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• REVIEW •

Chromosomal aberrations related to metastasis of human solid tumors

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Abstract

The central role of sequential accumulation of genetic alterations during the development of cancer has been firmly established since the pioneering cytogenetic studies successfully defined recurrent chromosome changes in specific types of tumor. In the course of carcinogenesis, cells experience several genetic alterations that are associated with the transition from a preneoplastic lesion to an invasive tumor and finally to the metastatic state. Tumor progression is characterized by stepwise accumulation of genetic alterations. So does the dominant metastatic clone. Modern molecular genetic analyses have clarified that genomic changes accumulate during the development and progression of cancers. In comparison with the corresponding primary tumor, additional events of chromosomal aberrations (including gains or allelic losses) are frequently found in metastases, and the incidence of combined chromosomal alterations in the primary tumor, plus the occurrence of additional aberrations in the distant metastases, correlated significantly with decreased postmetastatic survival. The deletions at 3p, 4p, 6q, 8p, 10q, 11p, 11q, 12p, 13q, 16q, 17p, 18q, 21q, and 22q, as well as the over-representations at 1q, 8q, 9q, 14q and 15q, have been found to associate preferentially with the metastatic phenotype of human cancers. Among of them, the deletions on chromosomes 8p, 17p, 11p and 13p seem to be more significant, and more detail fine regions of them, including 8p11, 8p21-12, 8p22, 8p23, 17p13.3, 11p15.5, and 13q12-13 have been suggested harboring metastasis-suppressor genes. During the past decade, several human chromosomes have been functionally tested through the use of microcell-mediated chromosome transfer (MMCT), and metastasis-suppressor activities have been reported on chromosomes 1, 6, 7, 8, 10, 11, 12, 16, and 17. However, it is not actually known at what stage of the metastatic cascade these alterations have occurred. There is still controversial with the association between the chromosomal aberrations and the metastatic phenotype of cancer. As the progression of human genome project and the establishment of more and more new techniques, it is hopeful to make clear the genetic mechanisms involved in the tumor metastasis in a not very long future, and provide new clues to predicting and controlling the metastasis.

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INTRODUCTION

The central role of sequential accumulation of genetic alterations during the development of cancer has been firmly established since the pioneering cytogenetic studies successfully defined recurrent chromosome changes in specific types of tumor. In the course of carcinogenesis, cells experience several genetic alterations (including gains and deletions) that are associated with the transition from a preneoplastic lesion to an invasive tumor and finally to the metastatic state. High frequency of chromosomal deletions elicited as losses of heterozygosity (LOH) is a hallmark of genomic instability in cancer. Functional losses of tumor suppressor genes caused by LOH at defined regions during clonal selection for growth advantage define the minimally lost regions as their likely locations on chromosomes. LOH is elicited at the molecular or cytogenetic level as a deletion, a gene conversion, single or double homologous and nonhomologous mitotic recombinations, a translocation, chromosome breakage and loss, chromosomal fusion or telomeric end-to-end fusions, or whole chromosome loss with or without accompanying duplication of the retained chromosome. Because of the high level of specificity, LOH has recently become invaluable as a marker for diagnosis and prognosis of cancer[1].

Many new molecular cytogenetic techniques, including various kinds of fluorescent in situ hybridization (FISH), comparative genomic hybridization (CGH), allelic imbalance (AI) and genotyping analyses, single nucleotide polymorphism (SNP) analysis, etc., have been established in recent years. These new techniques allow positional identification of gains and losses of DNA sequences in the entire tumor genome. These analytic approaches, particularly CGH and AI analysis, have already been applied over a wide range of tumor specimens, cell lines, and archival materials to define chromosomal imbalances. Molecular genetic analyses with these new strategies have clarified that genomic changes accumulate during the development and progression of cancers. A considerable amount of genetic alterations on solid tumors has been accumulated during the past few years.

Tumor progression is characterized by stepwise accumulation of genetic alterations. The dominant metastatic clone is also characterized by an accumulation of genetic alterations, but it is not actually known at what stage of the metastatic cascade these alterations have occurred. In comparison with the corresponding primary tumor, additional events of chromosomal aberrations (including gains or allelic losses) are frequently found in metastases and the incidence of combined chromosomal alterations in the primary tumor, plus the occurrence of additional aberrations in the distant metastases, correlated significantly with decreased postmetastatic survival. It is hypothesized that the occurrence of additional genetic aberrations is either involved in termination of dormancy of micrometastatic tumor cells at distant organ sites or acquired during further progression of metastases. However, only a few indications as to which genetic alterations among the multitude of changes might be

preferentially associated with the metastatic phenotype[2-8].

During the past decade, several human chromosomes have been functionally tested through the use of microcell-mediated chromosome transfer (MMCT), and metastasis-suppressor activities have been reported on chromosomes 1, 6, 7, 8, 10, 11, 12, 16, and 17. Such functional studies, combined with positional and expression-based gene cloning techniques, have enabled the identification of KAI1, KISS-1, MKK4/SEK1, and BRMS1 as metastasis-suppressor genes[9]. In this paper, we will review the chromosomal aberrations associated with the metastatic phenotype of solid tumor.

CHROMOSOME 8

Alterations of human chromosome 8p have been commonly detected in many tumor types[10-12]. Some studies have shown that loss of 8p is associated with the advance of tumors, and plays an important role in the tumor progression of many tumors including colorectal[13], bladder[14,15], breast[10] and liver cancers[16]. Recently, some studies have also shown that loss of 8p may be associated with the metastasis of laryngeal carcinoma[17], bladder cancer[18], renal cell carcinoma[19], colorectal carcinoma[20], lung cancer[21], mantle cell lymphoma (MCL)[22], and the poor prognosis of colorectal cancer patients [23]. Bockmuhl *et al* found that 8p23 allelic loss was an independent prognostic marker for disease-free interval, and was associated with poor prognosis in head and neck squamous cell carcinoma and could be useful in refining diagnosis of these tumors[24]. So, 8p might harbor one or more tumor suppressor genes that are important in the progression,especially in the metastasis of cancers, which was confirmed by irradiated MMCT technique[25, 26].

The presence of at least three tumor suppressor or metastasis suppressor genes loci on 8p (8p21, 8p22, and 8p23) that may be cooperative events has been suggested in HCC and ovarian cancer[12,27]. Several candidate tumor suppressor genes have been mapped to 8p including DLC-1(8p21.3-22)[28], FEZ1 gene (8p22)[29] and liver-related putative tumor suppressor (LTPS) gene (8p23)[30]. However, alterations of these genes may occur as an early event in the development of cancer, and their association with the metastasis is not confirmed[31]. Oba *et al*. found two putative tumor suppressor genes on chromosome 8p might play different roles, deletions on 8p22-p21.3 play an important role in tumor differentiation, while an 8p21.1-p21.2 deletion plays a role in the progression and metastasis of prostate cancer[32]. Allelic loss at 8p22 was associated with higher tumor grade, and no tumor that retained heterozygosity for markers at 8p22 had metastasized to distant organs, whereas a substantial portion of tumors that lost alleles in that region had done so. These imply that loss or inactivation of tumor-suppressing activity encoded on 8p contributes to malignancy and to the metastatic potential of bladder cancers[18]. Arai' s results suggest that putative tumor suppressor genes, which may be involved in the metastatic process of colorectal cancer, are located on chromosomes 8p21-22. Allelic losses in these regions are possible risk factors for early lymph node metastasis[33]. Nihei *et al*[26] used a functional positional cloning strategy to define the region harboring the metastasis suppressor gene in 8p21-12, and localized it to a 60-kb cloned region.

