Molecular Therapy
Oncolytics
Review

Chromosome Abnormalities: New Insights into Their Clinical Significance in Cancer

Fan Kou,[1,2,3,4,5,7] Lei Wu,[1,2,3,4,5,7] Xiubao Ren,[1,2,3,4,5,6] and Lili Yang[1,2,3,4,5]

[1]Department of Immunology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [2]National Clinical Research Center for Cancer, Tianjin, China; [3]Key Laboratory of Cancer Immunology and Biotherapy, Tianjin, China; [4]Key Laboratory of Cancer Prevention and Therapy, Tianjin, China; [5]Tianjin's Clinical Research Center for Cancer, Tianjin, China; [6]Department of Biotherapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

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

https://doi.org/10.1016/j.omto.2020.05.010.

[7]These authors contributed equally to this work.

Correspondence: Xiubao Ren, Department of Immunology, Tianjin Medical University Cancer Institute and Hospital, Huanhuxi Road, Tiyuanbei, Hexi District, Tianjin 300060, China.
E-mail: renxiubao@tjmuch.com
Correspondence: Lili Yang, Department of Immunology, Tianjin Medical University Cancer Institute and Hospital, Huanhuxi Road, Tiyuanbei, Hexi District, Tianjin 300060, China.
E-mail: yanglili@tjmuch.com

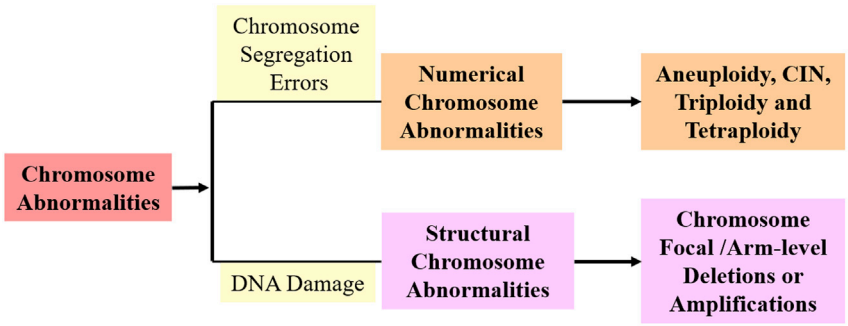

Figure 1. Classification of Chromosome Abnormalities

Based on the mechanism of chromosome segregation errors or DNA damage, chromosome abnormalities are divided into numerical and structural chromosome abnormalities, respectively. Numerical chromosome abnormalities mainly consist of aneuploidy, CIN, triploidy, and tetraploidy, while structural chromosome abnormalities mostly present chromosome focal /arm-level deletions or amplifications.

chromosome aneuploidy and segmental aneuploidy.[14] Aneuploidy is a class of somatic copy number alterations (SCNAs) that predicts clinical benefit and survival.[13] 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.[15,16] 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.[17,18] In two independent cohorts of patients treated with immune checkpoint inhibitor (ICI) anti-CTLA4, Davoli et al.[13] 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.[19] 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.[20] 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.[21] 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.[22,23] 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.[5] Aneuploidy, which affects individual genes and also implies complex genetic alterations, contributes to cancer aggressiveness and recurrence.[5,24] Shukla et al.[25] 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 CAAs 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.[13] 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.[26,27] Furthermore, the genes involved in SCNA contribute to aggressive disease.[28] SCNA is prognostic for cancer-related death in biopsies of conservatively treated prostate cancer, independent of clinical criteria.[27] 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.[29] 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.[30] 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.[9,31] 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.[32] 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,[33] 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.[6,34] Furthermore, CIN and its leading karyotypic heterogeneity drive tumor metastasis.[35] 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.[36] In patients with locally advanced head and neck squamous cell carcinoma (HNSCC), CIN-high tumors are significantly associated with lymph node metastasis.[37] 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.[38–40] For example, overexpression of MASTL promoting CIN has been found in many cancers, which resulted in increased aggressiveness and poor prognosis.[41] 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.[42] 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.[38] 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.[43,44] Swanton et al.[45] 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.[44] 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.[46]

Meta-analysis of cancer triploidy revealed a relatively high proportion of near-triploidy in colon adenoma and adenocarcinoma.[47] 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.[48]

Tetraploidy is a transient state on the path to aneuploidy, which has been reported in primary tumors.[49] Wangsa et al.[50] 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.[51] 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.[52]

Structural Chromosome Abnormalities

Chromosome amplification and deletion are the most common structural chromosome abnormalities, which occur in 88% of cancer samples.[53] 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.[53] Distinct molecular characteristics have an impact on chromosome abnormalities. Glioblastomas without isocitrate dehydrogenase (IDH) mutations feature chr7 gain and chr10 loss.[53,54] Glioblastomas with IDH mutations are characterized by 19q gain and 1p loss. Gain of chr2p and 17q and deletion of chr1p and 11q are well known in neuroblastoma.[55] 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.[56] 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.[53,57]

HNSCC

A molecular characteristic of HNSCC is the gain of chr3 (3q26-29), which is correlated with poorer patient outcome.[58] 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.[59] 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.[60] 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.[60,61]

