Chromosome Abnormalities: New Insights into Their Clinical Significance in Cancer

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Chromosomal abnormalities, consisting of numerical and structural chromosome abnormalities, are a common characteristic of cancer. Numerical chromosome abnormalities, mainly including aneuploidy and chromosome instability, are caused by chromosome segregation errors in mitosis, whereas structural chromosome abnormalities are a consequence of DNA damage and comprise focal/arm-level chromosome gain or loss. Recent advances have started to unveil the mechanisms by which chromosomal abnormalities can facilitate tumorigenesis and change the cellular fitness and the expression or function of RNAs and proteins. Accumulating evidence suggests that chromosome abnormalities represent a genomic signature that is linked to cancer prognosis and reaction to chemotherapy and immunotherapy. In this review, we discuss the most recent findings on the role of chromosome abnormalities in tumorigenesis and cancer progression, with a particular emphasis on how aneuploidy and chromosome instability influence cancer therapy and prognosis. We also highlight the distribution and clinical application of the structural chromosome abnormalities in various cancer types. A better understanding of the role of chromosome abnormalities will be beneficial to the development of precision oncology and suggest future directions for the field.

Theodor Boveri first proposed that chromosomal abnormalities were a common characteristic of tumors over a century ago.1 Based on the observation of abnormal mitotic divisions in tumor cells, Boveri formalized the “chromosomal abnormalities hypothesis,” proposing the tendency of tumor cells to facilitate tumorigenesis via chromosomal abnormalities. The hypothesis has been confirmed in recent years with the advent of next-generation sequencing (NGS), a critical complement to conventional cytogenetics of chromosome profiles in cancer, allowing direct testing of the diverse and complex array of chromosomal abnormalities. It has now become evident that chromosome abnormalities present the potential to regulate cellular fitness by changing the expression or function of RNA and proteins.2–4 A common characteristic of all malignant tumors is that they promote tumor cell proliferation and affect the immune system, both of which are closely associated with chromosome abnormalities.5,6 Additionally, the amplification or deletion of some genes, as well as chromosome rearrangements, can reshape the genome and, thus, influence tumor progression and prognosis.3,7

Chromosome abnormalities consist of numerical and structural chromosome abnormalities, resulting in genomic instability (Figure 1).8 Numerical chromosomal abnormalities mainly include aneuploidy and chromosome instability (CIN), characterized by chromosome gain or loss.1,9 Notably, approximately 90% of cancers have lost or gained at least one chromosome.10 Structural chromosomal abnormalities, caused by DNA damage, are characterized by varying degrees of complexity, ranging from chromosome arm-level deletions or amplifications to alterations of multiple chromosomes.8,11 Among the classes of structural chromosomal abnormalities, deletions are the most common, followed by amplifications and then unbalanced translocations.3 Moreover, structural chromosomal abnormalities show considerable heterogeneity in different types of cancer.12

Recent advances describe the importance of chromosome abnormalities in predicting the response to immune therapy.13 Careful analysis of these genomic anomalies will, therefore, influence the effectiveness of chemotherapy and immunotherapy. Here, we review the most recent and salient findings associated with numerical and structural chromosome abnormalities, including aneuploidy, CIN, chromosome gain and loss, and summarize the role of these aberrations in tumorigenesis and cancer therapy.

Numerical Chromosome Abnormalities
Aneuploidy
Aneuploidy, defined as the gain or loss of chromatid or chromosome regions, is a hallmark of cancer.1 According to different formation mechanisms, aneuploidy is divided into whole...
chromosome aneuploidy and segmental aneuploidy. Aneuploidy is a class of somatic copy number alterations (SCNAs) that predicts clinical benefit and survival. There is a growing appreciation of the critical role of aneuploidy during the process of tumorigenesis and prognosis.