Chromosome 8p deletion is also one of the recurrent chromosomal aberrations in HCC that are common detected either by CGH or by microsatellite analysis[34-36]. In our previous study, we compared the differences of genomic alterations between matched primary and metastatic HCC by CGH, and found that the majority of chromosomal aberrations in both primary and metastatic lesions of HCC were consistent with those in previous reports. The most interesting finding in this study is the deletion of 8p which was detected in 8 metastatic lesions but only in 3 corresponding primary HCC, 5 cases of HCC acquired deletion on 8p as they progressed to metastatic stage, although some differences of genomic alterations between primary and its corresponding metastatic lesion were also found. These suggest that 8p may harbor one or more tumor suppressor genes that are important in the HCC progression especially in the tumor metastasis[37]. This result was confirmed in the metastatic model of HCC and its cell line[38]. Recently, in another genome-wide microsatellite analysis, deletion on chromosome 8p was further proved to be related to progression and metastasis of HCC, and 8p23.3, 8p11.2 were two likely regions harboring metastasis-related genes[39].

CHROMOSOME 17

The frequency of allele loss on 17p has been correlated significantly with prognostic features such as the number and size of liver secondaries, the depth of invasion, metastasis to the lymph nodes, and venous invasion of cancers[40-42]. Multiple regression analysis identified the numerical aberrations of chromosome 17 as independent significant determinants of lymph node metastasis. A similar result is also found in HCC. LOH on 17p13 of HCC correlates with the stage, portal invasion, intrahepatic metastasis, and nuclear morphometry of cancer cells. These suggest that the LOH on 17p13 is closely connected to the progression of HCC[43].

p53 is an important TSG on 17p13.1, and its aberration has been linked to the development and progress of human cancers including HCC[44]. However, in addition to 17p13.1, many studies showed that the frequently deleted region was 17p13.3[45-49]. The minimum region of LOH on chromosome 17p13.3 in HCC has been defined within the region between D17S643 and D17S1574. Moreover, D17S926 in the minimum region of LOH has the highest frequency of LOH, and its sequencing analysis has been accomplished. In this region, 6 novel genes have been characterized. One of them is designated HCC suppressor 1 (HCCS1)[45]. Our recent study showed that the AI ratio of chromosome 17p was as high as 74-87 % in primary lesions, and 73-87 % in metastasis lesions of HCC. Moreover, high level of AI was also identified in 17p11.2-12 (74-87 %). A 20cM segment within 17p11.2-13.1 was found related to metastasis phenotype, with the highest increased-grade AI (28-44 %) in metastatic lesions[39]. All these suggested that in addition to the p53 gene at 17p13.1, an as yet unidentified TSG(s) residing at 17p13.3 might play a role in development, progression and metastasis of HCC.

Discontinuous portions of human chromosome 17 (D17S952-D17S805, D17S930-D17S797, and D17S944-qter) that together suppress the metastatic ability of AT6.1 Dunning rat prostatic cancer cells when introduced via MMCT have been identified[50,51]. PCR and Southern blot analyses demonstrated that three of the four markers on 17p13, including HIC1 and TP53, and 12 of the 13 markers in 17q21-23, including BRCA1 and the metastasis-suppressor gene NME1 (nm23), were not retained in this region[50]. AT6.1 microcell hybrids containing this portion of chromosome 17 were tested in vivo in spontaneous metastasis assays. Spontaneous metastasis is measured by the ability of tumor cells to form a locally growing tumor at the site of injection and disseminate to and grow at secondary sites thereafter. At the experimental end point, the number of overt surface metastases observed in the lungs from mice with AT6.1-17 tumors was reduced 15- to 30-fold compared with lungs from mice bearing parental AT6.1 tumors[50]. This suppression could be due to the inhibition of any step within the metastatic cascade. A series

of in vivo experiments were conducted, and no evidence was found to suggest that there is a decrease in the number and/or viability of tumor cells colonizing the lung[51]. Development of overt metastases was associated with loss of the metastasis-suppressor region of chromosome 17[10,52,53].

CHROMOSOME 1

Frequent allelic losses on the short arm of chromosome 1 have been observed in a wide variety of human tumors. Allelic loss at 1p22-p31 was correlated with lymph node metastasis. Alterations of one or more tumor suppressor genes at 1p22-p31 may play a role at late stages of carcinogenesis, especially with regard to local progression and lymph node metastasis[54]. There may be at least two distinct tumor suppressor genes inactivated by allelic deletion on 1p36.1 and 1p36.3, respectively[55].

Amplification of 1q was also commonly detected in esophageal carcinoma, breast cancer, and colon cancer[56-58]. Gain of 1q might be one of the early genetic changes in HCC since it was one of the most commonly detected alterations in HCC[59, 60]. In most cases, the gain of 1q involved whole long arm. However, in our previous study, high copy number amplification on 1q was detected in 4 primary and 6 metastatic HCC with a minimum amplification region at 1q12-q22. Most interestingly, in two cases amplification of 1q12-q22 was only detected in metastatic HCC. This imply that overexpression of an oncogene(s) at 1q12-q22 confers a selective advantage in HCC. High copy number amplification of 1q12-22 may only occur in late stage of HCC and provide more advantage of growth selection. This suggests that 1q might harbor one or more oncogenes related to the development or progression of many cancers. Moreover, this provides us a candidate minimum amplification region on 1q12-q22 for further study to clone genes related to the development and progression of HCC[37]. A correlation of metastatic events with an increase in the copy number of genes located at 1q, in particular at 1q21-q23 is also found in renal clear cell carcinomas[61]. And more, an insertion of chromosome 13 material in the short arm of chromosome 1 has been only observed in micrometastatic cells[62].

CHROMOSOME 6

Highly frequent loss of 6q is found in many kinds of solid tumors, and is considered later events associated with tumor progression, and is thought to confer metastatic potential to the carcinomas (such as in biliary tract, etc.)[63]. Yoshida *et al*. introduced an intact chromosome 6 into the highly metastatic C8161 human melanoma cells by MMCT. Parental cells formed tumors in every mouse given an intradermal injection of 1×10^6 cells, and more than 90 % of the mice developed regional lymph node and lung metastases. In contrast, chromosome 6-C8161 hybrids (neo6/C8161) were still tumorigenic, but completely suppressed for metastasis. Intravenous injection of neo6/C8161 cells also did not produce metastases. Introduction of a version of chromosome 6 with deletions on the long arm allowed refinement of the metastasis-suppressor locus to a 40-megabase (Mb) region represented by chromosomal bands 6q16.3-q23. The neo6/C8161 cells were still locally invasive, and cells were even detected in efferent vessels. This finding implied that the step(s) in the metastatic cascade inhibited by introduction of chromosome 6 occurred subsequent to intravasation[9,64-71]. Shirasaki *et al*[72] found that inactivation of a tumor suppressor gene(s) mapping to 6q16.3-q23 by deletion or mutation coupled with LOH may lead to the down-regulation of a putative metastasis suppressor gene, KiSS1.

CHROMOSOME 10

LOH on chromosome 10q is found associated with tumour progression in SCC, SCLC, and prostate cancer. It may become a useful genetic marker in the assessment of the malignant potential and a potential genetic discriminator between progressors and nonprogressors after radical surgery of these tumour types[73,74]. Deletions on chromosome 10q25-q26 is responsible for the metastatic phenotype of squamous cell carcinomas in head and neck[75], and colorectal carcinomas[76], which may play a particular pathogenetic role in the metastatic process. One gene, LAPSER1 [an LZTS1(or FEZ1)-related gene] maps within a subregion of human chromosome 10q24.3 that has been reported to be deleted in various cancers, including prostate tumors, as frequently as the neighboring PTEN locus. This gene is involved in the regulation of cell growth, loss of its function may contribute to the development of cancer[77].