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.[53] In terms of translocation, non-reciprocal/reciprocal translocation was detected in 18.7% of the 150 patients with NSCLC examined.[62] 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,[53,63] which indicates shorter overall survival.[64] 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.[65] 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.[63,66,67]

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.[68] 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.[69] 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.[70]

Additionally, chr3q and 8q amplifications were found in TNBC with lung metastasis.[71] Moreover, 3q, as a predictive factor for response to neoadjuvant chemotherapy, is strongly correlated with features of aggressiveness in TNBC.[71,72]

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.[53] Liu et al.[73] 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,

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 10 loss	without IDH mutations	53,54
	chr19q gain and 1p loss	with IDH mutations	55
Neuroblastoma	chr2p and 17q gain; chr1p and 11q deletion	common feature	55
	focal loss of chr7q14.1 and chr14q11.2	a predictive indicator for poorer prognosis	55
Low-grade glioma	chr1p and 19q deletion	responsive to chemoradiotherapy	53,57
Head and neck squamous cell carcinoma	chr3q, 5p, 8p, and 11q gain	tumorigenesis	60,61
	chr3 (3q26-29) gain	a predictive indicator for poorer prognosis	58
Oral squamous cell carcinoma	chr11q22.1-q22.2 amplification	correlation with recurrence and radiotherapy	59
Lung squamous cell carcinoma	chr3q gain and 3p loss	common feature	53
Lung adenocarcinoma	chr1q gain	cancer feature	53,63
	chr7p gain	correlation with prognosis in patients with EGFR mutation	67
Breast cancer	chr1q21.3 amplification	relation with recurrence	68
	chr16q loss	low-grade breast neoplasia	69
	Few copy number variations (CNVs) in chr17	relation with male breast cancer	70
Gastrointestinal cancer	chr3q and 8q amplifications	triple-negative breast cancer (TNBC) with lung metastasis	71
Gastrointestinal tract adenocarcinoma (GIAC)	chr13q gain	common feature	53
Esophageal squamous cell carcinoma (ESCC)	chr9p21.3 and 2q35 loss; and chr2q31.2, 3q27, 5p15.33, 7q22.1, 8q24, 8p11.23, 11q13.3 gain	common feature	74
Adrenocortical carcinoma	chr19 gain	relation with stage III/IV	75
	chr5, 12, 19, and 20 gain; and chr1, 10, 18, and 22 loss	common feature	75,76
	chr11p, 17p loss, and 9q gain	pediatric adrenocortical carcinoma	77,78
Clear cell renal cell carcinoma	chr3p loss and 9q gain	common feature	79–81
Hematologic malignancies	chr20q loss	common feature	82,83
Lymphoid neoplasms	chr1p36 loss	diffuse follicular lymphoma	84
Burkitt-like lymphoma	chr11q aberration	common feature	84
Myelodysplastic syndromes	chr5q loss	common feature	84
B cell acute lymphoblastic leukemia	chr21 gain	common feature	84
B cell precursor acute lymphoblastic leukemia (B-ALL)	chr21 gain	relation with 12q abnormalities in B-ALL	85
Testicular germ cell cancers	chr12p gain	common feature	87
Ovarian cancer and endometrial cancers	chr1q gain	common feature	53
Prostate cancer	chr16p13.3 gain	an elevated risk of distant metastases	88
	chr8q24 variation	a major contributor to prostate cancer	89

and 11q13.3 were common in both.[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.[75] Moreover, in this type of cancer, amplification at chr5, 12, 19, and 20 and deletion at chr1, 10, 18, and 22 were observed.[75,76] In pediatric adrenocortical carcinoma, instead, most patients present loss of chr11p and 17 and gain of 9q.[77,78] Clear cell renal cell carcinoma (ccRCC) is marked by loss of 3p and 9p.[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.

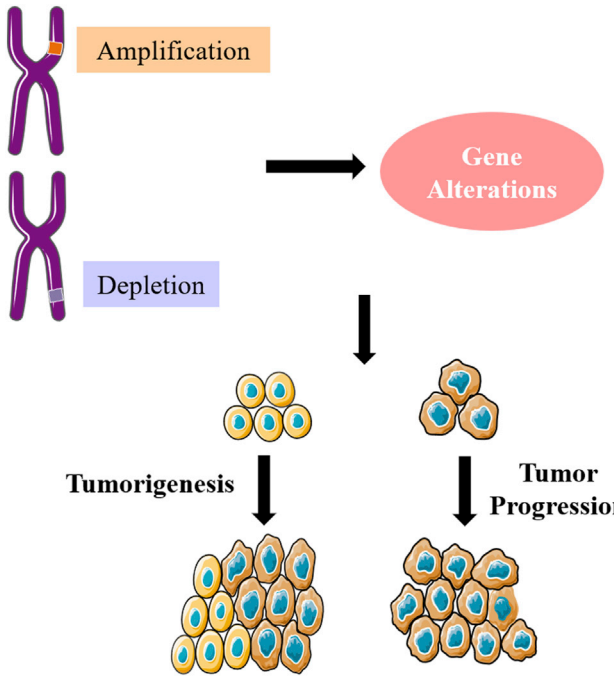

Figure 2. The Role of Structural Chromosome Abnormalities in Tumorigenesis and Progression

Chromosome focal-level amplifications or deletions cause specific gene alterations located by chromosome region, further resulting in the activation of oncogene or silencing of antioncogene. These alterations can promote tumorigenesis and tumor progression.