Aneuploidy and Immunotherapy

Immunotherapy is the most promising approach to activating therapeutic antitumor immunity, which has remarkable clinical benefits in various cancer types. Tumor mutation burden (TMB) affects the presentation of neoantigens on major histocompatibility complex (MHC) molecules and thereby influences immunotherapy response in patients. High TMB is significantly predictive of response and survival. Recent studies have reported that TMB alone is not a sensitive marker of the efficacy of immunotherapy. In two independent cohorts of patients treated with immune checkpoint inhibitors (ICI) anti-CTLA4, Davoli et al. assessed tumor SCNAs and TMB in patients who did or did not achieve long-term survival after treatment and found that SCNA was a better survival predictor than TMB. Moreover, evaluating a The Cancer Genome Atlas (TCGA) dataset of melanoma patients not receiving ICI, they found that a higher number of TMBs and a lower number of SCNAs predicted better survival. However, the correlation between SCNA level and survival did not reach statistical significance. Nonetheless, SCNA may be a better predictor to identify cancer patients who are most likely to benefit from immunotherapy. Analysis of a pan-cancer dataset showed proliferation signatures mainly related to focal SCNA and immune evasion signatures mainly associated with arm- and chromosome-level SCNA. In a similar study subsequently performed using a larger TCGA dataset, individual chromosome arm-level alterations were found to be related to expression changes in immune and cell-cycle markers, independent of aneuploidy level. Cell-cycle and proliferation signatures, as well as immune markers, therefore correlate with different types of aneuploidy that likely induce specific gene expression changes via distinct mechanisms. One hypothesis is that arm-level SCNA and focal SCNA affect a different number of gene products and, consequently, influence proteotoxic stress.

Given the contribution of genomic features to immunotherapy, it is reasonable to consider SCNAs as predictive indicators of response to therapy. Indeed, in patients with advanced non-small-cell lung cancer (NSCLC) treated with anti-PD-(L)1 therapy, SCNAs are lower in patients with durable clinical benefit (DCB) than in those with nondurable benefit (NDB); moreover, TMB and PD-L1 protein expressions are significantly different in two cohorts of patients with DCB or NDB, which was confirmed in two cohorts. Targeted NGS shows that SCNA is lowest in patients with NSCLC treated with anti-PD-(L)1 (alone or in combination with anti-CTLA4 therapy) who also present DCB. Moreover, SCNA is clearly higher in patients with NDB than in those with non-ICI NSCLC. A higher burden of SCNA with copy number loss was found in non-responders to PD-1 and CTLA-4 blockades and was shown to be correlated with decreased expression of genes in immune pathways. The mechanism underlying this correlation between SCNA and resistance to ICI may be associated with immune evasion and/or immune pathways involved in this process that are yet to be discovered.

Correlation between Aneuploidy, Metastasis, and Drug Responses

Numerous studies have reported that aneuploidy participates in tumorigenesis, metastasis, and drug response and predicts cancer prognosis. Aneuploidy, which affects individual genes and also implies complex genetic alterations, contributes to cancer aggressiveness and recurrence. Shukla et al. compared 5,778 primary solid tumor samples using the MSK-IMPACT dataset, a targeted tumor-sequencing test and found higher chromosome arm aneuploidy (CAA) burden in metastatic samples than in matched primary samples. Consistent with this, the number of CAs significantly increases in advanced tumor stages, particularly from stage I to II and from stage II to III. Notably, CAA prior to mutations and focal deletions/amplifications or combined with these indicators predicts chemotherapy response in numerous cancers, such as pancreatic adenocarcinoma, brain lower grade glioma, liver hepatocellular carcinoma, sarcoma, stomach adenocarcinoma, prostate adenocarcinoma, colon and rectum adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, kidney renal papillary cell carcinoma, breast invasive carcinoma, uterine corpus endometrial carcinoma, testicular germ cell tumors, and thyroid carcinoma. Levels of aneuploidy vary significantly in different tumor types, influencing the analysis of the relationship between aneuploidy, drug response, and prognosis. Notably, CAA is not a sensitive indicator predicting non-ICI response in melanoma, which is
consistent with the study from Davoli et al. Ongoing work is devoted to determining whether aneuploidy uniquely predicts ICI efficacy and specific chemotherapy drug in cancers.