A telomerase repressor gene may be located on 10p15.1 by deletion mapping using MMCT, radiated microcell fusion (RMF), FISH and STS analysis. 10p15.1 harbors a gene involved in repression of telomerase RNA component in human somatic cells and each putative repressormay act independently [78].

CHROMOSOME 11

A strong relationship between LOH at chromosome 11q23.3 and the presence of extensive tumor plugs in lymphvascular spaces (LVS) has been demonstrated, which suggests that genes at this locus may regulate vasculoinvasion. Patients with LOH at 11q23.3 are significantly more likely to have disease recurrence than patients without LOH at 11q23.3. Although unlikely to have an impact early in carcinogenesis, tumor-suppressor genes located in the region of 11q23.3 appear to be important in tumor progression, facilitating lymphvascular space invasion and, by inference, spread to lymph nodes in squamous cell carcinoma of the cervix[79] and melanoma[80]. Deletion on 11q22-qter, together with the gains of 8q23-qter and 20q was observed in tumors metastatic to the lymph nodes. Gains of 8q23-qter and 20q and loss of 11q22-qter allow the prediction of lymph node metastasis[81]. LOH at 11q13.1-5, the region around the MEN1 locus, may be valuable in predicting the invasiveness of pituitary adenomas[82]. However, Pairwise found metastasizing tumors are characterized by overrepresentations on chromosomes 11q13 and 22q, and deletions on 18q[83].

The centromeric part of chromosome segment 11p15.5 contains a region of frequent allele loss in many adult solid malignancies. This region, called LOH11A, is lost in 75 % of lung cancers and is thought to contain a gene that may function as a metastasis suppressor. Genetic complementation studies have shown suppression of the malignant phenotype including reduction of metastasis formation. Bepler *et al*. constructed a high-resolution physical map and contig over 1.4 Mb that includes the beta-hemoglobin gene cluster and the gene for the large subunit of ribonucleotide reductase (RRM1). Through sequencing and computerized analysis, we determined that this region contains an unusually large number of transposable elements, which suggests that double-stranded DNA breaks occur frequently here. Twenty-two putative genes were identified. Because of its location at the site of maximal allele loss in the 650-kb LOH11A region and previous functional studies, RRM1 is the most likely candidate gene with metastasis suppressor function. The malignant phenotype results from a relative loss of function rather than a complete loss[84]. Two distinct tumor suppressor loci on chromosome 11p15, one is between D11S1318 and D11S4088 (approximately 500 kb)

within 11p15.5, a second, critical region of LOH spans the markers D11S1338-D11S1323 (approximately 336 kb) at 11p15.5-p15.4, may contribute to tumor progression and metastasis in breast cancer and lung cancer[85,86]. The human SRBC gene (hSRBC), a candidate tumor suppressor gene, is mapped to chromosome region 11p15.5-p15.4, close to marker D11S1323, at which frequent LOH has been observed in sporadic breast, lung, ovarian, and other types of adult cancers as well as childhood tumors[87]. Introduction of human chromosome 11 by MMCT could suppress MDA-MB-435 breast carcinoma cell metastasis[88]. One important metastasis-suppressor gene, KAI1, maps to 11p11.2-p13.

CHROMOSOME 13

LOH of 13q is a common event in oncogenesis and/or progression of oral SCC and larynx carcinoma, and significant correlation between LOH of 13q14.3 and lymph node metastasis is found. These suggest the existence of a new suppressor gene near D13S273-D13S176 loci which may play a role in these events[18,89]. Allelotype analysis of whole chromosomes showed that allelic loss at 13q12-13 of the primary ESC was closely associated with lymph node metastasis, and unidentified tumor suppressor gene(s) in this region might be involved[90]. The high LOH rate for different microsatellite markers in and around the putative TSG locus C13 on chromosome 13q13 has been found[91]. However, Hyytinen et al. found that gain of the 13q12-q13 chromosomal region as well as losses of 4, 6q24-qter, 20p and 21q were associated with androgen independence and tumorigenicity with additional changes correlating with metastasis[92].

CHROMOSOME 14

Significantly more LOH events at markers D14S62 and D14S51 in primary breast cancers from patients with lymph node-negative disease than these with lymph node-positive disease were found, suggesting the presence of a gene in this region that affects metastatic potential. Analysis of small interstitial or terminal deletions in the tumors of six especially informative patients with lymph node-negative disease places the putative metastasis-related gene in a 1490-kilobase region near D14S62. LOH in the D14S62 region may impede the process of metastasis. Therefore, the D14S62 region LOH profile may have prognostic implications, and the isolation of the metastasis-related gene(s) in this region may lead to better diagnosis and treatment of breast cancer[93]. This unusual observation suggests that, whereas the LOH of this region promotes primary breast cancer formation, some gene(s) mapping to this 1.6-Mb region is rate-limiting for breast cancer metastasis. Thus, if primary breast cancers delete this region, their ability to metastasize decreases. To identify this gene(s), Martin *et al*[94] physically mapped this area of chromosome 14q, confirmed the position of two known genes and 13 other expressed sequence tags into this 1.6-Mb region. One of these, the metastasis-associated 1 (MTA1) gene, previously identified as a metastasis-promoting gene, mapped to the center of our 1.6-Mb target region. Thus, MTA1 represents a strong candidate for this breast cancer metastasis-promoting gene.

CHROMOSOME 16

Genomic aberration at the chromosome 16q arm is one of the most consistent abnormalities observed by LOH and CGH analyses in human prostate cancer, suggesting that there are tumor suppressor or metastasis suppressor genes encoded by this chromosomal region. When the MMCT hybrid cells containing whole human chromosome 16 were injected, the number of metastatic lesions in the lung was significantly reduced as much as 99 % on average. Therefore, chromosome 16 has a strong activity to suppress the metastatic ability of AT6.1 cells while it did not affect the tumorigenesis and tumor growth rate. A PCR analysis of various microcell hybrid clones with sequence-tagged site markers indicates that the metastasis suppressor activity is located in the q24.2 region of chromosome 16. These suggest that there is a metastasis suppressor gene in this region that may play an important role in the progression of prostate cancer[95]. Deletion of chromosome 16q23-24 appears in a high frequency in metastases of prostate cancer. The strong correlations suggest that they may be important risk factors, contributing to the metastatic potential of the tumor[96-98]. The presence of putative tumor-suppressor genes on chromosome 16q23.2-24.1 has been suggested by LOH analysis in several cancer types. The candidate gene WWOX/FOR has been mapped within this region[99-101].

CHROMOSOME 18

Deletion on 18p is shown as one of the most frequent losses in metastasizing tumors in primary larynx tumor[102]. Two distinct minimum regions of AI on 18q have been identified. The first region is between the genetic markers D18S1119 and D18S64. The second region lies more distal on the long arm of the chromosome and is between the genetic markers D18S848 and D18S58. Significantly higher AI was found in the metastatic samples, which is consistent with 18q losses occurring late in tumor progression[103]. Detailed deletion mapping in these tumors identified a distinct commonly deleted region within a 5-cM interval in 18q21.1. The primary tumors had either no detectable abnormality of chromosome 18 or the region involving LOH was limited while the metastatic foci showed more frequent and extended allelic losses on this chromosome. These suggest that inactivation of one or more putative tumor suppressor genes on 18q21 other than DCC and DPC4 plays an important role in the progression of human prostate cancer[104]. Loss of 18q in metastatic and locally recurrent tumors, but not in primary tumors from the same patients, suggests that a tumor suppressor gene in this region may be important in the progression of breast cancer, squamous cell carcinoma, etc.[7,105,106].