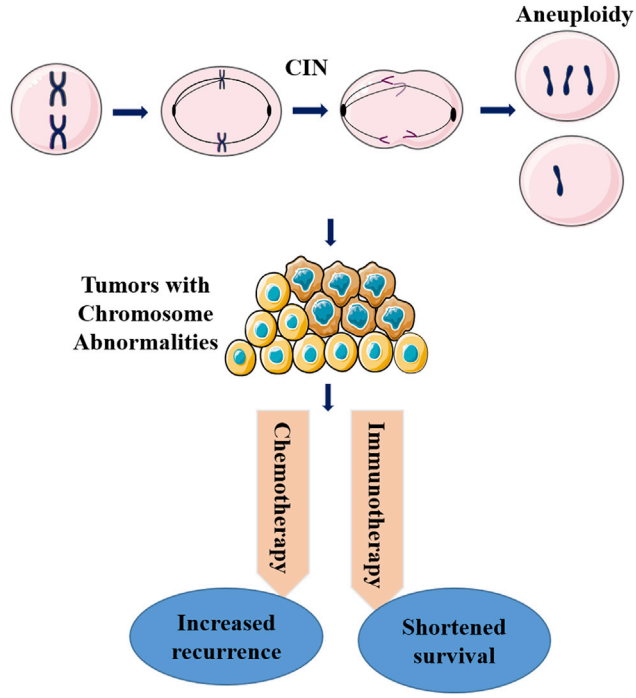

Figure 3. Schematic Representation of Aneuploidy and CIN in Relation to Cancer Chemotherapy and Immunotherapy

CIN, derived from chromosome missegregation errors, is the process that leads to aneuploidy. Tumors with aneuploidy or CIN, referred to as chromosome abnormalities, cause increased recurrence as well as shortened survival of cancer chemotherapy and immunotherapy.

Hematological Cancers

Chr20q deletion is a common cytogenetic abnormality in hematologic malignancies.[82,83] For example, copy numbers of functional genes in 20q are significantly downregulated in myelodysplastic syndrome and myeloproliferative neoplasm.[82] 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 intrachromosomal amplification of chr21 (iAMP21).[84] Importantly, iAMP21 occurs in over 30% of B cell precursor acute lymphoblastic leukemia (B-ALL). Chr21 also correlates with 12q abnormalities in B-ALL.[85] Interestingly, 12q abnormalities are associated with poor prognosis in iAMP21-ALL. In chronic lymphocytic leukemia (CLL), drug response is linked to trisomy 12, an important driver of CLL, and consequent amplification of the B cell receptor signaling.[86]

Other Cancers

Gains of 12p and aneuploidy are nearly ubiquitous in germ-cell tumors (GCTs).[87] 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.[53] In prostate cancer, the gain of 16p13.3 is frequently observed and linked to an elevated risk of distant metastases.[88] Matejcic et al.[89] 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.[90]

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.[25] 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,[91,92] 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.[13] 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,[13,20] 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.

ACKNOWLEDGMENTS

This work was supported by grants from the National Key Technology R&D Program (no. 2018YFC1313400), Key Projects of Tianjin Health Industry (no. 15KG145), and the National Natural Science Foundation of China (nos. 81974246 and 81572265).