**Aneuploidy and Prognosis**

In prostate cancer samples from TCGA and follow-up patients, SCNA appears in the early stages of tumor growth. Furthermore, the genes involved in SCNA contribute to aggressive disease. SCNA is prognostic for cancer-related death in biopsies of conservatively treated prostate cancer, independent of clinical criteria. In a conservative treatment cohort, SCNA as a continuous variable was significantly correlated with prostate cancer-specific death. However, SCNA was related to overall survival in primary cancer but not significantly in metastatic cancer, suggesting that aneuploidy correlates with the tumor status. Karn et al. analyzed 193 triple-negative breast cancer (TNBC) samples and found an inverse correlation between immune metagenes, referring to immune gene expression signatures, and SCNA levels. Additionally, immune-rich TNBC samples with good prognosis had significantly lower mutation, lower neoantigen load, and fewer SCNAS. These findings highlighting the predictive value of SCNA were further supported by a different study. The integrative features of aneuploidy, wherein individual genes affect the aneuploidy score not only by their copy number or mRNA expression but also by their genomic location, may explain why aneuploidy is so strongly associated with prognosis.

**Chromosomal Instability (CIN)**

CIN derives from chromosome missegregation errors. CIN and aneuploidy are deemed common features of cancer that involve gain or loss of chromosomes. CIN is the process that leads to chromosome copy number alterations and thereby results in aneuploidy. However, aneuploidy can occur even without CIN, and cells with relatively stable karyotypes can also become aneuploid. CIN is a complex, continuous, and heterogeneous process that initiates carcinogenesis. Considering the different characteristics and mechanisms of CIN, we discuss it separately in our review. Since CIN enhances the intratumoral heterogeneity and drives tumor evolution and drug resistance, we will review the role of CIN in these aspects.

**CIN as a Driver of Tumor Progression and Poor Prognosis**

CIN is one of the most common causes of tumor evolution and has impacts on genomic alterations and cellular fitness that are likely to lead to tumor progression and poor survival in various malignancies. Furthermore, CIN and its leading karyotypic heterogeneity drive tumor metastasis. Mice injected with CIN-high breast cancer cells experience rapid metastasis and shortened survival compared to mice receiving CIN-low breast cancer cells. RNA sequencing (RNA-seq) of CIN-high and CIN-low breast cancer cells also showed that cells with high CIN are enriched in mesenchymal genes, including metastasis-associated genes. In patients with locally advanced head and neck squamous cell carcinoma (HNSCC), CIN-high tumors are significantly associated with lymph node metastasis. Interestingly, single-cell (sc)RNA-seq data analysis revealed that CIN induces chronic activation of cytosolic DNA sensing and the innate immunity pathway, thereby contributing to metastasis, suggesting that CIN promotes metastasis through sustaining a cancer-cell-autonomous reaction to cytosolic DNA. Notably, the expression levels of some CIN-targeted genes are related to increased invasiveness and poor prognosis. For example, overexpression of MASTL promoting CIN has been found in many cancers, which resulted in increased aggressiveness and poor prognosis. According to the first trial that prospectively tracked tumor evolution and genetic heterogeneity (TRACERx), lung cancers with high CIN are more likely to relapse after surgery. Additionally, the effect of the CIN70 score, a gene expression profile composed of 70 genes associated with CIN, on disease-specific survival (DSS) was studied in all subgroups of breast cancer. Regardless of the subtype, cancers with a high CIN70 score had significantly worse 5- and 10-year DSS than those with a low CIN70 score. Collectively, these studies suggest that elevated expression of some genes as a result of CIN may lead to DNA damage, thereby further promoting CIN in cancer.