OTHERS

In addition, losse of 9p and gains of 17q and Xq are other genomic changes which frequently occurred in metastases but not in the corresponding primary tumor[19].

The deletions at 3p12-p14, 3p21, 4p15-p16, 6q24-qter, 8p22-p23, 10q21-qter and 21q22, as well as the over-representations at 1q21-q25, 8q, 9q34, 14q12 and 15q12-q15, occurred significantly more often in the metastatic tumour group[107]. Areas of deletion predominantly or completely common to the colorectal and the metastatic tumour were detected on chromosomes 5q, 8p, 17p, 18q, and 22q. Preferential loss in metastatic tumours was observed on chromosomal arm 3p[108]. Chu *et al*[109] compared the genetic abnormalities specifically associated with varying metastatic potential of prostate cancer cell lines by CGH, and found that PC3M-LN4, the derivative line that produced significantly larger metastatic tumors in the lymph nodes and had higher incidences of distant metastases, had a specific gain of 1q21-q22 and losses of 10q23-qter and 18q12-q21. LNCaP-LN3, a derivative line that had a significantly higher incidence of

lymph node metastases and produced significantly larger metastatic tumors in the lymph nodes, had specific losses of 16q23-qter and 21q.

A strong association between 12p12-13 LOH and distant metastasis has been found, which raises the possibility that mutational inactivation of a gene at 12p12-13, possibly p27/kip1, plays a pivotal role in the development of metastatic disease[110, 111].

LOH of 19q13 was associated with overall survival in local-regional International Neuroblastoma Staging System stages 1, 2, and 3 patients and was specifically present in tumors at the site of recurrence[112].

The gain of chromosome 20 may be available as a genetic marker for the diagnosis or prediction of liver metastasis[113,114].

The Xq25 region harbors a putative tumor suppressor gene whose inactivation in breast cancer is associated with tumor progression and metastasis. LOH at this region, therefore, potentially could be used as a prognostic marker for disease development[115].

QUESTIONS AND PROSPECTS

There is still controversial with the association between the chromosomal aberrations and the metastatic phenotype of cancer. Some reports showed the frequencies of the most common aberrations were relatively similar in primary tumors and metastases, but no aberrations specific to metastases were detected[116]. And more, among of the chromosomes mentioned above, which one plays the most important role in the metastatic process. Based on the published data and the author' s experience, chromosomes 8 and 17 should be paid more attention to. To date, combined analyses of the different aberrations of various chromosomal regions would be much more valuable in predicting the metastatic potential and prognosis of human solid tumors[8]. As the progression of human genome project and the establishment of more and more new techniques, it is hopeful that the genetic mechanisms involved in the tumor metastasis could be made clear in a not very long future, and provide new clues to predicting and controlling the metastasis.

REFERENCES

1 **Thiagalingam S**, Foy RL, Cheng KH,Lee HJ, Thiagalingam A, Ponte JF. Loss of heterozygosity as a predictor to map tumor suppressor genes in cancer: molecular basis of its occurrence. *Curr Opin Oncol* 2002;**14**:65-72

2 **Bockmuhl U**, Petersen S, Schmidt S, Wolf G, Jahnke V, Dietel M, Petersen I. Patterns of chromosomal alterations in metastasizing and nonmetastasizing primary head and neck carcinomas. *Cancer Res* 1997;**57**: 5213-5216

3 **Schwendel A**, Langerck H, Reichel M, Schrock E, Ried T, Dietel M, Peteren I. Primary small-cell lung carcinomas and their metastases are characterized by a recurrent pattern of genetic alterations. *Int J Cancer* 1997; **74**: 86-93

4 **Nishizaki T**, Devries S, Chew K, Goodson IIIWK, Ljung BM, Thor A, Waldman FM. Genetic alterations in primary breast cancers and their metastases: direct comparison using modified comparative genomic hybridization. *Genes Chromosome Cancer* 1997; **19**: 267-272

5 **Cobaleda C**, Perez-Losada J, Sanchez-Garcia I. Chromosomal abnormalities and tumor development: from genes to therapeutic mechanisms. *Bio Essays* 1998;**20**: 922-930

6 **Adeyinka A**, Mertens F, Idvall I, Bondeson L, Ingvar C, Mitelman F, Pandis N. Different patterns of chromosomal imbalances in metastasising and non-metastasising primary breast carcinomas. *Int J Cancer* 1999;**84**:370-375

7 **Hampl M**, Hampl JA, Reiss G, Schackert G, Saeger HD, Schackert HK. Loss of heterozygosity accumulation in primary breast carcinomas and additionally in corresponding distant metastases is associated with poor outcome. *Clin Cancer Res* 1999;**5**:1417-1425

8 **Choi SW**, Choi JR, Chung YJ, Kim KM, Rhyu MG. Prognostic implications of microsatellite genotypes in gastric carcinoma. *Int J Cancer* 2000;**89**:378-383

9 **Yoshida BA**, Sokoloff MM, Welch DR, Rinker-Schaeffer CW. Metastasis-Suppressor Genes: a Review and Perspective on an Emerging Field. *J Natl Cancer Inst* 2000; **92**:1717-1730

10 **Yokota T**, Yoshimoto M, Akiyama F, Sakamoto G, Kasumi F, Nakamura Y, Emi M. Localization of a tumor suppressor gene associated with the progression of human breast carcinoma within a 1-cM interval of 8p22-p23.1. *Cancer* 1999; **85**:447-452

11 **Perinchery G**, Bukurov N, Nakajima K, Chang J, Hooda M, Oh BR, Dahiya R. Loss of two new loci on chromosome 8 (8p23 and 8q12-13) in human prostate cancer. *Int J Oncol* 1999;**14**:495-500

12 **Wright K**, Wilson PJ, Kerr J, Do K, Hurst T, Khoo SK, Ward B, Chenevix-Trench G. Frequent loss of heterozygosity and three critical regions on the short arm of chromosome 8 in ovarian adenocarcinomas. *Oncogene* 1998;**17**:1185-1188

13 **Takanishi DM Jr**, Kim SY, Kelemen PR, Yaremko ML, Kim AH, Ramesar JE, Horrigan SK, Montag A, Michelassi F, Westbrook CA. Chromosome 8 Losses in Colorectal Carcinoma: Localization and Correlation With Invasive Disease. *Mol Diagn* 1997;**2**:3-10

14 **Muscheck M**, Sukosd F, Pesti T, Kovacs G. High density deletion mapping of bladder cancer localizes the putative tumor suppressor gene between loci D8S504 and D8S264 at chromosome 8p23.3. *Lab Invest* 2000;**80**:1089-1093

15 **Wagner U**, Bubendorf L, Gasser TC, Moch H, Gorog JP, Richter J, Mihatsch MJ, Waldman FM, Sauter G. Chromosome 8p deletions are associated with invasive tumor growth in urinary bladder cancer. *Am J Pathol* 1997; **151**: 753-759

16 **Emi M**, Fujiwara Y, Ohata H, Tsuda H, Hirohashi S, Koike M, Miyaki M, Monden M, Nakamura Y. Allelic loss at chromosome band 8p21.3-p22 is associated with progression of hepatocellular carcinoma. *Genes Chromosomes Cancer* 1993;**7**:152-157