REFERENCES

1. Holland, A.J., and Cleveland, D.W. (2009). Boveri revisited: chromosomal instability, aneuploidy and tumorigenesis. Nat. Rev. Mol. Cell Biol. *10*, 478–487.
2. Hata, T., Suenaga, M., Marchionni, L., Macgregor-Das, A., Yu, J., Shindo, K., Tamura, K., Hruban, R.H., and Goggins, M. (2018). Genome-Wide Somatic Copy Number Alterations and Mutations in High-Grade Pancreatic Intraepithelial Neoplasia. Am. J. Pathol. *188*, 1723–1733.
3. Li, Y., Roberts, N.D., Wala, J.A., Shapira, O., Schumacher, S.E., Kumar, K., Khurana, E., Waszak, S., Korbel, J.O., Haber, J.E., et al.; PCAWG Structural Variation Working Group; PCAWG Consortium (2020). Patterns of somatic structural variation in human cancer genomes. Nature *578*, 112–121.
4. ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium (2020). Pan-cancer analysis of whole genomes. Nature *578*, 82–93.
5. Hieronymus, H., Schultz, N., Gopalan, A., Carver, B.S., Chang, M.T., Xiao, Y., Heguy, A., Huberman, K., Bernstein, M., Assel, M., et al. (2014). Copy number alteration burden predicts prostate cancer relapse. Proc. Natl. Acad. Sci. USA *111*, 11139–11144.
6. Gerstung, M., Jolly, C., Leshchiner, I., Dentro, S.C., Gonzalez, S., Rosebrock, D., Mitchell, T.J., Rubanova, Y., Anur, P., Yu, K., et al.; PCAWG Evolution & Heterogeneity Working Group; PCAWG Consortium (2020). The evolutionary history of 2,658 cancers. Nature *578*, 122–128.
7. Johnson, S.C., and McClelland, S.E. (2019). Watching cancer cells evolve through chromosomal instability. Nature *570*, 166–167.
8. Ly, P., Brunner, S.F., Shoshani, O., Kim, D.H., Lan, W., Pyntikova, T., Flanagan, A.M., Behjati, S., Page, D.C., Campbell, P.J., and Cleveland, D.W. (2019). Chromosome segregation errors generate a diverse spectrum of simple and complex genomic rearrangements. Nat. Genet. *51*, 705–715.
9. van Jaarsveld, R.H., and Kops, G.J.P.L. (2016). Difference Makers: Chromosomal Instability versus Aneuploidy in Cancer. Trends Cancer *2*, 561–571.
10. Knouse, K.A., Davoli, T., Elledge, S.J., and Amon, A. (2017). Aneuploidy in Cancer: Seq-ing Answers to Old Questions. Annu. Rev. Cancer Biol. *1*, 335–354.
11. Janssen, A., van der Burg, M., Szuhai, K., Kops, G.J.P.L., and Medema, R.H. (2011). Chromosome segregation errors as a cause of DNA damage and structural chromosome aberrations. Science *333*, 1895–1898.
12. Alexandrov, L.B., Kim, J., Haradhvala, N.J., Huang, M.N., Tian Ng, A.W., Wu, Y., Boot, A., Covington, K.R., Gordenin, D.A., Bergstrom, E.N., et al.; PCAWG Mutational Signatures Working Group; PCAWG Consortium (2020). The repertoire of mutational signatures in human cancer. Nature *578*, 94–101.
13. Davoli, T., Uno, H., Wooten, E.C., and Elledge, S.J. (2017). Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy. Science *355*, eaaf8399.
14. Orr, B., Godek, K.M., and Compton, D. (2015). Aneuploidy. Curr. Biol. *25*, R538–R542.
15. Budczies, J., Allgäuer, M., Litchfield, K., Rempel, E., Christopoulos, P., Kazdal, D., Endris, V., Thomas, M., Fröhling, S., Peters, S., et al. (2019). Optimizing panel-based tumor mutational burden (TMB) measurement. Ann. Oncol. *30*, 1496–1506.
16. Havel, J.J., Chowell, D., and Chan, T.A. (2019). The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. Nat. Rev. Cancer *19*, 133–150.
17. Snyder, A., Makarov, V., Merghoub, T., Yuan, J., Zaretsky, J.M., Desrichard, A., Walsh, L.A., Postow, M.A., Wong, P., Ho, T.S., et al. (2014). Genetic basis for clinical response to CTLA-4 blockade in melanoma. N. Engl. J. Med. *371*, 2189–2199.
18. Van Allen, E.M., Miao, D., Schilling, B., Shukla, S.A., Blank, C., Zimmer, L., Sucker, A., Hillen, U., Foppen, M.H.G., Goldinger, S.M., et al. (2015). Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science *350*, 207–211.
19. Taylor, A.M., Shih, J., Ha, G., Gao, G.F., Zhang, X., Berger, A.C., Schumacher, S.E., Wang, C., Hu, H., Liu, J., et al. (2018). Genomic and Functional Approaches to Understanding Cancer Aneuploidy. Cancer Cell *33*, 676–689.e3.
20. Kim, H.S., Cha, H., Kim, J., Park, W.Y., Choi, Y.L., Sun, J.M., Ahn, J.S., Ahn, M.J., Park, K., and Lee, S.H. (2019). Genomic scoring to determine clinical benefit of immunotherapy by targeted sequencing. Eur. J. Cancer *120*, 65–74.

21. Rizvi, H., Sanchez-Vega, F., La, K., Chatila, W., Jonsson, P., Halpenny, D., Plodkowski, A., Long, N., Sauter, J.L., Rekhtman, N., et al. (2018). Molecular Determinants of Response to Anti-Programmed Cell Death (PD)-1 and Anti-Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non-Small-Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing. J. Clin. Oncol. *36*, 633–641.

22. Roh, W., Chen, P.L., Reuben, A., Spencer, C.N., Prieto, P.A., Miller, J.P., Gopalakrishnan, V., Wang, F., Cooper, Z.A., Reddy, S.M., et al. (2017). Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance. Sci. Transl. Med. *9*, eaah3560.

23. Keenan, T.E., Burke, K.P., and Van Allen, E.M. (2019). Genomic correlates of response to immune checkpoint blockade. Nat. Med. *25*, 389–402.

24. Bonney, M.E., Moriya, H., and Amon, A. (2015). Aneuploid proliferation defects in yeast are not driven by copy number changes of a few dosage-sensitive genes. Genes Dev. *29*, 898–903.

25. Shukla, A., Nguyen, T.H.M., Moka, S.B., Ellis, J.J., Grady, J.P., Oey, H., Cristino, A.S., Khanna, K.K., Kroese, D.P., Krause, L., et al. (2020). Chromosome arm aneuploidies shape tumour evolution and drug response. Nat. Commun. *11*, 449.

26. Stopsack, K.H., Whittaker, C.A., Gerke, T.A., Loda, M., Kantoff, P.W., Mucci, L.A., and Amon, A. (2019). Aneuploidy drives lethal progression in prostate cancer. Proc. Natl. Acad. Sci. USA *116*, 11390–11395.