**CIN and Drug Resistance**

CIN is characterized by drug resistance, mainly owing to intratumoral heterogeneity. Swanton et al. identified some genes downregulated upon treatment with microtubule-stabilizing agents, such as taxanes, and found increased expression of these genes in tumors with CIN. They also showed that, in a clinical trial, taxane resistance was found in CIN-high ovarian cancers. CIN induced by Mad2 overexpression can overcome oncogene addiction to further reduce the efficacy of targeted therapies, thereby promoting tumor relapse in lung and breast cancer models. Whole-genome sequencing analysis demonstrated that, regardless of the initial CIN level, cancer genomes acquire a certain level of CIN as a mechanism to evade oncogene addiction. The complex effects and the intratumoral heterogeneity induced by CIN suggest that this anomaly is both a challenge and a promising field for cancer therapy.

**Triploidy and Tetraploidy**

SCNA and CIN are the major chromosome abnormalities considered in current analyses of oncogenesis and tumor progression. However, triploidy and tetraploidy may also promote oncogenesis. It has been reported that triploid, diploid, and tetraploid cells coexist and cause whole-genome rearrangement in cancer cell lines. Meta-analysis of cancer triploidy revealed a relatively high proportion of near-triploidy in colon adenoma and adenocarcinoma. However, triploidy in colon adenoma was higher than in adenocarcinoma. Based on analysis of published data, the extent of triploidy was related to poor prognosis, particularly in cancers with higher mortality such as lung cancer, pancreatic cancer, gastric cancer, and colon cancer.

Tetraploidy is a transient state on the path to aneuploidy, which has been reported in primary tumors. Wangsa et al. found that tetraploid cancer cells present increased migratory and invasive ability in vitro and in primary colorectal cancer,
suggesting that tetraploidy can promote aggressive behavior in cancer. In a study combining tetraploidy and CIN, interestingly, the tetraploid clones showing a CIN phenotype also showed deregulation of the p53 pathway after drug-induced chromosome missegregation, although p53 was not stabilized. However, tetraploidy alone did not induce changes in p53 regulation in the absence of treatment and under normal conditions. This study, therefore, suggests that tetraploidy and CIN together are a dangerous combination. Moreover, tetraploid cells tended to be more resistant to chemotherapy. Considering that tetraploidy promotes CIN and decreases cellular fitness, it is likely to accelerate tumorigenesis.

**Structural Chromosome Abnormalities**

Chromosome amplification and deletion are the most common structural chromosome abnormalities, which occur in 88% of cancer samples. Chr8q is the most frequently gained (33%), and 8p and 17p are the most commonly lost (33% and 35%, respectively); 2p and 2q are the least altered (18% and 16%, respectively). Deletions of 3p, 8p, 13q, and 17p are positively associated with immune signatures, while deletions of 4q, 5q, and 14q are negatively correlated with immune signatures. The different correlations with immune signatures suggest that specific gene or chromosome region alterations, rather than overall aneuploidy, are crucial to oncogenesis and cancer therapy. In the following sections, we focus on the recent findings about chromosome amplification and deletions in cancer.

**Neural Lineage Cancers**

Neural lineage cancers, including low-grade glioma, glioblastoma, and melanoma, are marked by recurrent chr7 gain. Distinct molecular characteristics have an impact on chromosome abnormalities. Glioblastomas without isocitrate dehydrogenase (IDH) mutations feature chr7 gain and chr10 loss. Glioblastomas with IDH mutations are characterized by 1q gain and 1p loss. Gain of chr2p and 17q and deletion of chr1p and 11q are well known in neuroblastoma. Notably, focal loss of chr7q14.1 and chr14q11.2 can be used as a predictive indicator for poorer prognosis. The combination of chr7 gain and chr10 loss (7+/10−), EGFR amplification, and TERT promoter mutation are common alterations in IDH-wild-type (IDH-WT) glioblastoma. Furthermore, the 7+/10− signature and EGFR amplification are closely correlated with IDH-WT glioblastomas, while TERT promoter mutation shows a lower correlation. Additionally, low-grade gliomas with 1p/19q deletions are responsive to chemoradiotherapy regimens and exhibit better prognosis.