17 **Kujawski M**, Sarlomo-Rikala M, Gabriel A, Szyfter K, Knuutila S. Recurrent DNA copy number losses associated with metastasis of larynx carcinoma. *Genes Chromosomes Cancer* 1999;**26**:253-257

18 **Ohgaki K**, Iida A, Ogawa O, Kubota Y, Akimoto M, Emi M. Localization of tumor suppressor gene associated with distant metastasis of urinary bladder cancer to a 1-Mb interval on 8p22. *Genes Chromosomes Cancer* 1999;**25**:1-5

19 **Bissig H**, Richter J, Desper R, Meier V, Schraml P, Schaffer AA, Sauter G, Mihatsch MJ, Moch H. Evaluation of the clonal relationship between primary and metastatic renal cell carcinoma by comparative genomic hybridization. *Am J Pathol* 1999;**155**:267-274

20 **Parada LA**, Maranon A, Hallen M, Tranberg KG, Stenram U, Bardi G, Johansson B. Cytogenetic analyses of secondary liver tumors reveal significant differences in genomic imbalances between primary and metastatic colon carcinomas. *Clin Exp Metastasis* 1999;**17**:471-479

21 **Petersen S**, Aninat-Meyer M, Schluns K, Gellert K, Dietel M, Petersen I. Chromosomal alterations in the clonal evolution to the metastatic stage of squamous cell carcinomas of the lung. *Br J Cancer* 2000;**82**:65-73

22 **Martinez-Climent JA**, Vizcarra E, Sanchez D, Blesa D, Marugan I, Benet I, Sole F, Rubio-Moscardo F, Terol MJ, Climent J, Sarsotti E, Tormo M, Andreu E, Salido M, Ruiz MA, Prosper F, Siebert R, Dyer MJ, Garcia-Conde J. Loss of a novel tumor suppressor gene locus at chromosome 8p is associated with leukemic mantle cell lymphoma. *Blood*

2001;**98**:3479-3482
23 **Halling KC**, French AJ, McDonnell SK, Burgart LJ, Schaid DJ, Peterson BJ, Moon-Tasson L, Mahoney MR, Sargent DJ, O'Connell MJ, Witzig TE, Farr GH Jr, Goldberg RM, Thibodeau SN. Microsatellite Instability and 8p Allelic Imbalance in Stage B2 and C Colorectal Cancers. *J Natl Cancer Inst* 1999;**91**:1295-1303
24 **Bockmuhl U**, Ishwad CS, Ferrell RE, Gollin SM. Association of 8p23 deletions with poor survival in head and neck cancer. *Otolaryngol Head Neck Surg* 2001;**124**:451-455
25 **Nihei N**, Kouprina N, Larionov V, Oshima J, Martin GM, Ichikawa T, Barrett JC. Mapping of metastasis suppressor gene(s) for rat prostate cancer on the short arm of human chromosome 8 by irradiated microcell-mediated chromosome transfer. *Genes Chromosomes Cancer* 1996;**17**:260-268
26 **Nihei N**, Kouprina N, Larionov V, Oshima J, Martin JM, Ichikawa T, Barrett JC. Functional evidence for a metastasis suppressor gene for rat prostate cancer within a 60-kilobase region on human chromosome 8p21-p12. *Cancer Res* 2002; **62**:367-370
27 **Pineau P**, Nagai H, Prigent S, Wei Y, Gyapay G, Weissenbach J, Tiollais P, Buendia MA, Dejean A. Identification of three distinct regions of allelic deletions on the short arm of chromosome 8 in hepatocellular carcinoma. *Oncogene* 1999;**18**:3127-3134
28 **Yuan BZ**, Miller MJ, Keck CL, Zimonjic DB, Thorgeirsson SS, Popescu NC. Cloning, characterization, and chromosomal localization of a gene frequently deleted in human liver cancer (DLC-1) homologous to rat RhoGAP. *Cancer Res* 1998;**58**:2196-2199
29 **Ishii H**, Baffa R, Numata SI, Murakumo Y, Rattan S, Inoue H, Mori M, Fidanza V, Alder H, Croce CM. The FEZ1 gene at chromosome 8p22 encodes a leucine-zipper protein, and its expression is altered in multiple human tumors. *Proc Natl Acad Sci USA* 1999;**96**: 3928-3933
30 **Liao C**, Zhao MJ, Song H, Uchida K, Yokoyama KK, Li TP. Identification of the gene fro a novel liver-related putative tumor suppressor at a high-frequency loss of heterozygosity region of chromosome 8p23 in human hepatocellular carcinoma. *Hepatology* 2000;**32**:721-727
31 **Park WS**, Lee JH, Park JY, Jeong SW, Shin MS, Kim HS, Lee SK, Lee SN, Lee SH, Park CG, Yoo NJ, Lee JY. Genetic analysis of the liver putative tumor suppressor (LPTS) gene in hepatocellular carcinomas. *Cancer Lett* 2002;**178**:199-207
32 **Oba K**, Matsuyama H, Yoshihiro S, Kishi F, Takahashi M, Tsukamoto M, Kinjo M, Sagiyama K, Naito K. Two putative tumor suppressor genes on chromosome arm 8p may play different roles in prostate cancer. *Cancer Genet Cytogenet* 2001;**124**:20-26
33 **Arai T**, Akiyama Y, Yamamura A, Hosoi T, Shibata T, Saitoh K, Okabe S, Yuasa Y. Allelotype analysis of early colorectal cancers with lymph node metastasis. *Int J Cancer* 1998;**79**:418-423
34 **Guan XY**, Fang Y, Sham JS, Kwong DL, Zhang Y, Liang Q, Li H, Zhou H, Trent JM. Recurrent chromosome alterations in hepatocellular carcinoma detected by comparative genomic hybridization. *Genes Chromosomes Cancer* 2000; **29**:110-116
35 **Li SP**, Wang HY, Li JQ, Zhang CQ, Feng QS, Huang P, Yu XJ, Huang LX, Liang QW, Zeng YX. Genome-wide analyses on loss of heterozygosity in hepatocellular carcinoma in Southern China. *J Hepatol* 2001; **34**:840-849
36 **Wang G**, Zhao Y, Liu X, Wang L, Wu C, Zhang W, Liu W, Zhang P, Cong W, Zhu Y, Zhang L, Chen S, Wan D, Zhao X, Huang W, Gu J. Allelic loss and gain, but not genomic instability, as the major somatic mutation in primary hepatocellular carcinoma. *Genes Chromosomes Cancer* 2001; **31**: 221-227
37 **Qin LX**, Tang ZY, Sham JS, Ma ZC, Ye SL, Zhou XD, Wu ZQ, Trent JM, Guan XY. The association of chromosome 8p deletion and tumor metastasis in human hepatocellular carcinoma. *Cancer Res* 1999;**59**:5662-5665
38 **Qin LX**, Tang ZY, Ye SL, Liu Y K, Ma ZC, Zhou XD, Wu ZQ, Lin ZY, Sun FX, Tian J, Guan XY, Pack SD, Zhuang ZP. Chromosome 8p deletion is associated with metastasis of human hepatocellular carcinoma when high and low metastatic models are compared. *J Cancer Res Clin Oncol* 2001; **127**:482-488
39 **Zhang LH**, Qin LX, Ma ZC, Ye SL, Liu YK, Ye QH, Wu X, Huang W, Tang ZY. Identification of allelic imbalances regions related to metastasis of hepatocellular carcinoma: Comparison between matched primary and metastatic lesions in 22 patients by genome-wide microsatellite analysis. *Int J Cancer* 2002 *(submitted)*
40 **Ding SF**, Delhanty JD, Zografos G, Michail NE, Dooley JS, Habib NA. Chromosome allele loss in colorectal liver metastases and its association with clinical features. *Br J Surg* 1994;**81**:875-878
41 **Terada R**, Yasutake T, Yamaguchi E, Hisamatsu T, Nakamura S, Ayabe H, Tagawa Y. Higher frequencies of numerical aberrations of chromosome 17 in primary gastric cancers are associated with lymph node metastasis. *J Gastroenterol* 1999;**34**:11-17
42 **Hampl M**, Hampl JA, Schwarz P, Frank S, Hahn M, Schackert G, Saeger HD, Schackert HK. Accumulation of genetic alterations in brain metastases of sporadic breast carcinomas is associated with reduced survival after metastasis. *Invasion Metastasis* 1998;**18**:81-95
43 **Suzuki K**, Hirooka Y, Tsujitani S, Yamane Y, Ikeguchi M, Kaibara N. Relationship between loss of heterozygosity at microsatellite loci and computerized nuclear morphometry in hepatocellular carcinoma. *Anticancer Res* 2000;**20**: 1257-1262
44 **Park NH**, Chung YH, Youn KH, Song BC, Yang SH, Kim JA, Lee HC, Yu E, Lee YS, Lee SG, Kim KW, Suh DJ. Close correlation of p53 mutation to microvascular invasion in hepatocellular carcinoma. *J Clin Gastroenterol* 2001;**33**:397-401
45 **Zhao X**, Li J, He Y, Lan F, Fu L, Guo J, Zhao R, Ye Y, He M, Chong W, Chen J, Zhang L, Yang N, Xu B, Wu M, Wan D, Gu J. A novel growth suppressor gene on chromosome 17p13.3 with a high frequency of mutation in human hepatocellular carcinoma. *Cancer Res* 2001;**61**:7383-7387
46 **Nagai H**, Pineau P, Tiollais P, Buendia MA, Dejean AH. Comprehensive allelotyping of human hepatocellular carcinoma. *Oncogene* 1997;**14**: 2927-2933
47 **Boige V**, Laurent-Puig P, Fouchet P, Flejou JF, Monges G, Bedossa P, Bioulac-Sage P, Capron F, Schmitz A, Olschwang S, Thomas G. Concerted nonsyntenic allelic losses in hyperploid hepatocellular carcinoma as determined by a high-resolution allelotype. *Cancer Res* 1997;**57**: 1986-1990
48 **Piao Z**, Park C, Park JH, Kim H. Allelotype analysis of hepatocellular carcinoma. *Int J Cancer* 1998;**75**:29-33
49 **Charroux B**, Pellizzoni L, Perkinson RA, Yong J, Shevchenko A, Mann M, Dreyfuss G. Gemin4. A novel component of the SMN complex that is found in both gems and nucleoli. *J Cell Biol* 2000;**148**:1177-1186
50 **Chekmareva MA**, Hollowell CM, Smith RC, Davis EM, LeBeau MM, Rinker-Schaeffer CW. Localization of prostate cancer metastasis-suppressor activity on human chromosome 17. *Prostate* 1997;**33**:271–280
51 **Rinker-Schaeffer CW**, Hawkins AL, Ru N, Dong J, Stoica G, Griffin CA. Differential suppression of mammary and prostate cancer metastasis by human chromosomes 17 and 11. *Cancer Res* 1994;**54**:6249–6256
52 **Chekmareva MA**, Kadkhodaian MM, Hollowell CM, Kim H, Yoshida BA, Luu HH. Chromosome 17-mediated dormancy of AT6.1 prostate cancer micrometastases. *Cancer Res* 1998;**58**:4963–4969
53 **Kim HL**, Griend DJ, Yang X, Benson DA, Dubauskas Z, Yoshida BA, Chekmareva MA, Ichikawa Y, Sokoloff MH, Zhan P, Karrison T, Lin A, Stadler WM, Ichikawa T, Rubin MA, Rinker-Schaeffer CW. Mitogen-activated protein kinase kinase 4 metastasis suppressor gene expression is