27. Hieronymus, H., Murali, R., Tin, A., Yadav, K., Abida, W., Moller, H., Berney, D., Scher, H., Carver, B., Scardino, P., et al. (2018). Tumor copy number alteration burden is a pan-cancer prognostic factor associated with recurrence and death. eLife *7*, e37294.

28. Bhattacharya, A., Bense, R.D., Urzúa-Traslaviña, C.G., de Vries, E.G.E., van Vugt, M.A.T.M., and Fehrmann, R.S.N. (2020). Transcriptional effects of copy number alterations in a large set of human cancers. Nat. Commun. *11*, 715.

29. Karn, T., Jiang, T., Hatzis, C., Sänger, N., El-Balat, A., Rody, A., Holtrich, U., Becker, S., Bianchini, G., and Pusztai, L. (2017). Association Between Genomic Metrics and Immune Infiltration in Triple-Negative Breast Cancer. JAMA Oncol. *3*, 1707–1711.

30. Smith, J.C., and Sheltzer, J.M. (2018). Systematic identification of mutations and copy number alterations associated with cancer patient prognosis. eLife *7*, e39217.

31. Ravichandran, M.C., Fink, S., Clarke, M.N., Hofer, F.C., and Campbell, C.S. (2018). Genetic interactions between specific chromosome copy number alterations dictate complex aneuploidy patterns. Genes Dev. *32*, 1485–1498.

32. Schukken, K.M., and Foijer, F. (2018). CIN and Aneuploidy: Different Concepts, Different Consequences. BioEssays *40* (1), https://doi.org/10.1002/bies.201700147.

33. Bakhoum, S.F., and Cantley, L.C. (2018). The Multifaceted Role of Chromosomal Instability in Cancer and Its Microenvironment. Cell *174*, 1347–1360.

34. Rowald, K., Mantovan, M., Passos, J., Buccitelli, C., Mardin, B.R., Korbel, J.O., Jechlinger, M., and Sotillo, R. (2016). Negative Selection and Chromosome Instability Induced by Mad2 Overexpression Delay Breast Cancer but Facilitate Oncogene-Independent Outgrowth. Cell Rep. *15*, 2679–2691.

35. Gao, C., Su, Y., Koeman, J., Haak, E., Dykema, K., Essenberg, C., Hudson, E., Petillo, D., Khoo, S.K., and Vande Woude, G.F. (2016). Chromosome instability drives phenotypic switching to metastasis. Proc. Natl. Acad. Sci. USA *113*, 14793–14798.

36. (2018). Chromosomal Instability Drives Metastasis Independent of Aneuploidy. Cancer Discov. *8*, OF7.

37. Bakhoum, S.F., Ngo, B., Laughney, A.M., Cavallo, J.-A., Murphy, C.J., Ly, P., Shah, P., Sriram, R.K., Watkins, T.B.K., Taunk, N.K., et al. (2018). Chromosomal instability drives metastasis through a cytosolic DNA response. Nature *553*, 467–472.

38. Meyer, F., Becker, S., Classen, S., Parplys, A.C., Mansour, W.Y., Riepen, B., Timm, S., Ruebe, C., Jasin, M., Wikman, H., et al. (2020). Prevention of DNA Replication Stress by CHK1 Leads to Chemoresistance Despite a DNA Repair Defect in Homologous Recombination in Breast Cancer. Cells *9*, 238.

39. Fagan-Solis, K.D., Simpson, D.A., Kumar, R.J., Martelotto, L.G., Mose, L.E., Rashid, N.U., Ho, A.Y., Powell, S.N., Wen, Y.H., Parker, J.S., et al. (2020). A P53-Independent DNA Damage Response Suppresses Oncogenic Proliferation and Genome Instability. Cell Rep. *30*, 1385–1399.e7.

40. Zhang, S., Pan, X., Zeng, T., Guo, W., Gan, Z., Zhang, Y.-H., Chen, L., Zhang, Y., Huang, T., and Cai, Y.D. (2019). Copy Number Variation Pattern for Discriminating MACROD2 States of Colorectal Cancer Subtypes. Front. Bioeng. Biotechnol. *7*, 407.

41. Rogers, S., McCloy, R.A., Parker, B.L., Gallego-Ortega, D., Law, A.M.K., Chin, V.T., Conway, J.R.W., Fey, D., Millar, E.K.A., O'Toole, S., et al. (2018). MASTL overexpression promotes chromosome instability and metastasis in breast cancer. Oncogene *37*, 4518–4533.

42. (2017). Chromosome Instability Drives Tumor Evolution. Cancer Discov. *7*, 546.

43. Jin, Y., Bao, H., Le, X., Fan, X., Tang, M., Shi, X., Zhao, J., Yan, J., Xu, Y., Quek, K., et al. (2020). Distinct co-acquired alterations and genomic evolution during TKI treatment in non-small-cell lung cancer patients with or without acquired T790M mutation. Oncogene *39*, 1846–1859.

44. Salgueiro, L., Buccitelli, C., Rowald, K., Somogyi, K., Kandala, S., Korbel, J.O., and Sotillo, R. (2020). Acquisition of chromosome instability is a mechanism to evade oncogene addiction. EMBO Mol. Med. *12*, e10941.