**HNSCC**

A molecular characteristic of HNSCC is the gain of chr3 (3q26-29), which is correlated with poorer patient outcome. Clinical data analysis of oral squamous cell carcinoma (OSCC) shows positive association of 11q22.1-q22.2 amplification with recurrence (p = 0.043) and poor survival. OSCC with 11q22.1-q22.2 amplification also fails to react to radiotherapy. Exome sequencing of 26 HNSCC cell lines revealed that, of the 103 genes with high expression found significantly amplified in HNSCC cell lines, 90 derive from 3q22-qter, and the others derive from 5p15, 11q13, and 8p11. These findings, compared with the genomic changes in HNSCC retrieved from TCGA, support the contribution of gain of 3q, 5p, 8p, and 11q to increased expression of oncogenes that potentially results in tumorigenesis.

**Lung Cancer**

In lung squamous cell carcinoma (LUSC) datasets from TCGA, gain of chr3q and deletion of chr3p were identified in over 60% and approximately 80% of LUSC, respectively. In terms of translocation, non-reciprocal/reciprocal translocation was detected in 18.7% of the 150 patients with NSCLC examined. Moreover, the co-occurrence of 3q gain and 3p loss was more frequent than the occurrence of each of these alone by chance. Instead, lung adenocarcinoma (LUAD) is characterized by 1q gain, which indicates shorter overall survival. In LUAD, researchers found the most significant correlation of immune infiltration with chr6p CNA, and 1q, which was also confirmed in the TCGA LUAD cohort. Additional chromosomes involved in lung cancer have been reported. For example, chr2 genes are altered in LUAD, 8p23.1 loss is frequent in NSCLC, and 7p genes predict overall and disease-free survival for patients with EGFR-mutated lung adenocarcinoma.

**Breast Cancer**

chr1q21.3 amplification occurs in 10%–30% of primary breast cancers but in over 70% of recurrent breast cancers, regardless of cancer subtype. Remarkably, the small-molecule kinase inhibitor pacritinib can preferentially impair the growth of 1q21.3-amplified breast cancers. Moreover, the 1q21.3-regulated S100A7/8/9-IRAK1 feedback loop is an important contributor to breast cancer recurrence. Low-grade breast neoplasia is characterized by loss of chr16q. Instead, there is no association between 16p gain and the aggressiveness of lesions of low-grade breast neoplasia. Importantly, chromosome abnormalities can also show gender-specific differences. For example, in male breast cancer, chr17 shows fewer copy number variations (CNVs) and fewer rearrangements than in female breast cancer.

Additionally, chr3q and 8q amplifications were found in TNBC with lung metastasis. Moreover, 3q, as a predictive factor for response to neoadjuvant chemotherapy, is strongly correlated with features of aggressiveness in TNBC.

**Digestive System Cancers**

Gastrointestinal tumors (non-squamous esophageal, stomach, pancreatic, and colorectal cancer) are characterized by concomitant gain of chr8q, 13q, and 20, regardless of other genomic features. Liu et al. analyzed SCNAs using NGS to identify amplifications and deletions more common in gastrointestinal tract adenocarcinomas (GIACs) and found that the gain of chr13q was specific for GIAC. NGS analyses of genetic characteristics in esophageal tissue from intraepithelial neoplasia and esophageal squamous cell carcinoma (ESCC) revealed that large-scale chromosome loss of 9p21.3 and 2q35 and gain of 2q31.2, 3q27, 5p15.33, 7q22.1, 8q24, 8p11.23,
and 11q13.3 were common in both.\textsuperscript{74} Although intraepithelial neoplasia and ESCC have similar genetic alterations, ESCC displays widespread and recurrent chromosome abnormalities. Identifying the genomic changes occurring in precancerous lesions might help to find patients at risk for ESCC.