inversely related to histological pattern in advancing human prostatic cancers. *Cancer Res* 2001;**61**:2833-2837
54 **Tsukamoto K**, Ito N, Yoshimoto M, Kasumi F, Akiyama F, Sakamoto G, Nakamura Y, Emi M. Allelic loss on chromosome 1p is associated with progression and lymph node metastasis of primary breast carcinoma. *Cancer* 1998;**82**: 317-322
55 **Araki D**, Uzawa K, Watanabe T, Shiiba M, Miyakawa A, Yokoe H, Tanzawa H. Frequent allelic losses on the short arm of chromosome 1 and decreased expression of the p73 gene at 1p36.3 in squamous cell carcinoma of the oral cavity. *Int J Oncol* 2002;**20**:355-360
56 **Du Plessis L**, Dietzsch E, Van Gele M, Van Roy N, Van Helden P, Parker MI, Mugwanya DK, De Groot M, Marx MP, Kotze MJ, Speleman F. Mapping of novel regions of DNA gain and loss by comparative genomic hybridization in esophageal carcinoma in the Black and Colored populations of South Africa. *Cancer Res* 1999; **59**: 1877-1883
57 **Guan XY**, Meltzer PS, Dalton WS, Trent JM. Identification of cryptic sites of DNA sequence amplification in human breast cancer by chromosome microdissection. *Nat Genet* 1994; **8**:155-161
58 **Ried T**, Knutzen R, Steinbeck R, Blegen H, Schrock E, Heselmeyer K, du Manoir S, Auer G. Comparative genomic hybridization reveals a specific pattern of chromosomal gains and losses during the genesis of colorectal tumors. *Genes Chromosomes Cancer* 1996; **15**: 234-245
59 **Marchio A**, Meddeb M, Pineau P, Danglot G, Tiollais P, Bernheim A, Dejean A. Recurrent chromosomal abnormalities in hepatocellular carcinoma detected by comparative genomic hybridization. *Genes Chromosomes Cancer* 1997;**18**:59-65
60 **Wong N**, Lai P, Lee SW, Fan S, Pang E, Liew CT, Sheng Z, Lau JW, Johnson PJ. Assessment of genetic changes in hepatocellular carcinoma by comparative genomic hybridization analysis: relationship to disease stage, tumor size, and cirrhosis. *Am J Pathol* 1999; **154**: 37-43
61 **Gronwald J**, Storkel S, Holtgreve-Grez H, Hadaczek P, Brinkschmidt C, Jauch A, Lubinski J, Cremer T. Comparison of DNA gains and losses in primary renal clear cell carcinomas and metastatic sites: importance of 1q and 3p copy number changes in metastatic events. *Cancer Res* 1997; **57**:481-487
62 **Hosch S**, Kraus J, Scheunemann P, Izbicki JR, Schneider C, Schumacher U, Witter K, Speicher MR, Pantel K. Malignant potential and cytogenetic characteristics of occult disseminated tumor cells in esophageal cancer. *Cancer Res* 2000;**60**:6836-6840
63 **Shiraishi K**, Okita K, Harada T, Kusano N, Furui T, Kondoh S, Oga A, Kawauchi S, Fukumoto Y, Sasaki K. Comparative genomic hybridization analysis of genetic aberrations associated with development and progression of biliary tract carcinomas. *Cancer* 2001;**91**:570-577
64 **Nakao K**, Shibusawa M, Ishihara A, Yoshizawa H, Tsunoda A, Kusano M, Kurose A, Makita T, Sasaki K. Genetic changes in colorectal carcinoma tumors with liver metastases analyzed by comparative genomic hybridization and DNA ploidy. *Cancer* 2001;**91**:721-726
65 **Miele ME**, Robertson G, Lee JH, Coleman A, McGary CT, Fisher PB, Lugo TG, Welch DR. Metastasis suppressed, but tumorigenicity and local invasiveness unaffected, in the human melanoma cell line MelJuSo after introduction of human chromosomes 1 or 6.*Mol Carcinog* 1996;**15**:284-299
66 **You J**, Miele ME, Dong C, Welch DR. Suppression of human melanoma metastasis by introduction of chromosome 6 may be partially due to inhibition of motility, but not to inhibition of invasion. *Biochem Biophys Res Commun* 1995; **208**:476–484
67 **Miele ME**, De La Rosa A, Lee JH, Hicks DJ, Dennis JW, Steeg PS, Welch DR. Suppression of human melanoma metastasis following introduction of chromosome 6 is independent of NME1 (Nm23). *Clin Exp Metastasis* 1997;**15**: 259–265
68 **Welch DR**, Goldberg SF. Molecular mechanisms controlling human melanoma progression and metastasis. *Pathobiology* 1997;**65**:311–330
69 **Welch DR**, Chen P, Miele ME, McGary CT, Bower JM, Stanbridge EJ, Weissman BE. Microcell-mediated transfer of chromosome 6 into metastatic human C8161 melanoma cells suppresses metastasis but does not inhibit tumorigenicity. *Oncogene* 1994;**9**:255–262
70 **Miele ME**, Jewett MD, Goldberg SF, Hyatt DL, Morelli C, Gualandi F, Rimessi P, Hicks DJ, Weissman BE, Barbanti-Brodano G, Welch DR. A human melanoma metastasis-suppressor locus maps to 6q16.3-q23. *Int J Cancer* 2000;**86**: 524-528
71 **Goldberg SF**, Harms JF, Quon K, Welch DR. Metastasis-suppressed C8161 melanoma cells arrest in lung but fail to proliferate. *Clin Exp Metastasis* 1999;**17**:601–607
72 **Shirasaki F**, Takata M, Hatta N, Takehara K. Loss of expression of the metastasis suppressor gene KiSS1 during melanoma progression and its association with LOH of chromosome 6q16.3-q23. *Cancer Res* 2001;**61**:7422-7425
73 **Petersen S**, Wolf G, Bockmuhl U, Gellert K, Dietel M, Petersen I. Allelic loss on chromosome 10q in human lung cancer: association with tumour progression and metastatic phenotype. *Br J Cancer* 1998;**77**:270-276
74 **Alers JC**, Rochat J, Krijtenburg PJ, Hop WC, Kranse R, Rosenberg C, Tanke HJ, Schroder FH, van Dekken H. Identification of genetic markers for prostatic cancer progression. *Lab Invest* 2000;**80**:931-942
75 **Bockmuhl U**, Petersen S, Schmidt S, Wolf G, Jahnke V, Dietel M, Petersen I. Patterns of chromosomal alterations in metastasizing and nonmetastasizing primary head and neck carcinomas. *Cancer Res* 1997;**57**:5213-5216
76 **Bardi G**, Parada LA, Bomme L, Pandis N, Johansson B, Willen R, Fenger C, Kronborg O, Mitelman F, Heim S. Cytogenetic findings in metastases from colorectal cancer. *Int J Cancer* 1997;**72**:604-607
77 **Cabeza-Arvelaiz Y**, Thompson TC, Sepulveda JL, Chinault AC. LAPSER1: a novel candidate tumor suppressor gene from 10q24.3. *Oncogene* 2001;**20**:6707-6717
78 **Miura N**, Onuki N, Rathi A, Virmani A, Nakamoto S, Kishimoto Y, Murawaki Y, Kawasaki H, Hasegawa J, Oshimura M, Travis WD, Gazdar AF. hTR repressor-related gene on human chromosome 10p15.1. *Br J Cancer* 2001;**85**:1510-1514
79 **O'sullivan MJ**, Rader JS, Gerhard DS, Li Y, Trinkaus KM, Gersell DJ, Huettner PC. Loss of heterozygosity at 11q23.3 in vasculoinvasive and metastatic squamous cell carcinoma of the cervix. *Hum Pathol* 2001;**32**:475-478
80 **Herbst RA**, Mommert S, Casper U, Podewski EK, Kiehl P, Kapp A, Weiss J. 11q23 allelic loss is associated with regional lymph node metastasis in melanoma. *Clin Cancer Res* 2000;**6**:3222-3227
81 **Tada K**, Oka M, Tangoku A, Hayashi H, Oga A, Sasaki K. Gains of 8q23-qter and 20q and loss of 11q22-qter in esophageal squamous cell carcinoma associated with lymph node metastasis. *Cancer* 2000;**88**:268-273
82 **Nam DH**, Song SY, Park K, Kim MH, Suh YL, Lee JI, Kim JS, Hong SC, Shin HJ, Park K, Eoh W, Kim JH. Clinical significance of molecular genetic changes in sporadic invasive pituitary adenomas. *Exp Mol Med* 2001;**33**:111-116
83 **Welkoborsky HJ**, Bernauer HS, Riazimand HS, Jacob R, Mann WJ, Hinni ML. Patterns of chromosomal aberrations in metastasizing and nonmetastasizing squamous cell carcinomas of the oropharynx and hypopharynx. *Ann Otol Rhinol Laryngol* 2000;**109**:401-410
84 **Bepler G**, O'briant KC, Kim YC, Schreiber G, Pitterle DM. A 1.4-Mb high-resolution physical map and contig of chromosome segment 11p15.5 and genes in the LOH11A metastasis suppressor region. *Genomics* 1999;**55**:164-175
85 **Karnik P**, Paris M, Williams BR, Casey G, Crowe J, Chen P. Two distinct tumor suppressor loci within chromosome