45. Swanton, C., Nicke, B., Schuett, M., Eklund, A.C., Ng, C., Li, Q., Hardcastle, T., Lee, A., Roy, R., East, P., et al. (2009). Chromosomal instability determines taxane response. Proc. Natl. Acad. Sci. USA *106*, 8671–8676.

46. Salmina, K., Gerashchenko, B.I., Hausmann, M., Vainshelbaum, N.M., Zayakin, P., Erenpreiss, J., Freivalds, T., Cragg, M.S., and Erenpreisa, J. (2019). When Three Isn't a Crowd: A Digyny Concept for Treatment-Resistant, Near-Triploid Human Cancers. Genes (Basel) *10*, 551.

47. Vainshelbaum, N.M., Zayakin, P., Kleina, R., Giuliani, A., and Erenpreisa, J. (2019). Meta-Analysis of Cancer Triploidy: Rearrangements of Genome Complements in Male Human Tumors Are Characterized by XXY Karyotypes. Genes (Basel) *10*, 613.

48. Schulze, S., and Petersen, I. (2011). Gender and ploidy in cancer survival. Cell Oncol. (Dordr.) *34*, 199–208.

49. Ganem, N.J., Storchova, Z., and Pellman, D. (2007). Tetraploidy, aneuploidy and cancer. Curr. Opin. Genet. Dev. *17*, 157–162.

50. Wangsa, D., Quintanilla, I., Torabi, K., Vila-Casadesús, M., Ercilla, A., Klus, G., Yuce, Z., Galofré, C., Cuatrecasas, M., Lozano, J.J., et al. (2018). Near-tetraploid cancer cells show chromosome instability triggered by replication stress and exhibit enhanced invasiveness. FASEB J. *32*, 3502–3517.

51. Kuznetsova, A.Y., Seget, K., Moeller, G.K., de Pagter, M.S., de Roos, J.A., Dürrbaum, M., Kuffer, C., Müller, S., Zaman, G.J., Kloosterman, W.P., and Storchová, Z. (2015). Chromosomal instability, tolerance of mitotic errors and multidrug resistance are promoted by tetraploidization in human cells. Cell Cycle *14*, 2810–2820.

52. Tanaka, K., Goto, H., Nishimura, Y., Kasahara, K., Mizoguchi, A., and Inagaki, M. (2018). Tetraploidy in cancer and its possible link to aging. Cancer Sci. *109*, 2632–2640.

53. Taylor, A.M., Shih, J., Ha, G., Gao, G.F., Zhang, X., Berger, A.C., Schumacher, S.E., Wang, C., Hu, H., Liu, J., et al.; Cancer Genome Atlas Research Network (2018). Genomic and Functional Approaches to Understanding Cancer Aneuploidy. Cancer Cell *33*, 676–689.e3.

54. Körber, V., Yang, J., Barah, P., Wu, Y., Stichel, D., Gu, Z., Fletcher, M.N.C., Jones, D., Hentschel, B., Lamszus, K., et al. (2019). Evolutionary Trajectories of IDH^{WT} Glioblastomas Reveal a Common Path of Early Tumorigenesis Instigated Years ahead of Initial Diagnosis. Cancer Cell *35*, 692–704.e12.

55. Ho, N., Peng, H., Mayoh, C., Liu, P.Y., Atmadibrata, B., Marshall, G.M., Li, J., and Liu, T. (2018). Delineation of the frequency and boundary of chromosomal copy number variations in paediatric neuroblastoma. Cell Cycle *17*, 749–758.

56. Stichel, D., Ebrahimi, A., Reuss, D., Schrimpf, D., Ono, T., Shirahata, M., Reifenberger, G., Weller, M., Hänggi, D., Wick, W., et al. (2018). Distribution of EGFR amplification, combined chromosome 7 gain and chromosome 10 loss, and TERT promoter mutation in brain tumors and their potential for the reclassification of IDHwt astrocytoma to glioblastoma. Acta Neuropathol. *136*, 793–803.

57. Alentorn, A., van Thuijl, H.F., Marie, Y., Alshehhi, H., Carpentier, C., Boisselier, B., Laigle-Donadey, F., Mokhtari, K., Scheinin, I., Wesseling, P., et al. (2014). Clinical value of chromosome arms 19q and 11p losses in low-grade gliomas. Neuro-oncol. *16*, 400–408.

58. Davidson, M.A., and Shanks, E.J. (2017). 3q26-29 Amplification in head and neck squamous cell carcinoma: a review of established and prospective oncogenes. FEBS J. *284*, 2705–2731.

59. Bhosale, P.G., Pandey, M., Cristea, S., Shah, M., Patil, A., Beerenwinkel, N., Schäffer, A.A., and Mahimkar, M.B. (2017). Recurring Amplification at 11q22.1-q22.2 Locus Plays an Important Role in Lymph Node Metastasis and Radioresistance in OSCC. Sci. Rep. *7*, 16051.

60. Cheng, H., Yang, X., Si, H., Saleh, A.D., Xiao, W., Coupar, J., Gollin, S.M., Ferris, R.L., Issaeva, N., Yarbrough, W.G., et al. (2018). Genomic and Transcriptomic Characterization Links Cell Lines with Aggressive Head and Neck Cancers. Cell Rep. *25*, 1332–1345.e5.