**Urinary System Cancers**

Exome sequencing of 19 patients with adrenocortical carcinoma shows that excessive chr19 gain is related to tumor stage III/IV.\textsuperscript{75} Moreover, in this type of cancer, amplification at chr\textsuperscript{19}, 12, 19, and 20 and deletion at chr\textsuperscript{11}, 10, 18, and 22 were observed.\textsuperscript{75,76} In pediatric adrenocortical carcinoma, instead, most patients present loss of chr11p and 17 and gain of 9q.\textsuperscript{77,78} Clear cell renal cell carcinoma (ccRCC) is marked by loss of 3p and 9p.\textsuperscript{79–81} Notably, 3p loss is the crucial driver for the early events occurring in childhood or adolescence in the majority of patients, before ccRCC diagnosis, while 9p loss is a highly selective event promoting metastasis and ccRCC-associated mortality.

| Table 1. Specific Chromosome Abnormalities Involved in Tumorigenesis and Cancer Recurrence |
|----------------|-----------------|----------------|----------------|
| Cancer Type | Chromosome Abnormalities | Characteristic | Reference |
| Neural lineage cancers | recurrent chr7 gain | common feature | 53 |
| Glioblastoma | chr7 gain and 10p loss and chr19q gain and 1p loss | | |
| Neuroblastoma | chr2p and 17q gain; chr1p and 11q deletion | common feature | 55 |
| Low-grade glioma | focal loss of chr7q14.1 and chr1q12.2 | a predictive indicator for poorer prognosis | 57 |
| Head and neck squamous cell carcinoma | chr3q, 5p, 8p, and 11q gain | tumorigenesis | 58 |
| Oral squamous cell carcinoma | chr1q22.1-q22.2 amplification | correlation with recurrence and radiotherapy | 59 |
| Lung squamous cell carcinoma | chr3q gain and 3p loss | common feature | 60 |
| Lung adenocarcinoma | chr1q gain | cancer feature | 61 |
| Breast cancer | chr1q21.3 amplification | correlation with prognosis in patients with EGFR mutation | 62 |
| Gastrointestinal cancer | chr1q gain | low-grade breast neoplasia | 63 |
| Gastrointestinal tract adenocarcinoma (GIAC) | chr9p21.3 and 2q35 loss; and chr2q31.2, 3q27, 5p15.33, 7q22.1, 8q24, 8p11.23, 11q13.3 gain | common feature | 64 |
| Esophageal squamous cell carcinoma (ESCC) | chr19 gain | relation with stage III/IV | 65 |
| Adrenocortical carcinoma | chr1p and 11q gain | common feature | 66 |
| Clear cell renal cell carcinoma | chr3p loss and 9q gain | common feature | 67 |
| Hematologic malignancies | chr22q loss | common feature | 68 |
| Lymphoid neoplasms | chr1p6 loss | diffuse follicular lymphoma | 69 |
| Burkitt-like lymphoma | chr1q aberration | common feature | 70 |
| Myelodysplastic syndromes | chr5q loss | common feature | 71 |
| B cell acute lymphoblastic leukemia | chr21 gain | common feature | 72 |
| B cell precursor acute lymphoblastic leukemia (B-ALL) | chr21 gain | relation with 12q abnormalities in B-ALL | 73 |
| Testicular germ cell cancers | chr1p2 gain | common feature | 74 |
| Ovarian cancer and endometrial cancers | chr1q gain | common feature | 75 |
| Prostate cancer | chr16p13.3 gain | an elevated risk of distant metastases | 76 |
| | chr8q24 variation | a major contributor to prostate cancer | 77 |
Hematological Cancers

Chr20q deletion is a common cytogenetic abnormality in hematologic malignancies. For example, copy numbers of functional genes in 20q are significantly downregulated in myelodysplastic syndrome and myeloproliferative neoplasm. Recent changes in the World Health Organization (WHO) classification define lymphoid neoplasms based on chromosome abnormalities; for example, predominantly diffuse follicular lymphoma with 1p36 deletion, Burkitt-like lymphoma with 11q aberration, myelodysplastic syndromes with 5q deletion, and B cell acute lymphoblastic leukemia with trisomy 12, an important driver of CLL, and consequent amplification of the B cell receptor signaling.

