Totowa, NJ, 1995.
[2] M.B. Gretzer, A.W. Partin, PSA markers in prostate cancer detection, Urol. Clin. North Am. 30 (2003) 677.
[3] N.P. Crawford, D.W. Colliver, S. Galandiuk, Tumor markers and colorectal cancer: utility in management, J. Surg. Oncol. 84 (2003) 239.
[4] K.L. Cheung, F.R. Robertson, Objective measurement of remission and

progression in metastatic breast cancer by the use of serum tumour markers, Minerva Chir. 58 (2003) 297.
[5] V. Trompetas, E. Panagopoulos, M. Priovolou-Papaevangelou, G. Ramantanis, Giant benign true cyst of the spleen with high serum level of CA 19-9, Eur. J. Gastroenterol. Hepatol. 14 (2002) 85.
[6] C. Anderiesz, M.A. Quinn, Screening for ovarian cancer, Med. J. Aust. 178 (2003) 655.
[7] S. Sell, Cancer Markers, Humana Press, Clifton, NJ, 1980.
[8] E.G. Krebs, J.A. Beavo, Phosphorylation–dephosphorylation of enzymes, Annu. Rev. Biochem. 48 (1979) 923.
[9] K.A. Burton, B. Treash-Osio, C.H. Muller, E.L. Dunphy, G.S. McKnight, Deletion of type IIalpha regulatory subunit delocalizes protein kinase A in mouse sperm without affecting motility or fertilization, J. Biol. Chem. 274 (1999) 24131.
[10] Y.S. Cho, Y.G. Park, Y.N. Lee, M.K. Kim, S. Bates, L. Tan, Y.S. Cho-Chung, Extracellular protein kinase A as a cancer biomarker: its expression by tumor cells and reversal by a myristate-lacking Calpha and RIIbeta subunit overexpression, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 835.
[11] M.E. Cvijic, T. Kita, W. Shih, R.S. DiPaola, K.V. Chin, Extracellular catalytic subunit activity of the cAMP-dependent protein kinase in prostate cancer, Clin. Cancer Res. 6 (2000) 2309.
[12] T. Kita, J. Goydos, E. Reitman, R. Ravatn, Y. Lin, W.C. Shih, Y. Kikuchi, K.V. Chin, Extracellular cAMP-dependent protein kinase (ECPKA) in melanoma, Cancer Lett. 208 (2004) 187.
[13] K. Ben Mahrez, I. Sorokine, D. Thierry, T. Kawasumi, S. Ishii, R. Salmon, M. Kohiyama, Circulating antibodies against c-*myc* oncogene product in sera of colorectal cancer patients, Int. J. Cancer 46 (1990) 35.
[14] L.V. Crawford, D.C. Pim, R.D. Bulbrook, Detection of antibodies against the cellular protein p53 in sera from patients with breast cancer, Int. J. Cancer 30 (1982) 403.
[15] R. Lubin, B. Schlichtholz, D. Bengoufa, G. Zalcman, J. Tredaniel, A. Hirsch, C.C. de Fromentel, C. Preudhomme, P. Fenaux, G. Fournier, Analysis of p53 antibodies in patients with various cancers define B-cell epitopes of human p53: distribution on primary structure and exposure on protein surface, Cancer Res. 53 (1993) 5872.
[16] S.F. Winter, J.D. Minna, B.E. Johnson, T. Takahashi, A.F. Gazdar, D.P. Carbone, Development of antibodies against p53 in lung cancer patients appears to be dependent on the type of p53 mutation, Cancer Res. 52 (1992) 4168.
[17] M. Nesterova, N. Johnson, C. Cheadle, Y.S. Cho-Chung, Autoantibody biomarker opens a new gateway for cancer diagnosis, Biochim. Biophys. Acta 1762 (2006) 398.
[18] M.J. Scanlan, I. Gout, C.M. Gordon, B. Williamson, E. Stockert, A.O. Gure, D. Jager, Y.T. Chen, A. Mackay, M.J. O'Hare, L.J. Old, Humoral immunity to human breast cancer: antigen definition and quantitative analysis of mRNA expression, Cancer Immun. 1 (2001) 4.
[19] S. Forti, M.J. Scanlan, A. Invernizzi, F. Castiglioni, S. Pupa, R. Agresti, R. Fontanelli, D. Morelli, L.J. Old, S.M. Pupa, S. Menard, Identification of breast cancer-restricted antigens by antibody screening of SKBR3 cDNA library using a preselected patient's serum, Breast Cancer Res. Treat. 73 (2002) 245.