61. Cancer Genome Atlas Network (2015). Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature *517*, 576–582.

62. Zhang, Y., Zeng, L., Zhou, C., Li, Y., Wu, L., Xia, C., Jiang, W., Hu, Y., Liao, D., Xiao, L., et al. (2020). Detection of non-reciprocal/reciprocal ALK translocation as poor predictive marker in patients with first-line crizotinib-treated ALK-rearranged NSCLC. J. Thorac. Oncol. *15*, 1027–1036.

63. Zhang, X.C., Wang, J., Shao, G.G., Wang, Q., Qu, X., Wang, B., Moy, C., Fan, Y., Albertyn, Z., Huang, X., et al. (2019). Comprehensive genomic and immunological characterization of Chinese non-small cell lung cancer patients. Nat. Commun. *10*, 1772.

64. Tan, X., Banerjee, P., Pham, E.A., Rutaganira, F.U.N., Basu, K., Bota-Rabassedas, N., Guo, H.F., Grzeskowiak, C.L., Liu, X., Yu, J., et al. (2020). PI4KIIIβ is a therapeutic target in chromosome 1q-amplified lung adenocarcinoma. Sci. Transl. Med. *12*, eaax3772.

65. Chen, H., Carrot-Zhang, J., Zhao, Y., Hu, H., Freeman, S.S., Yu, S., Ha, G., Taylor, A.M., Berger, A.C., Westlake, L., et al. (2019). Genomic and immune profiling of pre-invasive lung adenocarcinoma. Nat. Commun. *10*, 5472.

66. Bao, L., Zhang, Y., Wang, J., Wang, H., Dong, N., Su, X., Xu, M., and Wang, X. (2016). Variations of chromosome 2 gene expressions among patients with lung cancer or non-cancer. Cell Biol. Toxicol. *32*, 419–435.

67. Yuan, S., Yu, S.-L., Chen, H.-Y., Hsu, Y.-C., Su, K.-Y., Chen, H.-W., Chen, C.-Y., Yu, C.-J., Shih, J.-Y., Chang, Y.-L., et al. (2011). Clustered genomic alterations in chromosome 7p dictate outcomes and targeted treatment responses of lung adenocarcinoma with EGFR-activating mutations *29*, 3435–3442.

68. Goh, J.Y., Feng, M., Wang, W., Oguz, G., Yatim, S.M.J.M., Lee, P.L., Bao, Y., Lim, T.H., Wang, P., Tam, W.L., et al. (2017). Chromosome 1q21.3 amplification is a trackable biomarker and actionable target for breast cancer recurrence. Nat. Med. *23*, 1319–1330.

69. de Boer, M., Verschuur-Maes, A.H.J., Buerger, H., Moelans, C.B., Steenkamer, M., Savola, S., and van Diest, P.J. (2018). Role of columnar cell lesions in breast carcinogenesis: analysis of chromosome 16 copy number changes by multiplex ligation-dependent probe amplification. Mod. Pathol. *31*, 1816–1833.

70. Lacle, M.M., Moelans, C.B., Kornegoor, R., van der Pol, C., Witkamp, A.J., van der Wall, E., Rueschoff, J., Buerger, H., and van Diest, P.J. (2015). Chromosome 17 copy number changes in male breast cancer. Cell Oncol. (Dordr.) *38*, 237–245.

71. Xie, G., Yang, H., Ma, D., Sun, Y., Chen, H., Hu, X., Jiang, Y.Z., and Shao, Z.M. (2019). Integration of whole-genome sequencing and functional screening identifies a prognostic signature for lung metastasis in triple-negative breast cancer. Int. J. Cancer *145*, 2850–2860.

72. Qian, J., Chen, H., Ji, X., Eisenberg, R., Chakravarthy, A.B., Mayer, I.A., and Massion, P.P. (2017). A 3q gene signature associated with triple negative breast cancer organ specific metastasis and response to neoadjuvant chemotherapy. Sci. Rep. *7*, 45828.

73. Liu, Y., Sethi, N.S., Hinoue, T., Schneider, B.G., Cherniack, A.D., Sanchez-Vega, F., Seoane, J.A., Farshidfar, F., Bowlby, R., Islam, M., et al.; Cancer Genome Atlas Research Network (2018). Comparative Molecular Analysis of Gastrointestinal Adenocarcinomas. Cancer Cell *33*, 721–735.e8.

74. Liu, X., Zhang, M., Ying, S., Zhang, C., Lin, R., Zheng, J., Zhang, G., Tian, D., Guo, Y., Du, C., et al. (2017). Genetic Alterations in Esophageal Tissues From Squamous Dysplasia to Carcinoma. Gastroenterology *153*, 166–177.

75. Rubinstein, J.C., Brown, T.C., Goh, G., Juhlin, C.C., Stenman, A., Korah, R., and Carling, T. (2016). Chromosome 19 amplification correlates with advanced disease in adrenocortical carcinoma. Surgery *159*, 296–301.

76. Juhlin, C.C., Goh, G., Healy, J.M., Fonseca, A.L., Scholl, U.I., Stenman, A., Kunstman, J.W., Brown, T.C., Overton, J.D., Mane, S.M., et al. (2015). Whole-exome sequencing characterizes the landscape of somatic mutations and copy number alterations in adrenocortical carcinoma. J. Clin. Endocrinol. Metab. *100*, E493–E502.