Other Cancers

Gains of 12p and aneuploidy are nearly ubiquitous in germ-cell tumors (GCTs). NGS of primary (testicular and mediastinal) and metastatic human GCTs shows enrichment in high-frequency chromosome arm-level amplification and reciprocal deletions. Ovarian cancer and endometrial cancers are characterized by 1q gain. In prostate cancer, the gain of 16p13.3 is frequently observed and linked to an elevated risk of distant metastases. Matejcic et al. found that chr8q24 is a major contributor to prostate cancer risk. Finally, balanced chromosomal translocations t(2;13)(q35;q14) and t(1;13)(p36;q14) have been found in about 75% and 10% of sarcoma samples, respectively.

Conclusions

Chromosome abnormalities are commonly related to tumorigenesis and clinical outcomes. Gene amplification and deletion, as well as chromosome rearrangement, is a characteristic of different cancers and can restructure the genome and influence tumorigenesis (Table 1). Whether chromosome abnormalities occur early or late can reveal whether they drive tumor initiation or progression.

Understanding how chromosome abnormalities affect tumor growth and metastasis has been one of the hot research areas in cancer biology and clinical oncology. The influence of chromosome abnormalities in tumor progression ranges from altering the expression level of oncogenes to fostering proliferation, metastasis, and drug resistance. Over the past decade, remarkable technological advances have allowed researchers to both elucidate the contribution of numerical and structural chromosome abnormalities to tumorigenesis with
unprecedented details and analyze how these aberrations correlate with and influence immune signatures and response to cancer therapy. The current impression of structural chromosome abnormalities unequivocally reveals that they are closely associated with tumor progression and prognosis. However, there is a considerable difference in the total numbers and distribution of structural chromosome abnormalities in patients within a specific tumor type. In addition, numerical chromosome abnormalities are closely related with tumorigenesis as well as response to chemotherapy and immunotherapy. As shown in Figure 2, an important role for aneuploidy and CIN in response to cancer therapy has been established in human cancer. To date, numerical chromosome abnormalities and overexpression of the related gene signatures have been identified in 14 cancer types. However, whether numerical chromosome abnormalities exert a positive or negative influence depends on the therapeutic strategy. For example, tumors with high aneuploidy and CIN seem to be more sensitive to chemotherapy, but the opposite is true for immunotherapy (Figure 3). Because immunotherapy has shown effective results in the treatment of cancers, researchers have further found the relevance of chromosome abnormalities to immune escape. Tumors with high SCNA show a significant reduction in the immune signature score, especially CD8+ T cells and natural killer (NK) cell markers. Moreover, specific arm/focal-level amplifications or deletions are associated with immune signatures. Considering that aneuploidy, alone or combined with TMB, has emerged as a possible new predictive indicator for immunotherapy, we speculate that chromosome abnormalities can optimize precision immunotherapy.

Given the high frequency with which chromosome abnormalities occur in cancer and the confirmed impact of aneuploidy level on immune signature, it is likely that chromosome abnormalities alone or combination with TMB will be a more prevalent and efficient biomarker for immunotherapy than only TMB. Nonetheless, several challenges remain. Studies on the relevance of chromosome abnormalities to immunotherapy have just focused on SCNA or arm/focal-level chromosome loss and gain alone. Going forward, considerable efforts should be centered on the development of relevant quantitative models to assess combined numerical and structural chromosome abnormalities, which will have profound implications in the field of precision oncology.

AUTHOR CONTRIBUTIONS
Fan Kou and Lei Wu drafted the manuscript. Xiubao Ren and Lili Yang reviewed and revised the manuscript. All authors agreed on the final version.

CONFLICTS OF INTEREST
The authors declare no competing interests.

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