[20] M.H. Hansen, B. Ostenstad, M. Sioud, Antigen-specific IgG antibodies in stage IV long-time survival breast cancer patients, Mol. Med. 7 (2001) 230.
[21] F. Le Naour, D.E. Misek, M.C. Krause, L. Deneux, T.J. Giordano, S. Scholl, S.M. Hanash, Proteomics-based identification of RS/DJ-1 as a novel circulating tumor antigen in breast cancer, Clin. Cancer Res. 7 (2001) 3328.
[22] U. Sahin, O. Tureci, H. Schmitt, B. Cochlovius, T. Johannes, R. Schmits, F. Stenner, G. Luo, I. Schobert, M. Pfreundschuh, Human neoplasms elicit multiple specific immune responses in the autologous host, Proc. Natl. Acad. Sci. U. S. A. 92 (1995) 11810.
[23] T. Boon, L.J. Old, Cancer tumor antigens, Curr. Opin. Immunol. 9 (1997) 681.
[24] P.W. Brandt-Rauf, M.R. Pincus, Molecular markers of carcinogenesis, Pharmacol. Ther. 77 (1998) 135.
[25] A. Horwich, G. Ross, Circulating tumor markers, in: M.H. Bronchud, M.A. Foot, W. Peters, M.O. Robinson (Eds.), Principles of Molecular Oncology, Humana Press, Totowa, NJ, 2000, pp. 111–124.
[26] J. Myrtle, L. Ivor, Measurement of PSA in serum by two immunometric method, in: W. Catalona, D. Coffey, J. Karr (Eds.), Clinical Aspects of Prostate Cancer: Assessment of New Diagnostic and Management Procedures, Elsevier, New York, 1989, pp. 161–171.
[27] W.J. Catalona, M.A. Hudson, P.T. Scardino, J.P. Richie, F.R. Ahmann, R. C. Flanigan, J.B. deKernion, T.L. Ratliff, L.R. Kavoussi, B.L. Dalkin, Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: receiver operating characteristic curves, J. Urol. 152 (1994) 2037.
[28] X. Wang, J. Yu, A. Sreekumar, S. Varambally, R. Shen, D. Giacherio, R. Mehra, J.E. Montie, K.J. Pienta, M.G. Sanda, P.W. Kantoff, M.A. Rubin, J. T. Wei, D. Ghosh, A.M. Chinnaiyan, Autoantibody signatures in prostate cancer, N. Engl. J. Med. 353 (2005) 1224.
[29] P. Laurent-Puig, R. Lubin, S. Semhoun-Ducloux, G. Pelletier, C. Fourre, M. Ducreux, M.J. Briantais, C. Buffet, T. Soussi, Antibodies against p53 protein in serum of patients with benign or malignant pancreatic and biliary diseases, Gut 36 (1995) 455.
[30] F. Fernández-Madrid, N. Tang, H. Alansari, J.L. Granda, L. Tait, K.C. Amirikia, M. Moroianu, X. Wang, R.L. Karvonen, Autoantibodies to Annexin XI-A and other autoantigens in the diagnosis of breast cancer, Cancer Res. 64 (2004) 5089.
[31] D. Martino, H.I. Pass, Integration of multimodality approaches in the management of malignant pleural mesothelioma, Clin. Lung Cancer 5 (2004) 290.
[32] H.I. Pass, D. Lott, F. Lonardo, M. Harbut, Z. Liu, N. Tang, M. Carbone, C. Webb, A. Wali, Asbestos exposure, pleural mesothelioma, and serum osteopontin levels, N. Engl. J Med. 353 (2005) 1564.
[33] C.C. de Fromentel, F. May-Levin, H. Mouriesse, J. Lemerle, K. Chandrasekaran, P. May, Presence of circulating antibodies against cellular protein p53 in a notable proportion of children with B-cell lymphoma, Int. J. Cancer 39 (1987) 185.
[34] M.V. Nesterova, Y.S. Cho-Chung, Antisense protein kinase A RIalpha inhibits 7,12-dimethylbenz(a)anthracene-induction of mammary cancer: blockade at the initial phase of carcinogenesis, Clin. Cancer Res. 10 (2004) 4568.