77. Pinto, E.M., Chen, X., Easton, J., Finkelstein, D., Liu, Z., Pounds, S., Rodriguez-Galindo, C., Lund, T.C., Mardis, E.R., Wilson, R.K., et al. (2015). Genomic landscape of paediatric adrenocortical tumours. Nat. Commun. *6*, 6302.

78. Assié, G., Letouzé, E., Fassnacht, M., Jouinot, A., Luscap, W., Barreau, O., Omeiri, H., Rodriguez, S., Perlemoine, K., René-Corail, F., et al. (2014). Integrated genomic characterization of adrenocortical carcinoma. Nat. Genet. *46*, 607–612.

79. Mitchell, T.J., Turajlic, S., Rowan, A., Nicol, D., Farmery, J.H.R., O'Brien, T., Martincorena, I., Tarpey, P., Angelopoulos, N., Yates, L.R., et al.; TRACERx Renal Consortium (2018). Timing the Landmark Events in the Evolution of Clear Cell Renal Cell Cancer: TRACERx Renal. Cell *173*, 611–623.e17.

80. Turajlic, S., Xu, H., Litchfield, K., Rowan, A., Chambers, T., Lopez, J.I., Nicol, D., O'Brien, T., Larkin, J., Horswell, S., et al.; PEACE; TRACERx Renal Consortium (2018). Tracking Cancer Evolution Reveals Constrained Routes to Metastases: TRACERx Renal. Cell *173*, 581–594.e12.

81. Massari, F., Ciccarese, C., Bria, E., Porta, C., La Russa, F., Knuutila, S., Artibani, W., Porcaro, A.B., Bimbatti, D., Modena, A., et al. (2017). Reprofiling Metastatic Samples for Chromosome 9p and 14q Aberrations as a Strategy to Overcome Tumor Heterogeneity in Clear-cell Renal Cell Carcinoma. Appl. Immunohistochem. Mol. Morphol. *25*, 39–43.

82. Stoner, S.A., Yan, M., Liu, K.T.H., Arimoto, K.-I., Shima, T., Wang, H.-Y., Johnson, D.T., Bejar, R., Jamieson, C., Guan, K.L., and Zhang, D.E. (2019). Hippo kinase loss contributes to del(20q) hematologic malignancies through chronic innate immune activation. Blood *134*, 1730–1744.

83. Kurtin, P.J., Dewald, G.W., Shields, D.J., and Hanson, C.A. (1996). Hematologic disorders associated with deletions of chromosome 20q: a clinicopathologic study of 107 patients. Am. J. Clin. Pathol. *106*, 680–688.

84. Cazzola, M. (2016). Introduction to a review series: the 2016 revision of the WHO classification of tumors of hematopoietic and lymphoid tissues. Blood *127*, 2361–2364.

85. Sinclair, P.B., Ryan, S., Bashton, M., Hollern, S., Hanna, R., Case, M., Schwalbe, E.C., Schwab, C.J., Cranston, R.E., Young, B.D., et al. (2019). SH2B3 inactivation through CN-LOH 12q is uniquely associated with B-cell precursor ALL with iAMP21 or other chromosome 21 gain. Leukemia *33*, 1881–1894.

86. Dietrich, S., Oleś, M., Lu, J., Sellner, L., Anders, S., Velten, B., Wu, B., Hüllein, J., da Silva Liberio, M., Walther, T., et al. (2018). Drug-perturbation-based stratification of blood cancer. J. Clin. Invest. *128*, 427–445.

87. Taylor-Weiner, A., Zack, T., O'Donnell, E., Guerriero, J.L., Bernard, B., Reddy, A., Han, G.C., AlDubayan, S., Amin-Mansour, A., Schumacher, S.E., et al. (2016). Genomic evolution and chemoresistance in germ-cell tumours. Nature *540*, 114–118.

88. Bramhecha, Y.M., Guérard, K.-P., Rouzbeh, S., Scarlata, E., Brimo, F., Chevalier, S., Hamel, L., Dragomir, A., Aprikian, A.G., and Lapointe, J. (2018). Genomic Gain of 16p13.3 in Prostate Cancer Predicts Poor Clinical Outcome after Surgical Intervention. Mol. Cancer Res. *16*, 115–123.

89. Matejcic, M., Saunders, E.J., Dadaev, T., Brook, M.N., Wang, K., Sheng, X., Olama, A.A.A., Schumacher, F.R., Ingles, S.A., Govindasami, K., et al.; PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium (2018). Germline variation at 8q24 and prostate cancer risk in men of European ancestry. Nat. Commun. *9*, 4616.

90. Xiao, X., Garbutt, C.C., Hornicek, F., Guo, Z., and Duan, Z. (2018). Advances in chromosomal translocations and fusion genes in sarcomas and potential therapeutic applications. Cancer Treat. Rev. *63*, 61–70.

91. Jia, L., Zhang, Q., and Zhang, R. (2018). PD-1/PD-L1 pathway blockade works as an effective and practical therapy for cancer immunotherapy. Cancer Biol. Med. *15*, 116–123.

92. Yan, S., Zhao, P., Yu, T., and Gu, N. (2019). Current applications and future prospects of nanotechnology in cancer immunotherapy. Cancer Biol. Med. *16*, 486–497.