Chromosomal aberrations related to metastasis of human solid tumors

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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 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 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 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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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 DUC-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.[11]. Oba et al found two putative tumor suppressor genes on chromosome 8p might play different roles, deletions on 8p22-p22.1 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.[31]. 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.[31].

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 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 morphology 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)[49]. 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 20kM segment within 17p11.2-13.1 was found related to metastasis phenotype, with the highest increased-grade AI (28-44 %) in metastatic lesions.[48] 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[50,52,53].

**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-q22 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 1×10⁶ 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 effenter vessels. This finding implied that the step(s) in the metastatic cascade inhibited by introduction of chromosome 6 occurred subsequent to invrasvasion[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[39,40]. Deletions on chromosome 10q25-q26 is responsible for the metastatic phenotype of squamous cell carcinomas in head and neck[39], and colorectal carcinomas[76], which may play a particular pathogenetic role in the metastatic process. One gene, LAPSER1 [an LZTS1 (or FEZI)-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 repressormary 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 vascularoanoinvasion. 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 may be more 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 1p15.5, a second, critical region of LOH spans the markers D11S1338-D11S1323 (approximately 336 kb) at 1p15.5-p15.4, may contribute to tumor progression and metastasis in breast cancer and lung cancer\cite{83,86}. The human SRBC gene (hSRBC), a candidate tumor suppressor gene, is mapped to chromosome region 1p15.5-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\cite{87}. Introduction of human chromosome 11 by MMCT could suppress MDA-MB-435 breast carcinoma cell metastasis\cite{88}. One important metastasis-suppressor gene, KAI1, maps to 1p11.2-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\cite{89,90}. 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\cite{91}. The high LOH rate for different microsatellite markers in and around the putative TSG locus C13 on chromosome 13q13 has been found\cite{91}. However, Hytynen 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\cite{92}.

**CHROMOSOME 14**

Significantly more LOH events at markers D14S62 and D14S51 in primary breast cancers from patients with lymph node-negative disease than those 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\cite{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.\cite{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\cite{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\cite{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\cite{99-101}.

**OTHERS**

In addition, losses of 9p and gains of 17q and Xq are other genomic changes which frequently occurred in metastases but not in the corresponding primary tumor\cite{102}. 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\cite{103}. 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\cite{104}. Chu et al.\cite{105} 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 p27kip1, plays a pivotal role in the development of metastatic disease[108, 116, 117].

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, 113].

The gain of chromosome 20 may be available as a genetic marker for the diagnosis or prediction of liver metastasis[111, 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 chromosome regions would be much more valuable in predicting the metastatic potential and prognosis of human solid tumors[81]. 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.

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