11p15 implicated in breast cancer progression and metastasis. *Hum Mol Genet* 1998;**7**:895-903

86 **Bepler G**, Fong KM, Johnson BE, O'Briant KC, Daly LA, Zimmerman PV, Garcia-Blanco MA, Peterson B. Association of chromosome 11 locus D11S12 with histology, stage, and metastases in lung cancer. *Cancer Detect Prev* 1998;**22**:14-19

87 **Xu XL**, Wu LC, Du F, Davis A, Peyton M, Tomizawa Y, Maitra A, Tomlinson G, Gazdar AF, Weissman BE, Bowcock AM, Baer R, Minna JD. Inactivation of human SRBC, located within the 11p15.5-p15.4 tumor suppressor region, in breast and lung cancers. *Cancer Res* 2001;**61**:7943-7949

88 **Phillips KK**, Welch DR, Miele ME, Lee JH, Wei LL, Weissman BE. Suppression of MDA-MB-435 breast carcinoma cell metastasis following the introduction of human chromosome 11. *Cancer Res* 1996;**56**:1222–1227

89 **Ogawara K**, Miyakawa A, Shiba M, Uzawa K, Watanabe T, Wang XL, Sato T, Kubosawa H, Kondo Y, Tanzawa H. Allelic loss of chromosome 13q14.3 in human oral cancer: correlation with lymph node metastasis. *Int J Cancer* 1998; **79**:312-317

90 **Harada H**, Tanaka H, Shimada Y, Shinoda M, Imamura M, Ishizaki K. Lymph node metastasis is associated with allelic loss on chromosome 13q12-13 in esophageal squamous cell carcinoma. *Cancer Res* 1999;**59**:3724-3729

91 **Fiedler U**, Ehlers W, Meye A, Fussel S, Faller G, Schmidt U, Wirth MP. LOH analyses in the region of the putative tumour suppressor gene C13 on chromosome 13q13. *Anticancer Res* 2001;**21**:2341-2350

92 **Hyytinen ER**, Thalmann GN, Zhau HE, Karhu R, Kallioniemi OP, Chung LW, Visakorpi T. Genetic changes associated with the acquisition of androgen-independent growth, tumorigenicity and metastatic potential in a prostate cancer model. *Br J Cancer* 1997;**75**:190-195

93 **O'Connell P**, Fischbach K, Hilsenbeck S, Mohsin SK, Fuqua SA, Clark GM, Osborne CK, Allred DC. Loss of heterozygosity at D14S62 and metastatic potential of breast cancer. *J Natl Cancer Inst* 1999;**91**:1391-1397

94 **Martin MD**, Fischbach K, Osborne CK, Mohsin SK, Allred DC, O'Connell P. Loss of heterozygosity events impeding breast cancer metastasis contain the MTA1 gene. *Cancer Res* 2001;**61**:3578-3580

95 **Mashimo T**, Watabe M, Cuthbert AP, Newbold RF, Rinker-Schaeffer CW, Helfer E, Watabe K. Human chromosome 16 suppresses metastasis but not tumorigenesis in rat prostatic tumor cells. *Cancer Res* 1998;**58**:4572-4576

96 **Pan Y**, Matsuyama H, Wang N, Yoshihiro S, Haggarth L, Li C, Tribukait B, Ekman P, Bergerheim US. Chromosome 16q24 deletion and decreased E-cadherin expression: possible association with metastatic potential in prostate cancer. *Prostate* 1998;**36**:31-38

97 **Li C**, Berx G, Larsson C, Auer G, Aspenblad U, Pan Y, Sundelin B, Ekman P, Nordenskjold M, van Roy F, Bergerheim US. Distinct deleted regions on chromosome segment 16q23-24 associated with metastases in prostate cancer. *Genes Chromosomes Cancer* 1999;**24**:175-182

98 **Caligo MA**, Polidoro L, Ghimenti C, Campani D, Cecchetti D, Bevilacqua G. A region on the long arm of chromosome 16 is frequently deleted in metastatic node-negative breast cancer. *Int J Oncol* 1998;**13**:177-182

99 **Driouch K**, Prydz H, Monese R, Johansen H, Lidereau R, Frengen E. Alternative transcripts of the candidate tumor suppressor gene, WWOX, are expressed at high levels in human breast tumors. *Oncogene* 2002;**21**:1832-1840

100 **Paige AJ**, Taylor KJ, Taylor C, Hillier SG, Farrington S, Scott D, Porteous DJ, Smyth JF, Gabra H, Watson JE. WWOX: a candidate tumor suppressor gene involved in multiple tumor types. *Proc Natl Acad Sci USA* 2001;**98**: 11417-11422

101 **Bednarek AK**, Keck-Waggoner CL, Daniel RL, Laflin KJ, Bergsagel PL, Kiguchi K, Brenner AJ, Aldaz CM. WWOX, the FRA16D gene, behaves as a suppressor of tumor growth. *Cancer Res* 2001;**61**:8068-8073

102 **Kujawski M**, Aalto Y, Jaskula-Sztul R, Szyfter W, Szmeja Z, Szyfter K, Knuutila S. DNA copy number losses are more frequent in primary larynx tumors with lymph node metastases than in tumors without metastases. *Cancer Genet Cytogenet* 1999;**114**:31-34

103 **Padalecki SS**, Troyer DA, Hansen MF, Saric T, Schneider BG, O'Connell P, Leach RJ. Identification of two distinct regions of allelic imbalance on chromosome 18Q in metastatic prostate cancer. *Int J Cancer* 2000;**85**:654-658

104 **Ueda T**, Komiya A, Emi M, Suzuki H, Shiraishi T, Yatani R, Masai M, Yasuda K, Ito H. Allelic losses on 18q21 are associated with progression and metastasis in human prostate cancer. *Genes Chromosomes Cancer* 1997;**20**:140-147

105 **Nishizaki T**, DeVries S, Chew K, Goodson WH 3rd, Ljung BM, Thor A, Waldman FM. Genetic alterations in primary breast cancers and their metastases: direct comparison using modified comparative genomic hybridization. *Genes Chromosomes Cancer* 1997;**19**:267-272

106 **Frank CJ**, McClatchey KD, Devaney KO, Carey TE. Evidence that loss of chromosome 18q is associated with tumor progression. *Cancer Res* 1997;**57**:824-827

107 **Petersen S**, Aninat-Meyer M, Schluns K, Gellert K, Dietel M, Petersen I. Chromosomal alterations in the clonal evolution to the metastatic stage of squamous cell carcinomas of the lung. *Br J Cancer* 2000;**82**:65-73

108 **Blaker H**, Graf M, Rieker RJ, Otto HF. Comparison of losses of heterozygosity and replication errors in primary colorectal carcinomas and corresponding liver metastases. *J Pathol* 1999;**188**:258-262

109 **Chu LW**, Pettaway CA, Liang JC.Genetic abnormalities specifically associated with varying metastatic potential of prostate cancer cell lines as detected by comparative genomic hybridization. *Cancer Genet Cytogenet* 2001;**127**: 161-167

110 **Kibel AS**, Faith DA, Bova GS, Isaacs WB. Loss of heterozygosity at 12P12-13 in primary and metastatic prostate adenocarcinoma. *J Urol* 2000;**164**:192-196

111 **Luu HH**, Zagaja GP, Dubauskas Z, Chen SL, Smith RC, Watabe K, Ichikawa Y, Ichikawa T, Davis EM, Le Beau MM, Rinker-Schaeffer CW. Identification of a novel metastasis-suppressor region on human chromosome 12. *Cancer Res* 1998;**58**:3561–3565

112 **Mora J**, Cheung NK, Chen L, Qin J, Gerald W. Loss of heterozygosity at 19q13.3 is associated with locally aggressive neuroblastoma. *Clin Cancer Res* 2001;**7**:1358-1361

113 **Nanashima A**, Yamaguchi H, Yasutake T, Sawai T, Kusano H, Tagawa Y, Nakagoe T, Ayabe H. Gain of chromosome 20 is a frequent aberration in liver metastasis of colorectal cancers. *Dig Dis Sci* 1997;**42**:1388-1393

114 **Balazs M**, Adam Z, Treszl A, Begany A, Hunyadi J, Adany R. Chromosomal imbalances in primary and metastatic melanomas revealed by comparative genomic hybridization. *Cytometry* 2001;**46**:222-232

115 **Piao Z**, Malkhosyan SR. Frequent loss Xq25 on the inactive X chromosome in primary breast carcinomas is associated with tumor grade and axillary lymph node metastasis. *Genes Chromosomes Cancer* 2002;**33**:262-269

116 **Tarkkanen M**, Huuhtanen R, Virolainen M, Wiklund T, Asko-Seljavaara S, Tukiainen E, Lepantalo M, Elomaa I, Knuutila S. Comparison of genetic changes in primary sarcomas and their pulmonary metastases. *Genes Chromosomes Cancer* 1999;**25**:323-331

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